PhD-FSTC-2019-32
Faculty of Sciences, Technology and Communication

DISSERTATION

Presented on 23/04/2019 in Luxembourg

to obtain the degree of

DOCTEUR DE L'UNIVERSITÉ DU LUXEMBOURG

EN BIOLOGIE

by

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THE EFFECT OF ATP INDUCED CALCIUM DYNAMICS ON EPITHELIAL TO MESENCHYMAL TRANSITIONS

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The work for this dissertation was carried out in the “Integrative Cell Signalling group” at the Luxembourg Centre for Systems Biomedicine (LCSB) at the University of Luxembourg.

First of all, I would like to thank my supervisor, Dr. Alexander Skupin, for giving me the opportunity to work on this project. I am grateful for all your support and for his motivating, optimistic and always curious view on science, especially during these low sugar intake days. One of the first, and the most memorable phrases addressed to science “Lets rock it”!

I would like to thank the members of my CET committee, Prof. Dr. Rejko Krüger, Prof. Dr. Jens Schwamborn. I thank my fellow labmates in for the stimulating discussions, for the sleepless nights we were working together in the cell culture, and for the laugh and fun we have had in the last four years: Aymeric, Olga, Tomasz, Stefano, Luis, David, Guadalupe, Gabriela, Rashi, Dimitrios, Suresh, Mahsa, Niko, Francoise, Michela, Silvia, Marina, Patrick, Alice, Corrado and Sonja. Also I thank my friends in the ISB institute in Seattle: Irit Rubin, Xu Zhou, Michael Strasser. In particular, I am grateful to MD, Dr. Sui Huang for long, but always interesting discussions about science.

Moreover, I want to thank Gabriela Novak and Paul Antony for reviewing my thesis manuscript. I also thank the Fonds National de la Recherche Luxembourg (FNR) for providing the funding for this project (CaSCAD). I would also like to thank my family: my parents Urszula and Józef. Thank you for your support.

ABSTRACT

Cells respond to a multitude of external triggers by a limited number of signaling pathways activated by receptors on plasma membrane, such as receptor tyrosine kinases (RTKs) or G protein-coupled receptors (GPCRs). These pathways do not simply convey the downstream signal, but instead the signal is very often processed by encoding and integrated with the current state of the cell.

A traditional transcriptional analysis tends to provide an averaged output measured in a population, what often masks the behavior of individual cells. However, with recent single cell techniques developments, it is possible to investigate transcription in individual living cells. This contributed tremendously to the understanding of development and progression of many diseases including cancer. The more we understand about this high complexity of signaling mechanisms and multitude of cellular safety countermeasures, the more we see cancer as a microevolution state of “rebellious cells” (cells entering the fate opposite to the one intended) following a patch through a discreet system.

This thesis specifically focused on the temporal aspect of signaling in the context of the epithelia-to-mensenchymal transition (EMT) by combining single cell experiments and bioinformatics analysis. We investigated cellular signaling changes in response to different dynamical profiles of the stimuli. In particular, we used the HMLER cell line, which is a metastatic breast cancer model for the epithelial to mesenchymal transition. By applying stochastic or oscillatory pulses of extracellular ATP-induced Ca^{2+} signals with different interspike intervals, we were investigating different transcription states from those evoked by constant ATP-induced Ca^{2+} dose responses. In order to precisely apply those stimulation profiles, we have developed and established a perfusion system. This device allows to treat population of cells simultaneously with the exact same dynamical profiles. Cells treated by these well controlled signals were subsequently processed by the single cell RNA-seq technique Drop-seq for transcriptional analysis. The resulting high dimensional digital gene expression matrices were analyzed by a developed

high-throughput computational analysis pipeline. This analysis includes the identification of differentially expressed genes and cellular clusters (states) by dimensionality reduction methods (PCA, t-SNE) and pathway analysis. We evaluated changes and trends of genes from difference dynamical profiles by investigating their involvement in stress, stemness and regulation of motility.

First, we confirmed that oscillatory stimulation with extracellular ATP (eATP) tends to lower the burden of cellular stress and apoptosis related pathways while maintaining its other effector functions compared to constant eATP stimulation. Interestingly, stochastic spiking of extracellular ATP in our setup led to a massive (~80%) increase in overall differential gene expression compared to deterministic oscillatory stimulation with the same period. Consequentially, stochastic signaling seems to activate a much wider range of biological pathways, which indicates the much higher complexity in information processing capability of producing rebellious cells during cancer progression and metastasis. On the other hand, our findings suggests that oscillatory eATP stimulation could contribute to EMT by lowering *ID3* expression compared to stochastic stimulation where we observed a stronger upregulation of IRS2. Finally, we integrated the DEGs into biological processes involved in each conditions and put these new insights into the context of the eATP-induced Ca^{2+} induced epithelial to mesenchymal transition.

Overall, this thesis has applied recent single cell technologies to characterize underlying principles of cellular heterogeneity induced by cell signaling and specifically investigated the complex mechanisms of cell fate in the context of EMT

Table of Contents

1mO – 1 minute oscillation

2mO – 2 minute oscillation

6mO – 6 minute oscillation

6mS – 6 minute stochastic oscillation

AB – antibody

ARC - anti-reflective coating

ARID5B - AT-Rich Interactive Domain-Containing Protein 5B

ATP - adenosine 5'-triphosphate

BEAM - branched expression analysis modeling

BMP - Bone morphogenetic protein

BMPR2 – Bone morphogenetic protein receptor type 2

CD – critical dimension

CD44 – CD44 Molecule (Indian Blood Group)

CD55 - complement decay-accelerating factor

CITED2 – Cbp/P300-Interacting Transactivator 2

CLEC2D - C-type lectin domain family 2 member D

Ct - cycle threshold

CXCL1 - chemokine (C-X-C motif) ligand 1

CYR61 – Cellular Communication Network Factor 1

DEG - differentially expressed genes

DGE - digital gene expression

DMSO - dimethyl sulfoxide

DST – Dystonin

DUSP10 - Dual specificity protein phosphatase 10

DVL2 - Segment polarity protein dishevelled homolog DVL-2

eATP – extracellular ATP

EGFR - epidermal growth factor receptor

ENDOG - Endonuclease G

ERG1 - Early Growth Response 1

Ex/Em – excitation/emission (nm)

FBS - fetal bovine serum

FDTS – perfluorodecyltrichlorosilane

FGF - Fibroblast Growth Factor

FOSL2 - Fos-related antigen 2

FST – Follistantin

FTH1 – Ferritin Heavy Chain 1

GEMs - Gel Bead-In Emulsion

HDAC5 - Histone deacetylase 5

HES1 – Hes Family BHLH Transcription Factor 1

ID3 - DNA-binding protein inhibitor ID-3

IER3 - Radiation-inducible immediate-early IEX-1

IL-6 - Interleukin 6

IP- isopropanol

IP3R - Inositol trisphosphate receptor

IRS2 - Insulin receptor substrate 2

ITRIP - inositol 1,4,5-trisphosphate receptor interacting protein

LGALS1 – Galectin 1

min – minutes

MMP – Matrix Metallopeptidase family

MT1G - Metallothionein-1G

NFATc4 – Nuclear Factor Of Activated T Cells 4

PBS - phosphate-buffered saline

PCA - Principal component analysis

PCOLCE – Procollagen C-Endopeptidase Enhancer

PPP5C – Protein Phosphatase 5

Q-val – False Discovery Rate corrected p-value.

RF – radiofrequency

ROS - reactive oxygen species

RT – room temperature

S100A6 – S100 Calcium Binding Protein A6

sec - seconds

SL – soda lime glass

SOX9 - Transcription factor SOX9

SU-8 - permanent epoxy negative photoresist

t-SNE - t-Distributed Stochastic Neighbor Embedding

TGF-β1 - Transforming growth factor beta 1

TIMP1 – TIMP Metallopeptidase Inhibitor 1

TJP1 – Tight Junction Protein 1

TMSB4X – Prothymosin Beta-4

TOB1 – Transducer Of ErbB-2 1

TXNIP - Thioredoxin Interacting Protein

ZFAS1 – Long non-coding ZFAS1

1 Introduction

Complex life is based on multicellularity and the finely tuned spatiotemporal interaction between different cell types. To form ordered and specialized structures of a higher organism, such as building up organs from the same DNA content, cells have to sense their environment and adapt to it. For this they tailor gene expression for different cell types using epigenetic mechanisms. Epigenetic adaptation is, therefore, the essential foundation of complex life and perturbations of underlying processes can be linked to diseases such as non-genetically induced cancers. While intensive research during the last decades has identified different adaptation mechanisms, including methylation of the DNA, splicing of mRNAs or regulation of translation by microRNAs, our mechanistic understanding how cellular regulation is organized by cell signaling is still rather limited. The main reason for this lack in understanding are the complex cellular regulatory mechanisms and the accompanied large cellular heterogeneity, rendering systematic investigations problematic (Komin & Skupin, 2017). The present work is addressing this challenge of cell signaling by applying recently established single cell transcriptomics methods to a well-controlled in vitro model system for the epithelial-to-mesenchymal transition (EMT), which is an essential process during development and metastasis of cancer.

In general, signal dynamics encodes information, which can be defined by distinct features such as robustness to noise and high information capacity. In biology, an increasing number of studies highlights the functional importance of cell signaling dynamics at the single cell level (Wiley, 2017), (Handly, Yao, & Wollman, 2017). Only recently, we began to better understand how “dynamic signal encoding” applies to a multicellular context including developmental processes, wound healing or cancer metastasis (J. M. Yang et al., 2018). Multicellular organisms often use temporal modulation of specific signaling pathways like oscillations or signaling gradients to precisely control cell fate decisions and pattern formation (Sonnen & Aulehla, 2014).

Starting from a single cell, the development of a complex organism does not only require tight regulation in space but also in time. This

multitude of complex information also needs to be precisely and fully received by the cell. It is especially important during orchestrated processes such as those involved in ontogenesis (Abdallah et al., 2013).

Theoretical considerations of signaling dynamics might offer additional properties and layers of information of the system (Michael J Berridge, Lipp, & Bootman, 2000). Signaling dynamics, in contrast to a more static perspective, describes the temporal evolution of a signaling system. Perturbing and visualizing intracellular signaling with new technologies enable us to investigate the significance of dynamics at the signaling level (Handly et al., 2017). Growing experimental evidence suggests that upstream stimuli can be encoded in the dynamic properties of signals such as duration, delay, fold-change or frequency (Michael J Berridge et al., 2000; Bootman, 2006; Sonnen & Aulehla, 2014). Multicellular organisms often utilize temporal modulation of specific signaling pathways like oscillations or signaling gradients to robustly control cell fate decisions and pattern formation (Nelson, 2004) (**Figure 1**).

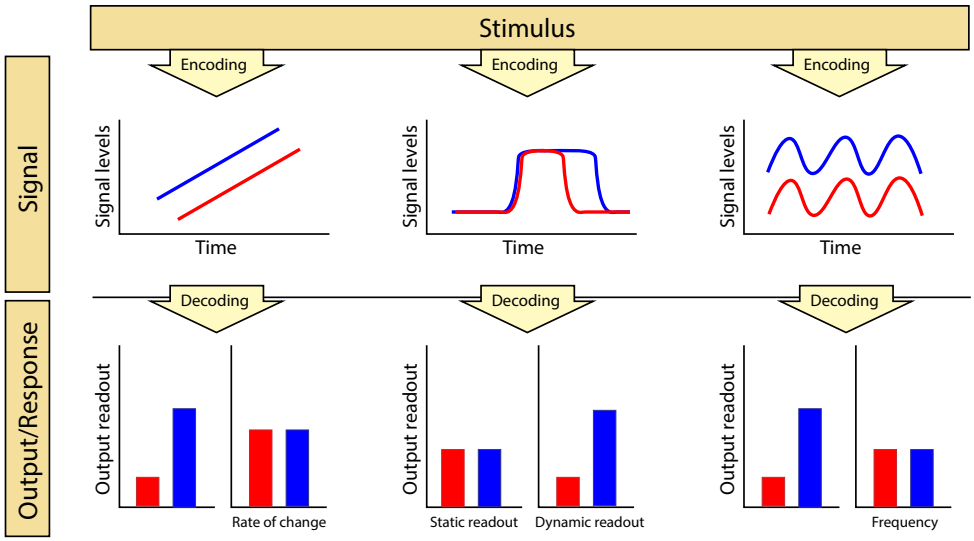


Figure 1. Information transmission and its underlying dynamics. Stimuli can be encoded in a specific intracellular signaling pattern as a result of cellular events. Next, the signal is decoded to activate a cellular response. The figure exemplifies absolute signaling levels and signaling dynamics (signal duration, rate of change or frequency) representing different readouts. Extracting features of this signal dynamics separately can result in qualitatively and quantitatively different responses. The differences are visible when two signals with the same amplitude but different durations result in the same response. But in case that the duration of the signal is critical, the responses could be different based on the absolute signal values. Another example shows that even if two signals have the same slope, the variation in stimulation may come from the fact that absolute levels of the signal could be different. Finally, we can have critical information encoded in oscillation frequency, therefore signals with different absolute levels and identical frequency may induce a similar cellular effect (Sonnen & Aulehla, 2014).

It is known that different cell types can respond to stimuli in very different ways (Whitaker, 2006; Zhu et al., 2008). When investigating even further the same population, we can still see a range of different responses (Ashall et al., 2009). Unfortunately, most technical and analytical methods either completely ignore heterogeneity or do not fully account for it, as heterogeneity has been typically considered as noise that needs to be eliminated (Abdallah et al., 2013; Komin & Skupin, 2017). This perspective may represent an oversimplification, and there are many reasons why genetically identical cells can be different, even if they share the same immediate environment. Given a distinct number of molecules interacting with cell receptors and a different number of functional receptors, these differences could be caused and further amplify by complex cellular states based on e.g. nuclear retention, transport of transcripts, stress or cell cycle (Battich, Stoeger, & Pelkmans, 2015; Legewie et al., 2017) This level of diversity may not be easy to correlate or characterize, but nevertheless it is important for a better understanding of cellular signaling. Fortunately, recent single cell analysis methods have significantly improved in their capacity to investigate cell heterogeneity, especially when coupled to unbiased profiling technique such as high throughout RNA sequencing (Goldman et al., 2019; Klein et al., 2015).

Another important property of information processing inside cells is frequency encoding as proven for e.g. Ca^{2+} spikes, cAMP or p54 (Purvis & Lahav, 2013; Smedler & Uhlén, 2014). It has been reported that even when individual cells varied with stimulus intensity, cell signaling on the population level still can be robust against perturbations (Parekh, 2011). When statistical properties of Ca^{2+} signals were evaluated, it became clear that more information could be transmitted by spike sequences than only by the frequency and that particularly the variability of spike timing is cell type and pathway specific (Thurley et al., 2014).

Based on these observations, the aim of the present work is to investigate if and how this potential variability signaling mechanism can have a physiological effect. Since the underlying subtitle and complex mechanisms can be disguised by the epigenetically related cellular heterogeneity, such an

investigation relies on the comprehensive characterization of individual cells. For this purpose, this works combines recently established single cell RNA sequencing (sc-RNAseq) methods with well-defined and controlled stimulation protocols to systematically investigate the interplay of specific stimuli (activation) patterns and resulting cell states. This methodology was applied to a biomedical relevant model system of breast cancer metastasis by epithelial-to-mesenchymal transition (EMT).

Therefore, the thesis will first give a detailed introduction into the biological background (Chapter 2) including breast cancer, cellular heterogeneity and Ca^{2+} signaling followed by the definition of the specific aims (Chapter 3). In Chapter 4, the used material and applied methods are introduced before the results are presented in Chapter 5 and discussed in Chapter 6. Finally, Chapter 7 will summarize the findings and give an outlook of future research directions.

2 Biological background

2.1 Breast cancer

Breast cancer is the most commonly occurring cancer in women worldwide according to Global Health Estimates, WHO 2015 (Press Release, 2018). Despite significant progress in diagnostics and treatment, breast cancer still remains a major unresolved clinical and scientific problem. Breast cancer comprise of a group of biologically and molecularly heterogeneous diseases originated from the breast tissue. While the risk factors linked with this cancer differ with respect to other cancer types, individual genetic predisposition like mutations in the *BRCA1* or *BRCA2* gene are often still an important causative agent for this malignancy. Tumor can originate from different areas of the breast, such as the lobules, the ducts, or from the tissue between them. Breast cancers differ based on their invasiveness relative to the primary sites of origin. It is critical to distinguish between various types of malignancies because each of them presents different prognoses and specific treatment options.

Unfortunately, normal development and breast cancer progression seems to be remarkably parallel, at least at the molecular level. It is believed within the scientific community that breast cancer may be derived from mammary cancer stem cells. Mammary stem cells and normal breast development are regulated by the same signaling pathways such as Wnt/β-catenin signaling pathways, estrogen receptors and the receptor tyrosine-protein kinase erbB-2 (HER2), which control stem cell proliferation, cell differentiation, cell death and cell motility. Moreover, emerging evidence are pointing out that epigenetic regulations and noncoding RNAs may play key roles in breast cancer development and progression. These different mechanisms may be also the reason for such high cellular heterogeneity and metastatic aspects of the tumor, especially in case of a triple-negative breast cancer (Polyak, 2007).

While the exact etiology of this malignancy is unknown, family history is one of the strongest risk factor. Germline mutations in a high-penetrance cancer susceptibility genes including *BRCA1, BRCA2* and *TP53*, account for less than 25% of tumors, whereas variations in low- and moderate-penetrance genes are likely to explain the majority of cases. Other factors strongly correlated with clinical cases of breast cancer include allele variants and SNPs in *FGFR2* (fibroblast growth factor receptor 2), *MAP3K1* (mitogen-activated kinase kinase kinase 1), *TNRC9* (thymocyte selection–associated high mobility group box 9), *CASP8* (caspase 8), *LSP1* (lymphocyte-specific protein) and *TGFB1* (Cox et al., 2007). In spite of large efforts from many laboratories to unravel this complexity, the mechanism by which these variants may influence breast tumorigenesis is still largely unknown. Hence, despite all the technological improvements in the treatment of advanced-stage tumors, early diagnosis and prevention are still the deciding factor in overall outcome (Stacey et al., 2007).

Therefore, an elusive goal in breast cancer oncology has been to improve the detection of tumors and correct identification of subtypes of cancer prior to empirical clinical testing. Ongoing approaches to tackle this obstacle focus on comprehensive sequencing of tumors, which is now possible due to high throughput sequencing. Several such studies have recently been published, some exclusively focusing on kinases (Greenman et al., 2007), others sequencing the whole transcriptome (Sjöblom et al., 2006). Results from

those studies clearly point out very high number of genes mutated in breast cancer, in particular signaling pathway of the PI3KCA/AKT/PTEN, TP53, and NF-κB were affected. Interesting here was the fact that in case of sporadic tumors the frequency of mutations in any given gene stayed relatively low.

Breast cancer evolution seems to follow defined pathological and clinical stages, starting with ductal hyperproliferation, later continuing into *in situ* and invasive carcinomas, and eventually progressing into metastatic disease. The microenvironment of breast tissue is primarily build by fibroblasts, leukocytes, myoepithelia, endothelial cells and myofibroblasts surrounded by extracellular matrix (ECM) molecules. *In vivo* and *in vitro* studies have shown that, in case of transformed breast cancer cells, paracrine signaling of the environment has a strong effect on cellular growth, survival, polarity, and invasive behavior (Bissell & Radisky, 2001) (Elenbaas & Weinberg, 2001). Experimental studies have shown that deletion of the type II TGF-β receptor in mice fibroblasts and mammary fat pad stroma in rats treated with carcinogen were able to induce formation of tumors and their progression (Cheng et al., 2005) (Bhowmick et al., 2004). These observations are highlighting the importance of stromal signals in cancerogenesis.

Chronic inflammation is a stromal inflammatory condition driven by the microenvironment, and is associated with a higher risk of developing cancer. According to human epidemiological data, prolonged usage of nonsteroidal anti-inflammatory drugs (NSAIDs) are significantly lowering this risk (Ulrich, Bigler, & Potter, 2006). From all tumor-associated leukocytes, macrophages have been the most extensively researched cells in progression of breast cancer. Many model systems have pointed out macrophages as the main players in promoting invasion, angiogenesis and metastatic spreading of cells (Lin & Pollard, 2007) (Lewis & Hughes, 2007).

2.1.1 HMLER model

To investigate the microenvironment of breast cancer and the interplay between epithelial and mesenchymal cells, a HMLER cell line was engineered by immortalization of primary human mammary epithelial cells (HMECs) (Elenbaas et al., 2001).

This model was created with minimal genetic alterations, by transforming primary human mammary epithelial cells (HMECs) to carcinoma cells through the introduction of three specific genes, the H-Ras oncoprotein, the telomerase catalytic subunit and the SV40 large-T antigen. The cell line was used to elucidating both the genetic and cell biological requirements for the development of breast cancer *in vivo* (Elenbaas et al., 2001). The cell line was further intensively investigated for so-called ‘‘cancer stem cells’’ (CSC) and their role in tumor initiation, as well as for the involvement of EMTs in the metastatic dissemination. By using this mammary tumor progression model, it was shown that cells can possess both stem and tumorigenic characteristics of ‘‘cancer stem cells’’ and that acquisition of these stem and tumorigenic characteristics was a consequence of EMT induction (Morel et al., 2008). In many cancerous breast cell lines with epithelial phenotype, such as HMLE, HMLER, and MCF7 cell lines (L. Chen et al., 2012), the CSC population was consistently associated with high expression of mesenchymal genes, whereas in cell lines with mesenchymal morphology, such as 4T07, BT-549, MDA-MB231, the CSC population expressed more epithelial genes. It was speculated that just by undergoing the transition cells could activate the stemness markers (Patsialou et al., 2012).

2.2 Epithelial-mesenchymal transition

Stationary epithelial cells are characterized by an apical-basal polarity, tight junctions, and expression of cell-cell adhesion markers such as E-cadherin. Until around ~600 million years ago, two-dimensional sheets of those cells were the main building blocks of multicellular eukaryotic life. Mesenchymal cells arise as the result of epithelial cell delamination through a reprogramming process, the EMT, an epithelial-to-mesenchymal transition. EMT is a reversible cellular process in which cells lose their cell-cell adhesion and cell polarity, and gain migratory and invasive properties of mesenchymal cells. The revers to this process is called mesenchymal-to-epithelial transition (MET) where mesenchymal cells do not make mature cell-cell contacts, but can invade tissue through the extracellular matrix, and express markers such as vimentin, fibronectin, N-cadherin (Baum, Settleman, & Quinlan, 2008).

The EMT is triggered in response to pleiotropic signaling factors that induce the upregulation of specific transcription factors, such as Zeb, Snail, Twist and miRNAs together with post-translation and epigenetic regulators, many of which are involved in development, wound healing, fibrosis, and cancer metastasis (**Figure 2**) (Nieto, Huang, Jackson, & Thiery, 2016).

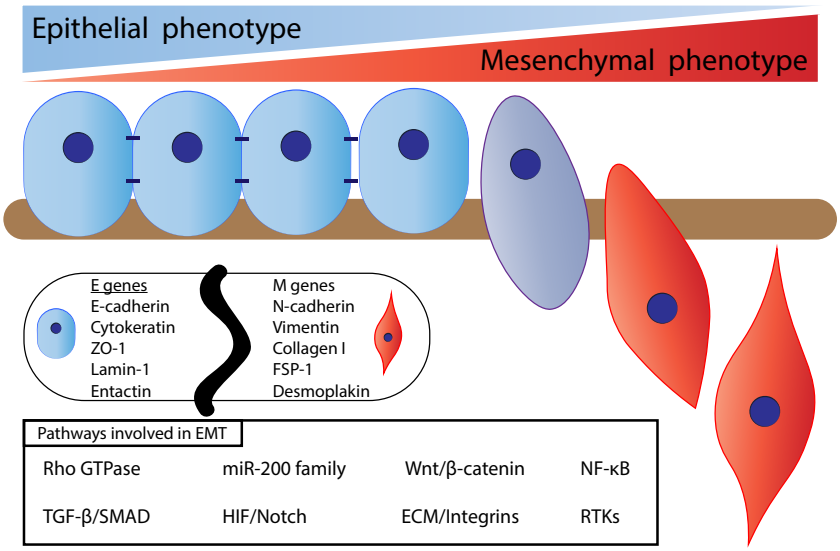


Figure 2. Most important hallmarks of epithelial–to–mesenchymal transition. Many pathways are able to trigger EMT including tyrosine kinase receptors (fibroblast growth factor, epidermal growth factor, connective tissue growth factor, insulin-like growth factor, platelet-derived growth factor, etc), integrins, Wnt, transforming growth factor β pathways, and nuclear factor NF-κB. Many of these pathways are linked by activation of master transcription factors (Twist-1, Snai-1/2, Slug, Zeb-1, Ovol-1/2, Prrx-1), which induce the EMT program in epithelial cells by downregulating E-cadherin expression and other genes characteristic for the epithelial phenotype and upregulating mesenchymal phenotype genes. The canonical TGF-β/SMAD signaling pathway is probably the most characteristic cause of tissue fibrosis. Activation of the canonical Wnt signaling pathway and β catenin changes epithelial cells to be more susceptible to EMT by inhibiting the growth arrest created by TGF-β. The extracellular matrix (ECM) is also modulating TGF-β signaling by integrin signaling, which further contributes to EMT. NF-κB activated through inflammatory cytokines is also involved in EMT associated with fibrosis (Fernandez & Eickelberg, 2012).

The classic description of EMT as the transformation of epithelial cells into mesenchymal cells is being perceived as a shift between two alternative states, mesenchymal or epithelial. However, recent work highlights a greater flexibility in this transitional process, where cells are no longer thought to oscillate between the a full mesenchymal and full epithelial states, but rather cover a continuous spectrum of intermediary steps. This purported plasticity means that cells could linger in intermediary phases and may undergo a partial EMT program. Identification of hybrid intermediate EMT states during organ fibrosis and in circulating tumor cells provides evidence that the spectrum of

EMT previously described in cell culture also reflects *in vivo* observations (Nieto et al., 2016)

2.2.1 EMT in embryogenesis

Mesenchymal cells are multipotent stromal cells that can differentiate into a variety of different cell types. Therefore, transition of epithelial cells into mesenchymal cells via EMT is essential for numerous developmental processes, including neural tube formation and mesoderm formation. EMT processes ongoing in embryogenesis are named “EMT Type I”. Since mesenchymal cells are free to migrate through the body cavity, the evolution of the mesenchyme opened up new avenues for morphological plasticity. As these cells acquired the ability to take up new positions within the embryo and establish novel cell–cell interactions, new types of internal tissues and organs such as bones and muscles can be formed. After migrating to a suitable site, mesenchymal cells adhere to each other and re-polarize to form secondary epithelia by the MET process. These switches between mesenchymal and epithelial states are present during gastrulation and neural crest formation (Baum et al., 2008).

Emigration of the first neural crest (NC) cells becomes apparent at levels opposite the epithelial somite. Furthermore, when the somite dissociate, NC cells continue exiting the neuroepithelium and simultaneously begin to invade the somite in a segmental fashion. NC formation still requires better understanding, although the zinc finger gene *Slug* has been identified to be involved in specifying EMT competence. Furthermore, also the activity of integrins in the extracellular matrix seems to play a very important role in EMT. Additionally, it had been reported that removal of β1-integrin from the neural crest in mouse cells is completely blocking colonization of the gut, leading to an aganglionosis of the descending colon, which seems to be similar phenotypically to the human Hirschsprung's disease (Breau, 2006). Changes in cell motility and cell shape occur at the same time as changes in the cytoskeleton. These concerted changes seem to be triggered by TGFβ family growth factors, of which TGFβ 1 appears to be particularly important. Additionally in the trunk region, interplay between BMP4 and noggin was

observed. Downregulation of noggin progressively relieves inhibition of BMP, which consequently triggers cell migration by upregulation of Wnt1 transcription and Wnt-dependent canonical signaling (Fernandez & Eickelberg, n.d.). On top of this, timing of EMT seems to be additionally controlled by opposing gradients of fibroblast growth factor (FGF) and retinoic acid in the paraxial mesoderm where local low expression of FGF seems to be required for noggin downregulation. When noggin activity is downregulated, but high BMP activity is preserved, N-cadherin is proteolytically degraded via a BMP and ADAM10-dependent manner with no apparent change at the transcriptional level (Kalcheim, 2015) (Bartis, Mise, Mahida, Eickelberg, & Thickett, 2014).

A consequence of this process is the formation of the soluble fragment CTF2, which is the end product of N-cadherin degradation. Next, CTF2 translocates into the nucleus and stimulates transcription of cyclinD1, an important protein for G1/S phase transition, and promotes together with CDK4/6 cell cycle progression, and eventually inducing EMT. An additional opposing player in this signaling system is overexpressed Cad6B, which leads to a disruption in NC migration and aggregation of cells adjacent to the NT (Kalcheim, 2015).

Rho GTPases are a family of well-documented contributors to EMT and cell motility as they control the dynamics of the actin cytoskeleton, gene transcription, cell polarity and cell cycle progression. Rho signaling has been shown to promote cell migration but surprisingly is also responsible for maintaining the epithelial state. It seems that blocking endogenous Rho or Rac activity will selectively remove cadherin complexes from junctions. The consequence of low cadherins protein levels is a decrease of CD44 and integrins expression, which normally are associated with migratory mesenchymal cells. This highlights the complexity of EMT regulation (Braga, Machesky, Hall, Hotchin, & Hotchin, 2013).

2.2.2 Wound healing and fibrosis

EMT is particularly important during wound healing where signaling mistakes could also lead to pathology. “EMT type II” is linked to regeneration

and fibrosis (scarring) of the tissue. Fibroblasts and inflammatory cells mediate the process of EMT. These cells secrete inflammatory molecules able to interact with proteins of the extracellular matrix (ECM) like collagens, elastin, laminins, and tenacins (Volk, Iqbal, & Bayat, 2013). Tissue wound healing progresses in three steps: the inflammatory, proliferative and maturation phases. The goal of inflammation is to limit tissue deterioration through phagocytosis. The second step leads to formation of granulation tissue, deposition of new ECM, angiogenesis and then re-epithelialization.

The most important phase of wound healing is the re-epithelialization. Keratinocytes acquire mobility and travel from the edges to the area of the wound. Fibroblasts and keratinocytes communicate with each other via double paracrine signaling loops, known as dynamic reciprocity. In healthy tissue the epithelial layer of keratinocytes goes through differentiation of progenitor cells until they reach cell death. This procell leads to the formation of the epidermis outer layer containing a mixture of lipids and cytokeratin skeleton. This mechanical barrier protects and hydrates the underlying tissue. The re-epithelialization is carried out by conversion of cells from stationary state to a migratory one. Within the wound, fibroblasts subsequently secrete paracrine factors such as keratinocyte growth factor (KGF/FGF-7), basic fibroblast growth factor (bFGF/FGF-2), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor A (VEGF-A). These signals further activate adjacent keratinocytes, which synthesize collagen and perform cross-linking in order to form an ECM, and differentiate into a myofibroblastic state to facilitate wound closure (Wojtowicz et al., 2014).

High expression of TGFβ have been detected in granulation tissue during healing of thermal burn wounds and is correlated with high expression of TGFβ receptors in fibroblasts involved in repair process. This indicates that the high levels of TGFβ can exceed the required quantity and in consequence creates hypertrophic scars (Rorison et al., 2010).

Another important player in this wound healing system is osteopontin (OPN), which is the Secreted Phosphoprotein 1. This protein is able to bind different integrin receptors and several transcription factors, which are regulated by TGFβ. Thus, OPN seems to play a central role in TGFβ-

dependent signaling and is involved in TGFβ dependent EMT (El-Tanani, Platt-Higgins, Rudland, & Campbell, 2004).

The most complete fibrosis model depicted in clinical pathology is renal interstitial fibrosis. Different factors like urinary tract obstruction, diabetes, chronic inflammation makes it a progressive and lethal disease (Border & Noble, 1997). EMT plays a key role in the progress of renal tubular fibrosis and synthesis of extracellular matrix. TGFβ upstream regulates many pathways in this pathology. Many of them include MAPK-PI3k signaling as well as Smad where TGFβ receptor kinase phosphorylates Smad 2 and 3. In consequence, Smad4 is activated and undergoes nucleus translocation for subsequent transcription regulation of TGFβ target genes. For the pathology of fibroses TGFβ/Smad3 regulation is essential since loss of Smad3 function blocks EMT and attenuates development of fibrotic sequelae (Roberts et al., 2006).

Patients with renal tubulointerstitial fibrosis show a progressive decline in renal function over time. Eventually, fibrosis leads to an end-stage renal failure. This process is also associated with ECM deposition, infiltration of inflammatory cells and fibroblasts accumulation with disappearance of tubular epithelial cells. As a result, tubular cells undergo EMT and drive this pathology with cells acquiring classical markers of this involved pathway where the transformation is again driven by TGFβ. When the factors stimulating EMT have been counteracted by BMP-7, the fibroblasts proliferation and deposition of ECM in the cortical interstitium was also hindered (Zeisberg et al., 2003). On the other hand, triggering hedgehog signaling induces TGFβ expression and has profibrogenic effects in the tissue (Syn et al., 2009). This activation is performed by binding of the ligands, such as sonic hedgehog (SHH) to membrane receptor patched 1 (PTCH1). Signal transduction by Smoothened (SMO), allows translocation of the transcription factor GLI1 to the cell nucleus. Hence, hedgehog can induce EMT driven fibrogenesis.

The involvement of EMT markers was also documented in signaling pathway leading to kidney failures (Galichon & Hertig, 2011). Experienced histopathologists have stated that among EMT markers used in immunohistochemistry, the markers associated with the highest EMT progression rate were vimentin and β-catenin. Additionally, they excluded that E-cadherin and fibroblast-specific protein (FSP1), as being not very reliable in

diagnosis based on. their observations on allografts after three months post-transplantation (Hertig et al., 2008).

Another way by which TGFβ promotes fibrosis and tissue repair is through the noncanonical focal adhesion kinase (FAK) pathway. This pathway is also known for myofibroblast differentiation. By further investigating the FAK pathway and small non-coding RNAs like e.g. mIR222HG a potential major target to treat fibrosis disease could be established. Silencing or blocking this pathway could analogously stop excessive scarring of the tissue (Sun et al., 2018).

2.2.3 EMT in Cancer

EMT associated with migration of cancer metastatic cells is referred to as “EMT Type III”. EMT modification of the cellular phenotype is clearly beneficial opposite to changes that occur in a tumor. Similarities between cancer and EMT re-epithelialization have clinical implications. Effectively, this similarity can give rise to conflict between cancer therapies and wound healing. It has been known for a long time that EMT can trigger dissociation of carcinoma cells from primary carcinomas, which subsequently migrate and disseminate to other parts of the body. It is believed that the MET process is the dangerous trigger, which terminates migration and induces cells to proliferate and seed new tumors at new locations.

There is a close connection between EMT, circulating tumor cells (CTC) and appearance of metastatic tumors. The activation of EMT often endows tumor cells with new features such as resistances to radio and chemotherapy. For this reason, it is particularly important to break this deleterious cycle present in cancer by targeting EMT. Then, after EMT, mobile cells invade the ECM and migrate along a newly formed matrix of type I collagen and fibronectin (Kalluri & Weinberg, 2009). Thereby cells can move individually or be part of a collective migration in clusters. Interestingly, the clusters are often made of mixed cellular phenotypes (epithelial-mesenchymal), which allow them to avoid anchorage-dependent cell death (anoikis) and far more likely lead to metastasis (Aceto et al., 2014) since mesenchymal cells are protecting epithelial cells from anoikis but also forming a kind of an “ark”, which can travel

through the body. In order to do so, cells cross the ECM to reach vessels and by extravasation they colonize specific niche in a distant organ. The cells surviving this migration are dormant micrometastatic tumor cells with a potential to grow into a macrometastasis. The success of growth in a new location is dependent on the MET and the degree of this process (Barriere, Fici, Gallerani, Fabbri, & Rigaud, 2015). Different degrees of epithelial-to-mesenchymal transitions have been found to occur in colon, breast and ovarian carcinoma, among others.

From an epithelial tumor, cancer cells can reach vessels leading to circulating tumor cells (CTC). Many factors induce EMT and the shedding of cancer cells as described above. Transcription factors acting on gene regulatory pathways are able to promote loss of cell-cell adhesions. As a result, there is a shift in cytoskeletal anatomy and a switch on of a signaling pathway dependent on TGFβ, NOTCH, BMP, WNT/β-catenin, receptor tyrosine kinases and hedgehog. Additionally, there is a range of micro RNAs that regulates EMT by interacting with ZEB1 and ZEB2 or EMT-associated kinase switch (Cano, Diaz-Lopez, & Moreno-Bueno, 2014). Decrease in the expression of tight junction such as ZO-1 (tjp1) and occludin and cytokeratins and overexpression of mesenchymal markers are the hallmark of EMT (Barrière, Riouallon, Renaudie, Tartary, & Rigaud, 2012). Furthermore, an abnormal cancer epigenome is also strongly involved in the control of stemness and state transitions. Epigenetic deregulation guided by a complex signaling machinery evidently needs to be investigated to understand profoundly the intricacy of those processes (Czerwinska & Kaminska, 2015).

2.3 Cellular heterogeneity

2.3.1 Epigenetic landscape and cell fate

Waddington's epigenetic landscape is a conceptual metaphor frequently used to describe how different cell types arise from the same DNA. It depicts the relationship between cell fates and gene activity during processes like development, reprograming or transdifferentiation. Recently, it also became a convenient framework for interpreting results from single-cell transcriptomics

experiments. The Waddington's landscape visualizes how, during fate transitions, cells undergo smooth, continuous progressions or discontinuous, stochastic jumps throughout transcriptional activity. Consequently, this can be described as pseudo-temporal dynamics in a quasi-energy landscape where fate decision events are often modulated by a corresponding probability (Moris, Pina, & Arias, 2016).

The degree of this association in e.g. *Caenorhabditis elegans* is extreme as the outcome of every cell division is predictable in terms of fate, identity and position of emerging cells. This high reproducibility points out the existence of an underlying protocol as a well-defined sequence of processes towards an end point of development. These programs are perfectly orchestrated functions of gene regulatory networks, which generate and maintain functional tissues by activating sequential, and largely irreversible, patterns of transcription that link genes to cellular lineages (Mathis & Nicolas, 2002). By describing the epigenetic landscape, Conrad Waddington highlighted the importance of single cells and tried to conceptualize the emergence of developmental choices as the outcome of intrinsic constraints (such as regulatory interactions), which were shaped during evolution (Nishida, 2005).

Recent technological advancements in single cell transcriptomics, together with the accompanying computational and statistical analysis tools, now offer the remarkable opportunity to unravel some of the complexity of cell fate decisions and to question some of the longstanding paradigms. The assumption is that the decisions about fate are stochastic and that many cells rolling down the Waddington landscape might choose one linage or another independently. When the decision is made, cell become restricted in its subsequent decisions by the chosen route, which consequently represents decreased cellular potential with each further step down the diagram (Lüer & Technau, 2009).

2.3.2 Population dynamics

Cells receive diverse signals to proliferate but how population growth rates and densities are controlled is still not well understood. High complexity of auto- and paracrine signaling together with specificity of microenvironment makes it difficult to predict dynamic growth of a cell population. Furthermore, a widespread feature of signaling in cell circuits is a paradoxical pleiotropy. Often the same secreted signaling molecule can evoke an opposite effects in the responding cells. It has been reported that a single secreted molecule establishes a bistable response by promoting both proliferation and death in lymphocytes. As a consequence, the population is driven to either extinction or growth to achieve a homeostatic density (Hart et al., 2014). In biology, there are many examples of stimuli that can have dramatically different outcome when the surrounding environment is changing (Coffey, 1992). By using a mathematical model for alternative ways to maintain homeostasis, it has been proven in T-cells that a single molecule is not necessary but it ensures robustness of the homeostasis against perturbations such as sudden changes in IL-2 levels. When a cell uses a single signaling pathway and makes an "error" in secreting, consuming, or responding to it, this "error" will likely affect only the proliferation and death rates in a proportional rate, which still preserve the crucial balance required for population homeostasis. When, on the other hand, the cell would use two distinct signaling pathways that independently control two opposing activities, the proportion between both rates could be disrupted in many ways because the two stimuli are uncoordinated (Youk et al., 2014).

Epithelial and mesenchymal cells that can undergo EMT and MET processes are present during cancer metastasis, as mentioned in section 2.2. These transitions are also associated with the potential to renew subpopulation of cancer stem cells (CSCs). Additionally, recent investigations have demonstrated that an E/M hybrid phenotype of a cell was recorded after EMT process, whereas it was not found in the reverse MET process (at least not in cancer cells which originate from epithelial tissue) (Grosse-Wilde et al., 2015)

2.4 Calcium as secondary messenger

Cellular heterogeneity of cell signaling is intensively studied in the context of intracellular Ca^{2+} signaling. Calcium is a ubiquitous intracellular signal responsible for controlling many cellular processes in dependence on extracellular stimuli. This versatility of the Ca^{2+} signaling mechanism is enabled by a large dynamic spectrum including properties such as amplitude, speed and spatio-temporal patterning.

Since persistent high cytosolic Ca^{2+} concentration have toxic effects, Ca^{2+} signals are often presented as brief cytoplasmic spikes lasting for tens of milliseconds or for a few seconds in dependence on the physiological context. In some cellular events, individual spikes are sufficient to activate a cellular response such as neurotransmitter release or skeletal muscle contraction. For some pathway activations, longer periods of signaling are required and spikes are repeated to generate a sequence of different frequencies, ranging from 1 to 60 seconds like in liver or pancreas cells up to 24 hours like in mitosis initiation of the cell cycle (M J Berridge, Lipp, & Bootman, 2000).

Cells often respond to changes in stimulus intensity by modulating the interspike intervals (ISI) of Ca^{2+} oscillations. In order to control such a frequency-modulated signaling system, cells have developed a sophisticated molecular system for decoding frequency-encoded Ca^{2+} signals. Two main Ca^{2+}-sensitive proteins that are involved in decoding those patterns are protein kinase C and Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII). Some of the processes known to be frequency coded are oocyte fertilization, T-cell activity, liver metabolism, smooth muscle contractility and differential gene transcription, especially during development (M J Berridge et al., 2000).

It has been report in astrocytoma cells that Ca^{2+} spikes can initiate gene expression more effectively than a steadily sustained concentration of the same average calcium concentration (Wen-hong, Llopis, Whitney, Zlokarnik, & Tsien, 1998). Moreover, a slow frequency of spiking activates the transcription factor NF-κB, whereas higher frequencies are required to switch on the NF-AT transcription factor (Dolmetsch, Xu, & Lewis, 1998). Calcium plays also an important role in orchestrating the circadian clock in the suprachiasmatic

nucleus and Ca^{2+} release from RYR-sensitive or $InsP_3R$-sensitive stores can delay or reset the cell cycle (Ding et al., 1998), (Hamada et al., 1999).

Ca^{2+} also controls cell proliferation through activation of transcription factors either in the cytoplasm (NFκB, NF-AT) or within the nucleus (cAMP response element-binding protein). The dynamics of Ca^{2+} stimulation in gene transcription of lymphocytes is similar to the one in neurons during learning. Another Ca^{2+} function reported in human endocardial cells is its ability to activate Ca^{2+}-sensitive protein phosphatase (calcineurin) to dephosphorylate NF-AT, which induces transport to nucleus (Crabtree, 1999). When calcium activation stops, kinases in the nucleus rapidly phosphorylate NF-AT, which subsequently exits the nucleus leading to termination of the transcription of NF-AT-responsive genes. Therefore prolonged period of Ca^{2+} signaling is necessary to induce proliferation, which further maintains NF-AT in its activated form. Breaking this signaling cascade at any point decreases gene transcription and cell division.

Mutants with defective store operated channels (SOCs) are not able to sustain Ca^{2+} signaling which terminates downstream gene transcription in T-cells (Luika A. Timmerman, Neil A. Clipstone, Steffan N. Ho, 1996). Similar effects have the immunosuppressants cyclosporin A and FK506, which prevent transcription by inhibiting the activity of calcineurin. Activating Ca^{2+} is also one of the impulses, which can trigger the inhibitory IκB subunit proteolysis allowing the active NF-κB subunit to access the nucleus. CREB-TF, in contrast to the mechanisms discussed above, is a nuclear Ca^{2+}-responsive transcription factor, which can be phosphorylated by CAMKII and CAMKIV. Moreover, Ca^{2+}sensitive transcriptional co-activator CREB-binding protein (CBP) can be activated by the presence of calcium in the nucleus (Chawla, Hardingham, Quinn, & Bading, 1998), (Hardingham, Chawla, Cruzalegui, & Bading, 1999). Another protein regulated by calcium is CAM inhibitory peptide, which can terminate DNA synthesis, cell-cycle progression and proliferation when translocated to the nucleus.

Overall, these examples of Ca^{2+}-sensitive transcription factors that mobilize a cascade of downstream genes emphasize the central role that Ca^{2+} plays in cell fate. Some of the induced pathways switch on DNA synthesis like in case of interleukin 2, whereas others take part in apoptosis by production of

components such as Fas and the Fas ligand. Together with controlling of NF-κB, Ca^{2+} seems to play an important role in deciding about growth and death of the cell (Jiahong Wang, Moreira, Campos, Kaetzel, & John, 1996).

2.4.1 Calcium dynamics machinery

The versatility of calcium signaling is a result of a complex interplay between activation and inactivation of extracellular and intracellular calcium channels and receptors. This complexity is evident from the pattern of calcium signals detected by stimulating cells with modest physiological concentrations of calcium-mobilizing agonists. The resulting activity can be often perceived as sequential regenerative discharges of stored calcium, an occurrence referred to as calcium oscillations (Dupont, Combettes, Bird, & Putney, 2011).

Calcium ions participate in a variety of physiological and pathological processes. One of the most important ones is the role of Ca^{2+} in cellular signal transmission. Increase in cytoplasmic Ca^{2+} triggers a plethora of cellular responses, from extremely rapid events such as neurosecretion or muscle contraction to slower and more subtle effects like differentiation, cell division or apoptosis. Fortunately, in contrast to most cellular messengers, it is a relatively simple to observe changes in cytoplasmic Ca^{2+} in living cells in real time by fluorescent microscopy. Many laboratories examine the effects of various stimulants on Ca^{2+} signaling by employing activating agonists,which produce a rapid, robust, and often sustained elevation in cytoplasmic Ca^{2+}. It has been intriguing for scientist for many years that these signals are an outcome of a coordinated release of intracellular stores and an increased Ca^{2+} influx across the plasma membrane (Putney, Poggioli, & Weiss, 1981).

The intracellular Ca^{2+} release often results from activation of the phospholipase C-derived messenger, inositol 1,4,5-trisphosphate ($InsP_3$) and release of Ca^{2+} from the endoplasmic reticulum (ER) through receptor channels (IP_3Rs or RyRs). The entry of Ca^{2+} into the cell is triggered by the activation of store-operated channels on the plasma membrane (Thevenod, Streb, Ullrich, & Schulz, 1986).

The IP_3Rs channels open in a Ca^{2+} dependent fashion inducing Ca^{2+} induced Ca^{2+} release (CICR) (Bootman, Berridge, & Lipp, 1997). If a

single channel opens, Ca^{2+} is released into the cytosol and diffuses to adjacent channels and increases their probability to be open in a concentration dependent manner. This cascade of calcium release may spread into the entire cell and lead to a global cytosolic spike of calcium (Skupin, Kettenmann, & Falcke, 2010).

Additionally, it is becoming apparent that these large sustained elevations rarely occur with physiological levels of stimulation. Rather the more common pattern of Ca^{2+} action, in both excitable and non-excitable cells, is a periodic discharge and entry of Ca^{2+} into the cytosol. In excitable cells, like in the case of heart muscles, these may be initiated by plasma membrane channel activation, the Ca^{2+} action potential with amplification by intracellular Ca^{2+} release (Agonists, Tsien, & Beant, 1986). In non-excitable cells, these spikes of Ca^{2+} arise from regenerative discharge of stored Ca^{2+} leading to Ca^{2+}oscillation (N. M. Woods, K.S. Cuthbertson, 1986). The period of oscillations often represents the strength of the stimuli but it is not the only factor that is involved in this phenomena. It has been reported in many human cell lines that even if some cells respond to a stimuli with same oscillation frequency of average interspike interval (ISI), there may still be a significant difference in the relation to standard deviation of signal ISI in a given population of cells (Skupin et al., 2010) (Thurley et al., 2014). These differences in the relationship between average ISI and standard deviation of ISI are likely to encode for an additional level of complexity of the signaling system. The presence of this linear relation has been proven to be surprisingly robust. It stays true even if we increase the single channel current by an order of magnitude. The slope of this relation characterizes individual cell types and activation pathways, and indicates the response to stimulation changes (Skupin et al., 2010). Despite the solid characterization of this relation, its physiologic function is not yet well understood.

2.4.2 Purinergic receptors and ATP ligand

Purinergic receptors are a family of plasma membrane molecules that are found in most of mammalian tissues. Some of the main functions for which these receptors are responsible include learning and memory formation, sleep,

locomotor behavior and feeding behaviors. Adenosine trisphosphate (ATP) is one of the main stimuli, which can activate P2Y and P2X subtypes of those receptors. ATP is a multifunctional molecule that acts not only intracellularly as the primary energy source for living cells but also extracellularly as a signal messenger that regulates diverse cellular events including synaptic transmission, apoptosis, nociception, ion transport, secretion, and bladder contraction (Novak, 2003), (Cooke, Wunderlich, & Christofi, 2019). ATP is an abundant molecule in the cell cytoplasm (3–5 mM) and can be released outside the cell by several mechanisms, such as exocytosis of ATP-containing vesicles transported by nucleoside transporters (Knight, Bodin, Groat, & Burnstock, 2019). Extracellular molecules of ATP act by binding to purinergic receptors on the cell-surface of the P2 class (including the 8 transmembrane P2Y receptors ($P2Y_1$, $P2Y_2$, $P2Y_4$, $P2Y_6$, $P2Y_8$, $P2Y_{11}$, $P2Y_{12}$, $P2Y_{13}$) and the ligand-gated ion-conducting P2X receptors, which include 7 described subnits ($P2X_1$–$P2X_7$) (North, 2019). Both P2Y and P2X purine receptors can mediate mitogenic responses.

3 Aims

The aim of this thesis was to understand how individual cells reacts to external signals and how they process that information. A significant part of our knowledge is based on independently acquired measurements on a population level. However, we need to keep in mind that cell-to-cell differences are always present in populations, and that the average cell state may only barely reflect the particular behavior of any individual cell. The goal of my research was to investigate this heterogeneity of cell signaling in depth and to extract generic features, which would support the development of a mechanistic understanding of this large variability in information encoding. For this purpose, we investigated a medically relevant model, the epithelial to mesenchymal transition in the breast cancer cell line HMLER, at single cell resolution. In particular, the thesis focuses on the following 4 main aims:

1. Establishing a methodology to synchronize cell cultures using well-defined stimuli and developing a pipeline for in-depth single cell characterization by capturing individual cells and performing RNAseq analysis (Section 4.4.1).

2. Establishing a robust model system for trans-differentiation characterization by investigating the stability of the epithelial and mesenchymal subpopulations of HMLER cells in normal and ATP stimulated conditions (Sections 5.1.).

3. Evaluating the effects of ATP-induced Ca^{2+} signaling on the epithelial-to-mesenchymal transition and stress related pathways. In this investigation we are analyzing the identified 10 clusters of defined HMLER subpopulations in does response experiments (Section 5.2).

4. Exploring the physiological effect of Ca^{2+} variability encoding and causality of its dynamics. My goal was to describe the relationship between external ATP stimulation, different Ca^{2+} signaling profiles and resulting gene expression states. This analysis evaluates the true potential of stimuli on

cell fate and transdifferentiation (Section 5.3.1).

By addressing these aims, we will better understand the dynamics of the epithelial niche and the underlying gene regulatory networks that maintain cell identity and, as a result, we advanced our understanding of breast cancer metastasis. These new insights into the microenvironment and paracrine regulation of cancer stem cell behavior indicate the existence of characteristic cell signaling features involved in epithelial to mesenchymal transition, however this information may also lead to future clinical applications.

4 Materials and Methods:

The first part of the methods (Section 4.4) focuses on the experimental model system and on characterization of laboratory assays and their chemistry. Section 4.5 describes the data processing pipeline and setup used during computational analysis.

4.1 Cell Culture and passaging

The human breast cancer epithelial cell line HMLER was grown in MEGM (1:1) with 25 mM HEPES (RPMI medium 1640, Gibco) supplemented with 2 mM L-glutamine, penicillin (100 U/mL, Gibco) and streptomycin (100 µg/mL, Gibco). MEGM is a mammary epithelial cell growth, serum-free medium supplemented with insulin, hydrocortisone, GA-1000, hEGF, BPE (CC-3150, Lonza). All adherent cells were grown in a humidified incubator at 37°C under 5% CO_2 condition and passaged every 3-4 days in subcultivation ratio depending on the confluence level. Cell monolayers were dissociated by TrypLE Express Enzyme (Cat. 12604013, Gibco) for 7-12 minutes at 37°C in humidified incubator. After culture media removal by centrifugation and one washing step with Dulbecco's phosphate-buffered saline 1X (Cat. 14190250, Gibco). Diluting with complete culture medium neutralized TrypLE, cells were re-suspended and seeded at the appropriate confluence depending on the experiment; all steps were conducted under sterile conditions.

4.1.1 Cell freezing and reculturing

Cells from one T75 Flasks (Nunc EasYFlask, Thermo Scientific) were grown to ~80% confluency as described above and transferred into a 15 ml falcon tube. Centrifugation at 250 g for 5 min followed to pellet the cells. The supernatant was aspirated and cells were resuspended into 1 ml of pre-cooled freezing solution (MEGM medium with 10% DMSO). Afterwards cells were transferred into a cryotube and placed directly in a freezing box (Coolcell, Biocision). After 24-48h in -80 °C, tubes were transferred in the liquid nitrogen cell storage (-170°C). For recovery of frozen cells, the frozen cells were directly

thawed and transferred to T75 Flasks with 10 ml fresh complete MEGM medium. Cells were allowed to attach for one day and then their medium was exchanged. Cell count with life/dead identification was performed using the cell counter Vi-Cell (Beckman Coulter) or C-Chip counting chambers (Incyto).

4.1.2 Oscillatory and stochastic effect of ATP simulation on cell fate

The goal of this experiment was to investigate the complexity of the relationship between the calcium signaling pathway and cell fate. In order to investigate this relationship, we used the HMLER cell line, which is a breast cancer model and carry on different stochastic and oscillatory patterns of stimulation. Cells were prepared as described in section 4.1, the ratio of epithelial to mesenchymal cells have been estimated with FACS as described in section 4.3.2. Two days before the experiment, $0.5x10^6$ cells per well have been seeded on 12-well plate. During the experiment cells have been treated with ATP using the perfusion system (Section 4.2.2). As visualized in **Table 1**, we perturbed the signaling system with 5 different patterns. After 1h of stimulation cell, medium has been exchange to 1:1 MEGM (Section 4.1) and incubated for 1h at 37°C. Finally, cell were harvested (Section 4.1), their cell count and viability measured (Section 4.1.1), and processed with the Drop-seq pipeline (Section 4.4.1.3). Digital data from sequencing were further processed as described in section 4.5.

	Exp 1	Exp 2
Control	✔	✔
Constant		✔
Oscillation	1 min	2 min, 6 min
Stochastic		6 min

Table 1. Stimulation of cells, by applying different ATP patterns. Study have been performed during 2 independed experiments (Exp1, Exp2.). Constant stimulation was done with 100 µM ATP.

4.1.3 HMLER subpopulation balance analyses

Experiment have been performed to investigate the stability of a ratio between epithelial and mesenchymal subpopulation. In which for the duration of 15 days different HMLER subpopulation have been seeded in T25 flasks and measured every 2-3 days, as described in section 4.1. Cell culture was maintained at low concentration ~$5x10^4$ – $1x10^5$ per flask. During each passage 10-15% of cells were labeled (Section 4.3.2.1) and analyzed using FACS (Section 4.3.2).

4.2 Perfusion system

In order to apply and control temporal effects of a range of well-defined stimuli on cell cultures, I have established an in-house perfusion system. The system uses a programmable perfusion system (PPS, Scientifica), which consist of ten pinch valves and a high-performance peristaltic pump. Nylon flexible tubing connects the device to different cellular media from one side and to the culture plate with cells from the other side. Inside the corresponding well plate, a syringe delivers medium from one side of the well, while its aspiration happens on the other side to maintain the liquid level at ~5 µm. Cells with perfusion medium were located in an incubating chamber on the stage of an Eclipse Ti-E inverted microscopes (Nikon Instruments) equipped for live cell imaging. Temperature conditions within the chamber were maintain at 37°C and pressurized with a mixture of 95% air and 5% CO_2. Temperature of tubes entering the chamber from the peristaltic pump have been maintained at 37°C by longer tubs submerged in water batch within the chamber.

4.2.1 Perfusion software

I have developed a computer-controlled solenoid valve to switch rapidly between medium containing stimulating factors and regular medium flowing over the cells in the chamber. The computational interface allows for modification of the medium flow rates. With this setup, I was able to define the timing of a spike, ISIs and its duration together with the total number of cycles per run. If needed, I was also able to generate and induce a well-characterized

stochastic spiking dynamics. Software and user interface have been developed using Matlab 2016 (MathWorks).

4.2.2 Experimental setups

Cells ($0.5x10^6$) have been re-plated in each well of adherent Nunclon Delta surface treatment 12-well plate (Cat. 140675, Thermo Fisher) 24h prior to the experiment. Medium was left inside the incubating chamber one hour prior to the experiment in order to equilibrate its temperature. After the software settings have been set, cells were placed on the stage of the Eclipse Ti-E inverted microscope, the suction was started and the top coverlid connected with tubing was placed, before starting the device. For most of the runs, a flow rate of 2 ml/min has been used to allow the exchange of the total stagnating medium volume in the well plate within ~4 sec (4 cm^2 of well surface). While testing the flow with colorized solutions, I observed that keeping the liquid level at ~5 µm height allowed us to minimize turbulences of the medium within the well. HBS (Hepes buffered saline) medium was prepared with 137mM NaCl, 4.9 KCl, 1.5 CaCl, 1.2 $MgSO_4$, 1.2 Na_2HPO_4, 15 mM D-glucose, 20 mM HEPES with pH of 7.4. Excitation medium additionally contained 20-100 µM ATP or 1-100 µM histamine.

4.3 Single cell imaging

4.3.1 Life cell microscopy

In order to evaluate cell shape and motility of the epithelial and mesenchymal subpopulations in the HMLER cell line, the Eclipse Ti-E inverted microscope (Nikon Instruments) was used. Besides the phonotypical morphology differences, dynamic measurements of the cytosolic calcium concentration have been implemented. To investigate the calcium dynamics, one hour prior to imaging (Subsection 4.1), cells have been incubated with a fluorescence dye, such as Fluo-4 -AM (Ex/Em of Ca^{2+}–bound form: 494/506 nm; Cat. F10471) or Fura-2 (Cat. F1221). Fura-2 as a ratiometric dye is excited at 340 nm and 380 nm, and the ratio of the emissions at those wavelengths is directly related to the amount of intracellular calcium. Image acquisition and

automatic microscope stage control were done using the OptoMorph version of MetaMorph software.

4.3.2 FACS analysis

Investigation of cell surface protein levels and cell sorting according to their presence have been done using a LSRFortessa and a FACSAria III (BD), respectively. The devices have been calibrated each time before the use by performing standarised protocol for “Cytometer Setup And Tracking” (CS&T) using research beads (BD) and drop delay using Accudrop beads (BD). Prior to the experiment, cells were usually labeled with florescent antibody (Section 4.3.2.1), washed with PBS and re-suspended in PBS with 1-2% FBS. Before being loaded into the flow cytometer, cells were filtered using a 40 µm Nylon strainer (Corning) and kept at 4°C. Data analyses after each experiment has been performed using FlowJo software version 10.5.3 (FlowJo LLC).

4.3.2.1 Antibody preparation and cell labeling

Antibodies “Anti-CD24” and “Anti-CD44” (BD Pharmingen) have been used in order to investigate surface proteins associated with epithelial and mesenchymal subpopulations of the HMLER cell line. Those molecules have been fluorescently labeled with 405(Ex 400, Em 420) and 488(Ex 493, Em 518) DyLight fluorescent dyes (Dyomics). Linking reaction have been performed by combining 100 µl of AB (0.5 g/L), 8 µl of Borate Buffer (0.67 M) and 70 µl of DyLight NHS Esters in DMF (10 mg/mL). After pipetting, the reaction was incubated in dark at room temperature for 60 min. Labeled AB were purified using Pro-Spin column (Thermo Scientific) and could be safely stored in 4°C in a dark container. For most experiments, a CD24:DL488-Green, CD44:DL405-Blue antibody combination was used.

After trypsinization and washing steps (Section 4.1), cells were incubated with antibody (pre-diluted 1:50 in PBS per ~10^5 cells). Hybridization took place at 4°C for around 30 min. Cells were subsequently washed, re-suspended in PBS/medium and kept on ice until measurement.

4.4 Single cell transcriptomics experiments

To investigate cell states and cellular responses to stimuli, several single cell methods have been implemented. All approaches focus to measure and quantify information encoded in cellular mRNA by different manners.

4.4.1 Drop-seq

By using single-cell transcriptomics detection method like Drop-seq I was able to characterize cell identity and function. Drop-seq based strategies allow for rapid mRNA profiling of thousands individual cells while simultaneously remembering which cell the sequences have originated from. The microfluidics based method was first published by McCarroll lab at the Harvard Medical School (Macosko et al., 2015) and subsequently established at the LCSB. In brief, Drop-Seq allows to isolate individual cells into oil droplets together with beads having a unique barcode and polyA-tails to capture mRNAs. Hence, cells are loaded into droplets by a microfluidics device, are lysed and mRNAs are captured by the beads. Subsequent paired-end sequencing identifies mRNAs and corresponding barcodes.

4.4.1.1 Chip fabrication

The core of the Drop-Seq methods is the microfluidics chip allowing for the separation of individual cells into droplets together with barcoded beads. For the generation of the microfluidics chip, I first had to produce a master mold which can subsequently be used for the generation of the actual PDMS based chip used in the experiments.

4.4.1.1.1 SU-8 processing on silicon wafer

To create the Drop-Seq master mold, I was using 100 mm diameter, SSP polished, 500-650 µm thick, mechanical grade crystalline silicon slices based on SU–8 2050 substrate. It is a high contrast, epoxy based photoresist, and was used to get a thick chemically and thermally stable layer of ~88 µm. Before processing, wafers have been cleaned using plasma cleaning (Harrick Plasma) for 5 min followed by Piranha solution for 5 min and subsequently

gently dried with compressed air. Optionally, cycles of 5 min IP and 2 min water cleaning were performed in Spin Coater (WS-650MZ-23NPPB, Laurell). The prepared wafers were baked for 20 min on a 200°C hot plate and placed inside the spin coater. From this step on, all SU-8 processing was done in 550 nm wavelength light. After ensuring that the wafer is in the center, vacuum was turned on. Using a 10 ml pipet with wide-end tips, 5 ml of thick SU-8 resin was slowly pipet into the center of the wafer. In order to get the desired thickness of the layer, the spin coater was set first to run for 10 sec at 500 rpm followed by 40 sec on 1450 rpm. Next, the wafer was removed from the spinner using dedicated SU-8 tweezers, and allocated on hotplates covered with aluminum with a temperature increase from 65°C to 75°C for 12 min of “pre-bake”. When the temperature droped to RT and no bubbles built on the surface, I could proceed to the photolithography step (Section 4.4.1.1.2).

4.4.1.1.2 Photolithography

To manage more efficiently the surface of the silicon wafer, the original design of the microfluidics chip was modified using the AutoCAD software what allowed us to acquire 18 chips from one PDMS mold. The photomask was then ordered with the following specifications: 5"x5"x0.090" (dimensions in inches) ARC SL with a CD of 40 µm +/- 0.50 µm from Micro Lithography Services Limited (**Figure 3**). Photomask was then used to generate features on the surfaces of “pre-baked” wafers (Section 4.4.1.1.1). This was enabled by an UV-LED mask aligner (UV-KUB 2). In this device, the mask was placed on top of the wafer with 525/2 mm gap setting, and UV was then set for 15 sec of continuous illumination. In this process, strong acids are formed in the exposed areas, which initializes the activation of these regions. For stress relaxation and cross-link the epoxy areas a “post-bake” time of 8 min in 65°C to 75°C turned out to be optimal. During the first 60 sec, the image of the mask in the SU-8 photoresist coating should be visible. The next step focuses on removal of not activated SU-8 resin. For this purpose, I deep the wafer in SU-8 developer using metal tweezers and gently rotate the glass container. Best results have been observed with 3 cycles of 4-1-1 min washing. After each washing step, gentle drying of the developer from the wafer features was performed with compressed air. In order to stop and wash off the remaining

residue of the developer, an additional 20 sec wash with IP and dry pressurized air was performed. To ensure that SU-8 properties do not change when exposed to thermal processing, a final “hard bake” in 150°C was done for 10 min. Final strengthening of the master mold features was ensured by coating its surface with a single layer of organofunctional alkoxysilane molecules. The silanization process was performed by puting ~2 drops of chlorotrimethylsilane on aluminium foil and enclosing it with the wafer in vacuume chamber for 30 min. This procedure was followed by 10 min incubation on a 150°C hotplate to cure and evaporate excessive silane.

4.1.1.1.3 PDMS molding process

Once the quality of master mold and its features was validated under the microscope, I could proceed to fabricate PDMS molds. The desired thickness was achieved by mixing curing agent/PDMS in a 1:10 ratio. A total volume of 30 ml was enough to get the desired mold thickness of 7 mm. The solution was then mixed for 2 min and defoamed for 10 min in vacuum. Next, the liquid was poured into a 150x15 mm aluminum covered petri dish and place in vacuum for another 30 min. Vacuum pushed remaining bubbles to the surface of the plate where they could be gently poped with compressed air. Curing of PDMS was carried out in a laboratory oven for a duration of 2 h at 60°C and followed by cooling down in RT. After PDMS hardening, 3 strips (each of them containing 6 chips) were cut out of the block and covered with adhesive tape from the side.

4.1.1.1.4 PDMS bonding and hydrophobic coating

After acquiring a PDMS mold (4.4.1.1.3), holes were punched in each inlet and outlet marked on the chip by using 1.2 mm PDMS Microfluidic Chip Biopsy Puncher Kit.

The PDMS layer was then cleaned together with a plain microscope slide (Corning) using IP and gently wiped with foam-cotton swabs. Next they were rinsed with Milli-Q water and dried with compressed air. Both components were then placed inside a plasma etcher (Harrick Plasma) with their bonding surfaces facing up. The vacuum pump was turned on, and when the pressure inside the chamber reached 0.17-0.35 Torr, I also switched the radiofrequency

power on “HI” (29.9 W). After 15 sec of plasma treatment RF and pump were switched off, followed by venting to the chamber with vent toggle switch. When the pressure inside and outside of chamber was equilibrated, both surfaces were taken out and gently aligned with their activated sides. To enhance the bond, newly formed chips were placed in a 65°C oven for 20 min. The strength of the bond was tested by trying to separate both components. Good quality chips were then injected with 1.8 % of FDTS in FC-40 oil (Fluorinert) solution for 3 h to ensure hydrophobic coating of the microfluidics channels inside the chip. The oil inside the chip was then blown out with compressed air and baked in a 65°C oven for 20 min.

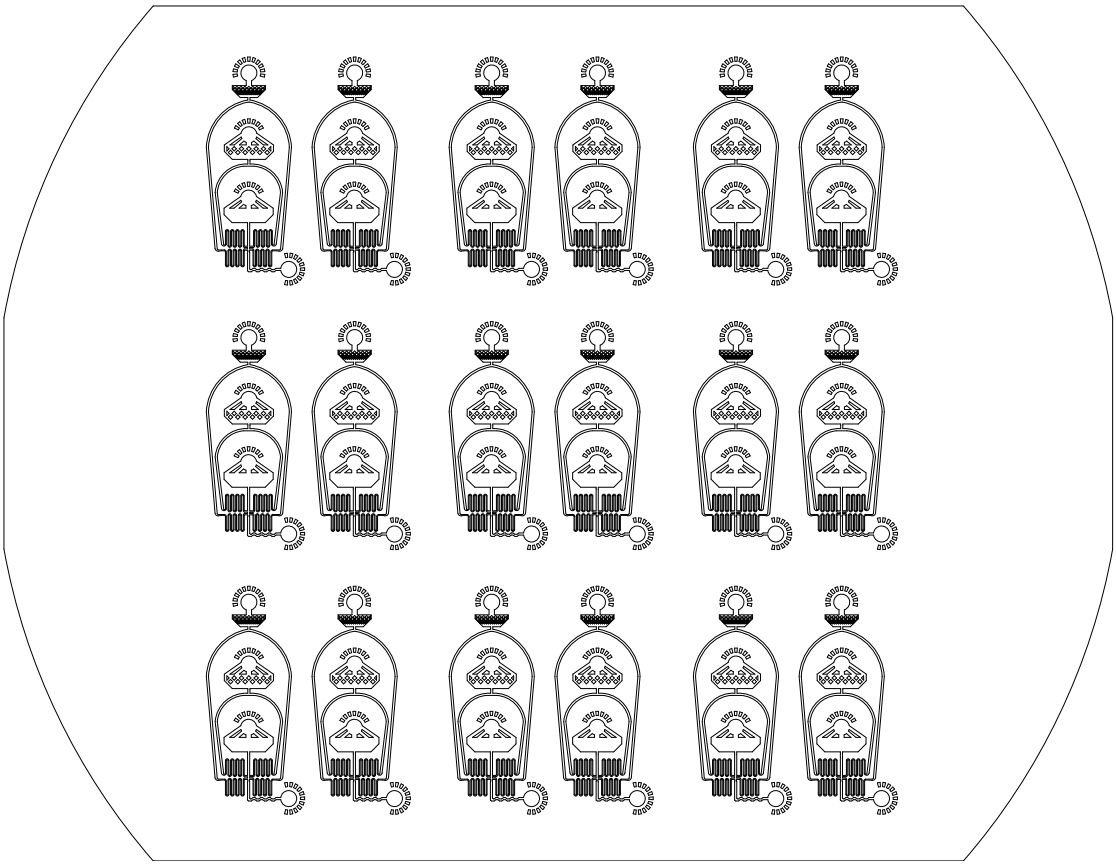


Figure 3. AutoCAD design of the modified Drop-Seq microfluidics chip used as a photomask.

4.4.1.2 Drop-seq experimental setup

Drop-Seq is one of the most popular setups of the emerging scRNA-seq methodologies. The strategy of generating droplets in microfluidic devices

gives unprecedented access to the transcriptomes of thousands of single cells and enables researchers to understand complex interactions and track identities of individual cells. As mentioned above, the core of this method involves encapsulating single cells with single barcoded beads in nanoliter-sized droplets. Good bead quality is one of the most important factors in each experiment since it ensures high amounts of captured mRNA. Beads were generated by split-pool oligo synthesis approach (Chemgenes), which resulted in large numbers of unique barcodes. The beads arrived as dry resin and were washed with 30 ml EtOH, and twice with 30 ml TE-TW buffer. Next, they were re-suspended in 20 ml TE-TW and passed through a 100 µm strainer. Finally they were counted with a Neubauer counting chamber (C-chip) and stored at 4°C for up to 6 months.

The droplet generation set-up consists of 2 syringe pumps (Legato) next to an inverted microscope. Syringe of 20 ml located on the first pump supply droplet generating oil to the device at a flow rate of 15 ml/h. Syringes of 3 ml with cells and beads are located on the second pump and run at a flow rate of 4 ml/h. Nylon flexible tubing of 0.5 ID connecting all syringes to the inlets of the microfluidics device (**Figure 4**). Outlets from the setup had a tube leading to a 50 ml falcon collecting encapsulated beads. Beads suspended in lysis buffer were kept at a concentration of 120-160 beads/µl, while cells suspended in PBS-BSA were at 100-144 cells/µl. During experiments, a magnetic stirrer was placed right next to syringe containing beads in order to keep the beads in suspension. Concentrations of 120 beads/µl have been used for most of the experiments, which generated around 5% beads doublets.

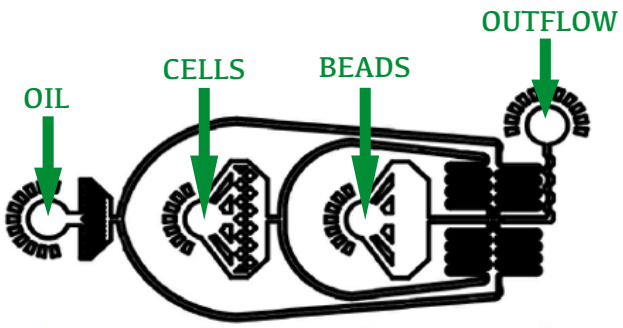
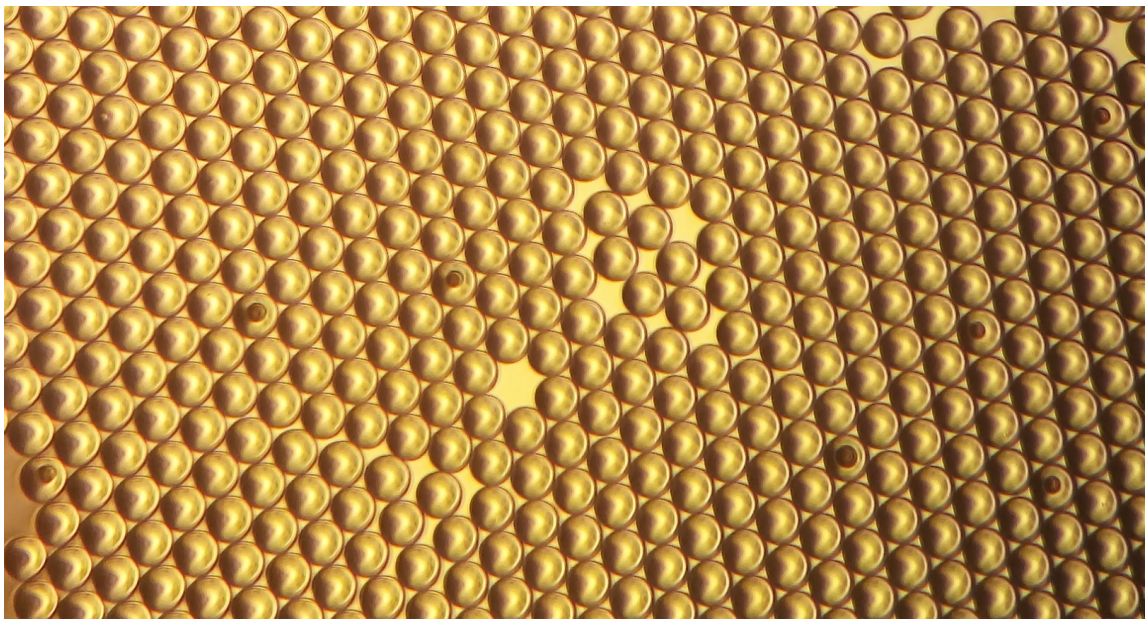


Figure 4. Single drop-seq chip-tubs connections order, or droplets quality control



Picture 1. Uniform size droplets (around 125 μm) generated through drop-seq chip. Each droplet contains almost exactly 1 nl of buffer mixture.

4.4.1.3 Drop-seq run

Trypsinised and PBS-BSA re-suspended cells (4.1) were prepared and loaded into the syringe just before the run. Connecting tubes were inserted into the device in the following order: cells, beads, oil. A run was started with the oil pump and then beads and cells pumps followed. The stream usually stabilizes after 30 sec, and if the droplet size and uniformity (**Picture 1**) was in the correct range, the outflow was collected for approximately 1h for a typical experiment. During that time, it was crucial to monitor the stream behavior. Once I stop the run, the transparent bottom oil layer was discarded. The remaining "milky" phase contained droplets with beads and lysed cells. To release the beads containing the cellular RNA from droplets, I added 30 ml of RT 6X SSC buffer and 1ml of perfluorooctanol. Droplets were then broken by 3-4 forceful vertical shakes, and centrifugation for 1 min at 1000g. The top volume of ~29 ml was carefully discarded (without kicking out the beads) and another wash with 30 ml of 6X SSC was performed. Next, I removed the supernatant until 1 ml above the oil layer, and subsequently I used a 1 ml pipet to gently re-suspend the beads and transfer this volume to a fresh low-binding 1.5 ml tube. I centrifuged the sample and performed two 6X SSC washes, followed by one wash with Maxima H Minus Reverse Transcriptase buffer.

4.4.1.4 Single cell library preparation

Tubes with beads (Section 4.4.1.3) were centrifuged and as much supernatant as possible was discarded. The pellet with a maximum of 90,000 beads was re-suspended in 200 µl of Reverse Transcriptase mix. The reaction was incubated for 30 min with rotation at RT, followed by 90 min incubation in a 42°C oven. Reaction was stopped by TE-SDS wash, followed by two washing steps in TE-TW. When proceeding to Exoluclease1 treatment, I washed the beads one more time in 1 ml of 10 mM Tris pH 8.0. The pellet was re-suspended in 200 µl exonuclease mix and incubated in a 37°C oven for 45 min with rotation. Reaction was stopped using one TE-SDS wash, followed by two TE-TW washes. For PCR reaction, two additional washes with 1 ml ddH_2O were performed. Next beads were counted using C-Chip counting chambers, and for each 50 µl PCR reaction volume I used a maximum of 10,000 beads. Using standard cells and beads concentrations during experiments allowed us to generate ~500 STAMPs (Single-cell Transcriptomes Attached to MicroParticles) in each PCR reaction. After adding 50 µl of PCR mix to the beads, the volume was well mixed and placed into a thermocycler with the following settings (**Table 2**).

Temperature (°C)	Time (min)	Cycles
95	3	x1
98	20 sec	x4
65	45 sec	
72	3	
98	20 sec	X9
67	45 sec	
72	3	
72	5	x1
4	∞	

Table 2. PCR setting for STAMP cDNA amplification.

Products of the PCR reactions (50 µl) were purified using AMPure XP beads with 30 µl resin and a 0.6 beads to sample ratio. Purification was performed according to the manufacturers instructions. The final product was eluted in 10 µl ddH_2O. The quality and quantity of the PCR product was evaluated by using BioAnalyzer High Sensitivity Chips according to the

manufacturer's instructions. As a sample input 1 µl was used and an acceptable readout was a smooth distribution peak of 1300-2000 bp. When 13 cycles were set during the PCR reaction, I was able to get on average 2000-5000 pg/µl for each of the 5000 beads.

When the satisfactory quality of the library was confirmed, I could perform tagmentation reactions preparing the samples for sequencing. For each sample, 600 pg of purified cDNA was combined with ddH_20 in a total volume of 5 µl. Next, I added to each tube 10 µl of Nextra TD buffer (Illumina) and 5 µl of Amplicon Tagment enzyme. The sample was then centrifuged and incubated for 5 min in a 55°C heat block. Further, I added 5 µl of Neutralization Buffer and centrifuged the sample again. Finally I added the Nextera PCR master mix and run the sample on a thermocycler with the following program (**Table 3**).

Temperature (°C)	Time (min)	Cycles
95	30 sec	x1
95	10 sec	} X12
55	30 sec	
72	30 sec	
72	5	x1
4	∞	

Table 3. PCR program for amplification of the tagmented library.

The products of the PCR reactions were purified twice using AMPure XP beads with a beads to sample ratio of 0.6. Purification was performed according to manufacturer's instructions. The final product was eluted in 10 µl ddH_2O. The quality and quantity of the PCR product was evaluated by using the BioAnalyzer High Sensitivity Chip according to the manufactures instructions. As a sample input 1 µl was used, acceptable readout was a smooth distribution peak of 400-700 bp. Additionally, the Qubit Fluorometric Quantification kit was used for more accurate DNA quantity measurement. Knowing the correct weight and length distribution, I was able to better estimate volumes needed for correct clustering on Illumina SOLiD sequencing chips. Samples were then diluted and denatured with NaOH to a final concentration of ~0.05 N. Samples were finally sequenced using a 500/550 High Output Kit v2 (75 cycles) on a NextSeq 500 sequencer. For most libraries

sequencing following settings were used: Read1- 20 bp, read2- 50 bp, Read1Index- 8 bp and a Custom Read 1 primer (Illumina) (Section 4.1.1.5).

4.4.1.5 Buffers and reagents

- Reverse Transcriptase Mix (for 200 µl)
    - 75 µl H_20
    - 40 µl Maxima 5x RT Buffer
    - 40 µl 20 % Ficoll PM-400
    - 20 µl 10 mM dNTPs (Clontech)
    - 5 µl RNase Inhibitor (Lucigen)
    - 10 µl 50 µM Template Switch Oligo
    - 10 µl Maxima H- RTase

- Exonuclease mix (for 200 µl)
    - 10 µl 10x Exo I buffer
    - 170 µl ddH_20
    - 10 µl Exo I

- PCR mix (per 50 µl)
    - 24.6 µl ddH_20
    - 0.4 µl 100 µM SMART PCR primer
    - 25 µl 2x Kapa HiFi Hotstart Readymix
- PBS-BSA
    - 1X PBS
    - 0.01% UltraPure BSA)

- Lyses Buffer (1 ml)
    - 500 µl ddH_20
    - 300 µl 20% Ficoll PM-400 (GE)
    - 10 µl 20% Sarkosyl (Sigma)
    - 40 µl 0.5 M EDTA (Life Technologies)
    - 100 µl 2 M Tris pH 7.5 (Sigma)
    - 50 µl 1M DTT

- Nextera PCR master mix
    - 15 µl of Nextera PCR mix
    - 8 µl ddH_2O
    - 1 µl of 10 µM New-P5-SMART PCR hybrid oligo
    - 1 µl of 10 µM NexteraN7xx oligo (added accordingly to sample)

- Droplet generation oil (Bio-Rad)

- Perfluorooctanol (Sigma)

- 6X SSC (prepare 20X SSC)
    - 3 M sodium chloride
    - 300 mM trisodium citrate)

- TE-SDS
    - 10 mM Tris pH 8.0 + 1 mM EDTA
    - 0.5% SDS

- TE-TW solution
    - 10 mM Tris pH 8.0 + 1 mM EDTA
    - 0.001% Tween-20

- 10 m Tris pH 8.0

Primer name	Sequence
Barcoded Bead SeqB	5'–Bead–Linker-TTTTTTTAAGCAGTGGTATCAACGCAG AGTACJJJJJJJJJJJJNNNNNNNNTTTTTTTTTTTTTTTTTTT TTTTTTTTTT-3'
TSO	AAGCAGTGGTATCAACGCAGAGTGAATrGrGrG
SMART PCR primer	AAGCAGTGGTATCAACGCAGAGT
New-P5-SMART PCR hybrid oligo	AATGATACGGCGACCACCGAGATCTACACGCCTGTCCGCG GAAGCAGTGGTATCAACGCAGAGT*A*C
Custom Read 1 primer	GCCTGTCCGCGGAAGCAGTGGTATCAACGCAGAGTAC
NFATc1	5'-GCCGCAGCACCCCTACCAGT-3' 3'-GAGACGGACATCGGGAGGAAGAA-5'
NFATc2	5'-GAAACTCGGCTCCAGAATCC-3' 5'-AAAAACAACATGAGGGCAACCA-3'
NFATc3	3'-ACCAGCCCGGGAGACTTCAATAGA-5' 5'-CCAGTATTGATTGTGCAGGTATTT-3'
NFATc4	3'-TCAGAAGACACGGCGGACTTCC-5' 5'-CCACTGACCCTACAGATGTTCA-3'
NFAT5	3'-GCTTTCTCAGCTTACCACGG-5' 5'-CAACGACTCTGGACGAGTGA-3'
CD49F (ITGA6)	5'-ACCAACACAGGTTCTCAAGG-3' 3'-CCTGATGTTGCTGTTGGT-5'
CDH1	5'-TGCCCAGAAAATGAAAA-3' 3'-GAACGCATTGCCACATACAC-5'
PCOLCE	5'- CTCCTCCGAAGGGAATGAAC -3' 3'-CTGAGCCTAAAGTCAAGCTG-5'
ERK2	5'-GCGCGGGCCCGGAGATGG TC-3' 3'-AAAAATCTTACTGCGCTTCA-5'
ACTB	5'-GGATGCAGAAGGAGATCACTG-3' 3'-CAAGTACTCCGTGTGGATCG-5'

Table 4. List of primers designed and ordered for single cell experiments; where N=random oligo, J=split-pool oligo.

4.4.2 Chromium (10x Genomics)

Some experiments have been performed using "Chromium Controller" technology, which is a single cell device commercialized by 10x Genomics. This technology is similar to Drop-seq, but based on the In-Drop method (Klein et al., 2015), where hydrogel microspheres are shielding revers transition reaction from the environment within generated droplets with GEMs (Gel Bead-In EMulsions).

4.4.2.1 Dose-response effect of ATP on HMLER cell fate

One of the experiments performed with this method has been used to investigate ATP dose response on fate transition of the HMLER cell population. Cells were prepared as described in section 4.1, the ratio of epithelial to mesenchymal cells has been estimated again by FACS as described in section 4.3.2. Two days before the experiment, $0.5x10^6$ cell per well have been seeded on 12-well plate. For the experiment 1 ml medium has been exchanged with medium containing 20 µM, 50 µM, 100 µM of ATP and a control with no ATP. After one hour of incubation at 37°C the medium was exchange to one without ATP for another hour. After that time, cells were trypsinized and cell count and viability was measured. When ensuring that the viability is above 90% and cell concentration was adjusted to 700 cells/µl, cells were loaded using the "chromium single cell reagent kit" and libraries were generated according to the manufacturer's protocol. Libraries were subsequently sequenced with NextSeq 500/550 High Output Kit v2 (150 cycles) and the digital data results were then further processed as described in section 4.5.

4.4.3 Targeted qPCR using Juno/C1 Fluidigm

In order to investigate presence of alternative splicing variants in the HMLER cell line subpopulations, custom primers for a set of genes were designed (including NFATc1, NFATc2, NFATc3, NFATc4). Cells were prepared as described in section 4.1. Targeted single cell libraries have been created using Juno device according to the manufacturer's protocol. Libraries were then transferred on another chip and processed on the C1 device with custom primers (**Table 4**). After the run, the device generated a digital matrix of qPCR Ct values for each gene in each cell. Analyses have been performed by the "Fluidimg Real-Time PCR Analyses" and R packages.

4.5 Processing of sequenced data

Single cell libraries were sequenced using NextSeq 500 (Illumina), and BCL files were transferred on our local HPC clusters (Gaia, Iris). Using Illumine

“BclToFastq” script I combined per-cycle BCL files and separated multiplexed samples. Drop-seq and 10x libraries produced paired-end reads. Read 1 contains in both cases the cell barcode and the molecular barcode as unique molecular identifier (UMI), while Read 2 is aligned to the reference genome (hg38). The goal of the following processing steps is to convert sequencing reads to a digital gene expression matrix (DGE) containing mRNA counts for each barcode. Next, I used the Picard script “FastqToSam” in order to acquire queryname-sorted BAM files. Further, I align reads into BAM files, which are suitable to produce the DGE results. The creation of the final BAM file included a set of operations such as: tagging barcodes, trimming primers, removal of PolyA fragments, correcting synthesis errors, add gene/exon annotation and mapping sequences onto the desired library. For some experiments 1 or 2 mismatches during aligning were allowed. For processing of 10X FASQ files into DGE, a standardized automated script was used, which was provided by the Chromium device vendor.

4.6 Single cell transcription analyses

4.6.1 Data normalization

In order to perform meaningful analyses, datasets had to be normalized. The first step was to estimate “true” number of captured cells. A rough estimation of captured cells was known from the number of STAMPs of GEMs used for processing (Section 4.4.1.4). For further confirmation of “true” captured barcodes representing cells, I estimated inflection points from cumulative distribution plot of the DGE. Normalization of single-cell RNA sequencing data was necessary to eliminate cell-specific biases prior to downstream analyses. For most of the data, I applied the global-scaling normalization methods. This method calculates cell-specific “scaling factor” which is a transcript count of a single cell divided by mean of total transcripts count divided by all cells. Next I divided all gene counts in a single cell by this factor leading to

$$\tilde{X}_{ij} = \frac{X_{ij}}{\hat{S}_j}$$

where X_{ij} represents the read count of gene i in cell j. $\hat{S}_j$ is the estimated scaling factor, while $\tilde{X}_{ij}$ is a normalized expression (Vallejos, Risso, Scialdone, Dudoit, & Marioni, 2017).

A general challenge during data processing was the so-called "zero inflation" in DGE. For this reason we typically discarded genes with less than 15 transcripts in the dataset.

4.6.2 Correlation analyses

Correlation is a bivariate analysis that estimates the strength of association between two elements and the direction of this relationship. In terms of the strength of relationship, the value of the correlation coefficient varies from +1 to -1. In order to investigate gene-gene and cell-gene relationships within a cell line subpopulations, correlation analyses of scRNA dataset was implemented. All performed analyses were done using Python and R packages, which include Pearson or Spearman correlation methods.

4.6.3 Differential Gene Expression analyses

A common method to estimate a difference between populations of cells from scRNA-seq data, is differential gene expression. For DEG selection, one of the most conservative method was used: One-way ANOVA, t-test, Kruskal–Wallis or mutual information. Genes from Monocle "differentialGeneTest" above 0.05 or 0.001 Q-val (for better control of "false discovery rate" script applies multiple test correction by Benjamini-Hochberg method) probabilities were selected for further steps. For in depth analyses of specific genes (**Figures 13, 14, 18, 19**) Q-values were not higher than 10^{-17}.

These lists of genes were next used to define cluster identities in PCA and t-SNE plots (Section 4.6.4), as well as fed into the online "Go enrichment analyses" (PANTHER website) tool. Enrichment analyses provided us with common functions of the resulted gene sets. The categories used for the evaluation were: molecular functions, biological processes and cellular

components. The lists of up-regulated and down-regulated DEG were analyzed separately. Computing the genes and plotting results were done using Monocle package (Trapnell & Cacchiarelli, 2017) and customized Python scripts.

4.6.4 Dimensionality reduction with PCA and t-SNE

Single-cell RNA-sequencing visualization has a great potential to identify cell states, discover cell types, trace trans-differentiation or reconstruct spatial organization of cells. However, interpretation of the structure in single-cell sequencing data still remains a challenge. For that reason, I perform correction for some technical biases, such as mitochondrial genes omission in some dimensionality reduction calculations.

Principal component analysis (PCA) is a statistical procedure that uses an orthogonal transformation to convert a set of observations of possibly correlated variables. This linear dimensionality reduction method was used to identify subpopulations in DGE by summarizing data into 2 or 3 dimensions enabling visual clusters identification.

Another method used to visualize data was t-Distributed Stochastic Neighbor Embedding (t-SNE). It is a non-linear dimensionality reduction method, which is well suited for the visualization of high-dimensional datasets. t-SNE keeps local distances and is increasing larger dissimilarities which allows for clearer visual representation of cell similarities and cell types. I perform t-SNE analyses using the sklearn.manifold.TSNE (Python) or the Rtsne package (R).

5 Results

Following the specific aims (Section 3), we first established the HMLER cell line as a robust model for trans-differentiation by EMT (Section 5.1) and subsequently used this model to investigate the effect of ATP-induced Ca^{2+} signaling on EMT (Section 5.2) and how signal variability is affecting cell fate (Section 5.3). The results will be discussed in detail in Chapter 6.

5.1 Characterization of the HMLER-based EMT model

Up to 90% of cancer cases related to its appetence and mortality can be connected with metastasis (Section 2.1). This shifted the focus of scientists towards the tumor microenvironment, its related signaling machinery, and the process of neoplastic progression in the direction of metastasis. As a useful model system, the breast cancer cell line HMLER has been used to understand some general properties of the role of the underlying microenvironment due to the coexistence of epithelial and mesenchymal subfractions within the parental population (Grosse-Wilde et al., 2015).

5.1.1 HMLER subpopulation balance investigation

In order to investigate first the stability of the epithelial and mesenchymal subpopulations of the HMLER cell line (Section 2.1.1), a 15 day cell culture experiment protocol was carried out (Section 4.1.3). For these experiments, each subpopulation was sorted for purity using FACS as described in Section 4.3.2 for which cells have been labeled with fluorescent antibody (Section 4.3.2.1).

It has been reported previously that the HMLER cell subpopulation $CD44^{High}$ corresponding to the mesenchymal (M) subfraction and the $CD44^{Low}$ corresponding to the epithelial (E) subfraction grow at similar rates and are able to recover the missing population after subfraction separation by FACS sorting (Morel et al., 2008). Furthermore, it also has been documented that in epithelial origin cell lines such as HMLER, the CSC-enriched cells are more associated with the mesenchymal subpopulation (Grosse-Wilde et al., 2015).

To validate this repopulation dynamics towards the parental population, first experiments were performed to evaluate the stability of the ratio between E and M subpopulations at low cell density (**Figure 5**). In red we can see the population ratio fluctuating around 50% (with ~17% deviation). When experiments were started with a pure $CD44^{Low}$ (epithelial) population (blue), the other $CD44^{High}$ (mesenchymal) population was able to recover. Similar conclusions were observed when staring from pure $CD44^{High}$ (mesenchymal) population (orange, green). The only population difference we observed was that the pure M population was dominating in high cell density conditions and exhibited very low growth rates at low cell densities.

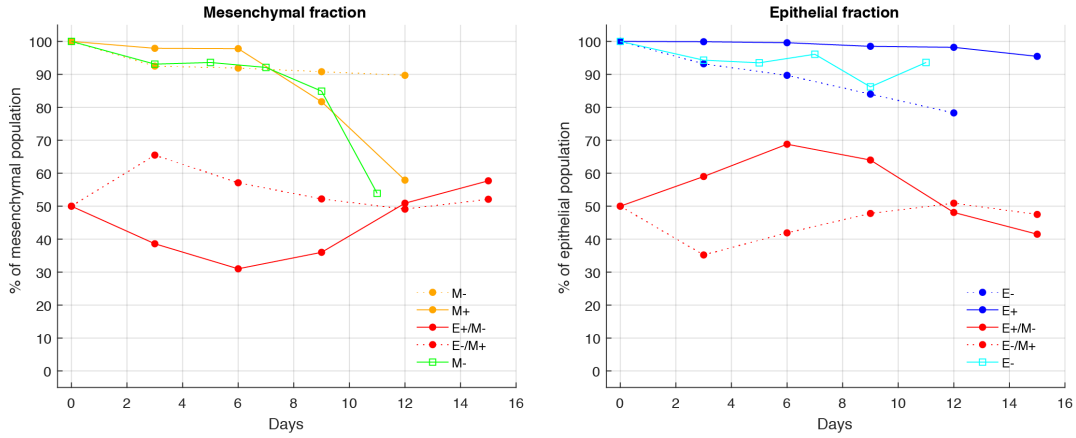


Figure 5. Diagram presents the balance between mesenchymal (M) and epithelial (E) fractions of the HMLER cells line. Identification of the subpopulations has been done using anti-CD44 straining. Orange and green samples are different passages of pure mesenchymal subpopulation sorted by FACS. Light and dark blue represent different passages of pure epithelial subpopulation sorted by FACS. Red samples are parental HMLER populations, which at day 0 were an equal mixture of two subpopulations ($1.2x10^4$ cells of each). Symbol (+) indicates different genetic background (cells transformed with YFP and mCheery reporters). Last measurements with low cell counts were excluded.

5.1.2 eATP effect on Epithelial and mesenchymal subpopulation dynamics

Extracellular adenosine triphosphate (eATP), which is the main intracellular energy currency, often accumulates within the tumor microenvironment. It takes part in cancer cell metabolism as well as in antitumor immunity. The well-known role of eATP as a growth modulator and a pro-inflammatory factor makes eATP and other purines important players in signaling between host and tumor. Recently it has been reported that eATP stimulate human cancer invasion in *in vitro* experiments where an increase of

migration and invasive ability was observed in human carcinoma cell lines (prostate, colon, breast, melanoma and lung) (Feng Wei-gang, 2017). Pro-invasive effects of eATP were also observed in nude mice experiments. eATP stimulation is carried out through P2Y2/P2X7 receptors, which are acting as mediators in eATP-induced EMT and invasiveness of cancer cells. In order to test this hypothesis, cells growth conditions have been evaluated (**Figure 6**).

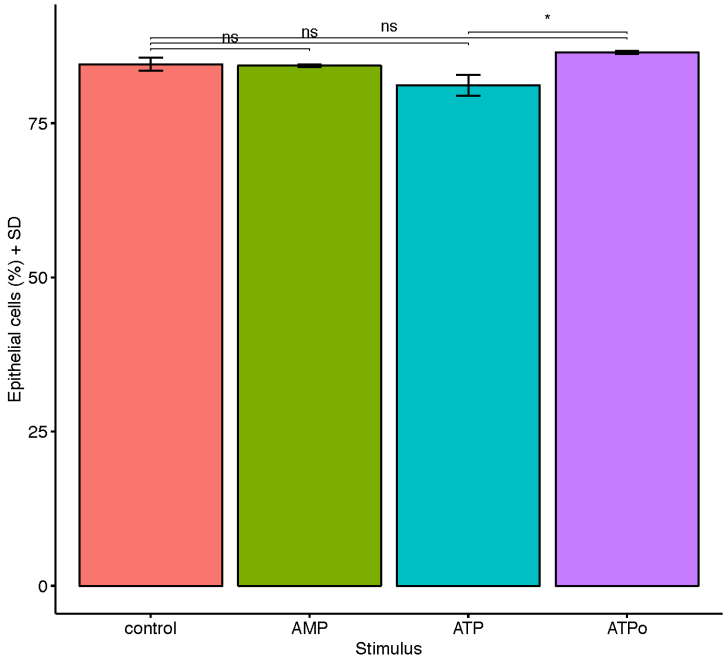


Figure 6. HMLER subpopulation stability (Epithelial fraction). Cells were treated with corresponding compounds (AMP - 100 μM of AMP, 48 h before the experiment, ATP - 100 μM of ATP, 48 h before the experiment; ATPo - 100 μM of ATP, twice 1 h treatment with 24 h intervals and medium exchange). Each condition was carried out in 3 replicates. Significant difference was only observed between ATP and ATPo (significance calculated using t-test, ns = not significant, * = $p<0.05$).

Pure subpopulations were seeded on 6-well plates ($0.5x10^6$ cells in each well), and stimulated the next day. After 48 hours of stimulation, the ratios between epithelial and mesenchymal cells were determined by FACS (Section 4.3.2). The same experiment was carried out on pure mesenchymal populations, but no significant differences were found between the conditions. The results indicate that the treatments did not alter significantly the recovery of missing epithelial fraction through MET or through growth modulation of mesenchymal cells. If similar percentage of newly formed epithelial fraction would be affected, the differences would not be visible because of the small size of the fraction.

Therefore, treatment with ATP seems not to have a significant effect on the ratio. In Epithelial fraction, prolonged eATP treatment seems to reduce the dividing potential of epithelial (through induction of apoptosis with Ca^{2+} induced oxidative stress and ROS production) or undergo enhanced EMT. During the short stimulations with a recovery period, we noticed increased epithelial growth which would be consistent with observations on wound healing and eATP-induced sustained EGFR activation (Jia Yin, Keping Xu, Jing Zhang, Ashok Kumar, 2007). While prolonged eATP stimulation could induce apoptosis through Ca^{2+} induced oxidative stress and ROS production. To investigate further those processes and how the decision-making takes place, single cell transcriptomics experiments have been employed (Section 5.3).

5.1.3 HMLER calcium profiles upon stimulation

In order to investigate how calcium-signaling pathways are processing information from the environment, we design a perfusion system (Section 4.2). With our in-house developed software, we were enforcing well-controlled temporal patters of calcium on the cells (**Figure 7**). This way treated cell were further processed using scRNA-seq methods (Section 4.1.1.2) and analyzed further using our computational pipeline (Section 5.2).

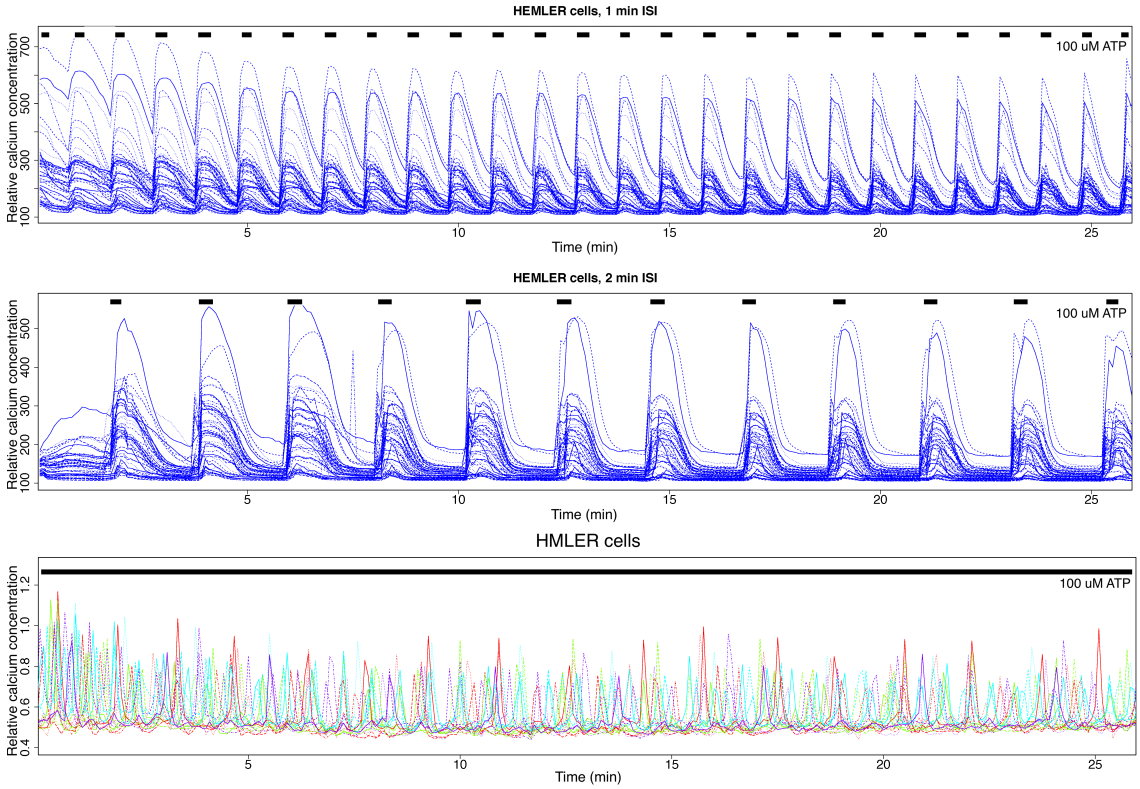


Figure 7. Three examples of calcium spiking traces extracted from HMLER cells (Section 4.3.1). Equal ratio of E and M cells were grown on 12-well plate and treated with our perfusion system. By repetitive changing of medium from regular HBS medium to stimulating medium (HBS + 100 μM ATP) intracellular calcium spikes were generated. **Top**: Ca^{2+} traces were extracted from 50 cells treated with 10 sec of ATP and 60 sec ISI (inter-spike interval) periods. **Middle**: Ca^{2+} traces were extracted from 50 cells treated with 10 sec of ATP and 120 sec ISI period. **Bottom**: Ca^{2+} traces were extracted from 20 cells treated with constant concentration of ATP. Treatment was carries out for 1 h, and followed by 1h of incubation (Section 4.1.2).

It is important to mention that eATP is affecting epithelial and mesenchymal subpopulations differentially (**Figure 8**), suggesting that, in each subpopulation, different components in the Ca^{2+} machinery processes signals from the external environment into intracellular responses. We noticed (**Figure 8, Bottom**) that mesenchymal cells recover from a spike much faster; they do not have prolonged calcium response for the full duration of the excitation, as observed in epithelial cells (**Figure 8, Top**). These differences could also be associated with different subpopulations behavior visible in Section 5.1.2.

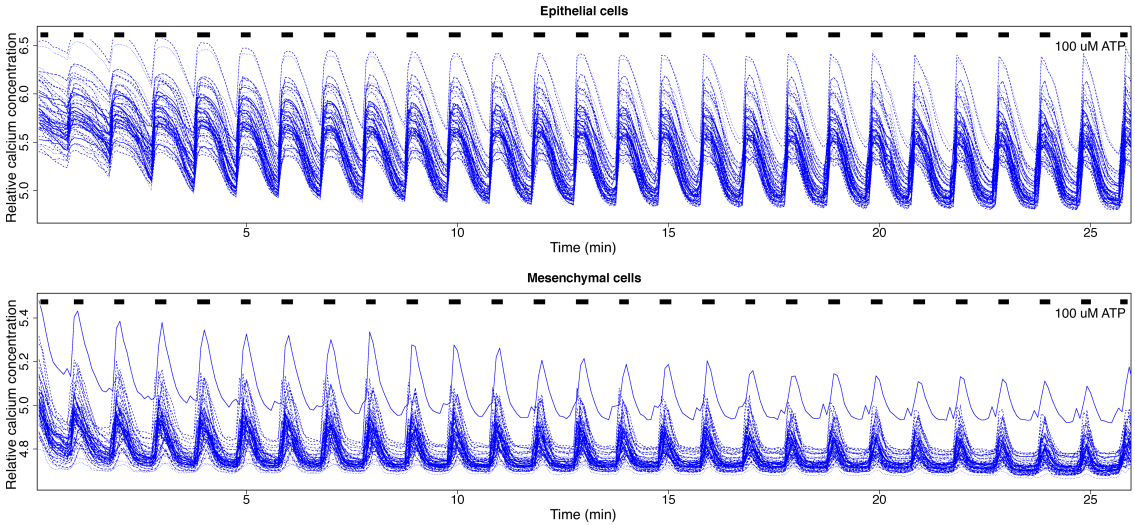


Figure 8. Calcium spiking patterns extracted from epithelial cells (**Top**) and mesenchymal cells (**Bottom**) stimulated with 60 sec ATP period, 10 sec pulse. Traces extracted as described in Section 4.3.1.

5.1.4 Gene splicing variants investigation using real-time qPCR (C1)

To obtain a better understanding of perturbed signaling pathway, a targeted single cell real time qPCR was performed using the Fluidgm C1 and Juno devices (Section 4.4.3). Calcium downstream genes have been investigates by custom-design primers (**Table 4**). The results are shown as an unsupervised clustered heatmap (**Figure 9**) where Ct values were normalized according to the housekeeping gene *ACTB* levels. With the high expression of genes like *PCOLCE* and low expression of *CDH1,* we can identify mesenchymal (subpopulation 3), and with opposite expression patterns we can map epithelial cells (subpopulation 2). Subpopulation 1 could be a combination of cells between both states. It is interesting to mention that as most of *NFAT* gene variants were present in the entire population (*NFATc1*, *NFATc2*, *NFATc3*, *NFATc4*, *NFATc5*), only *NFATc4* variant seems to be specifically expressed in the mesenchymal fraction. Furthermore, by analyzing the correlation matrix (**Figure 10**), we observed that the expression of the calcium binding *CD49F* protein is highly correlated with the epithelial genes *CD24* and *CDH1*. Surprisingly, gene expression of *CD44* does not seem to be specifically correlated with the mesenchyme fraction.

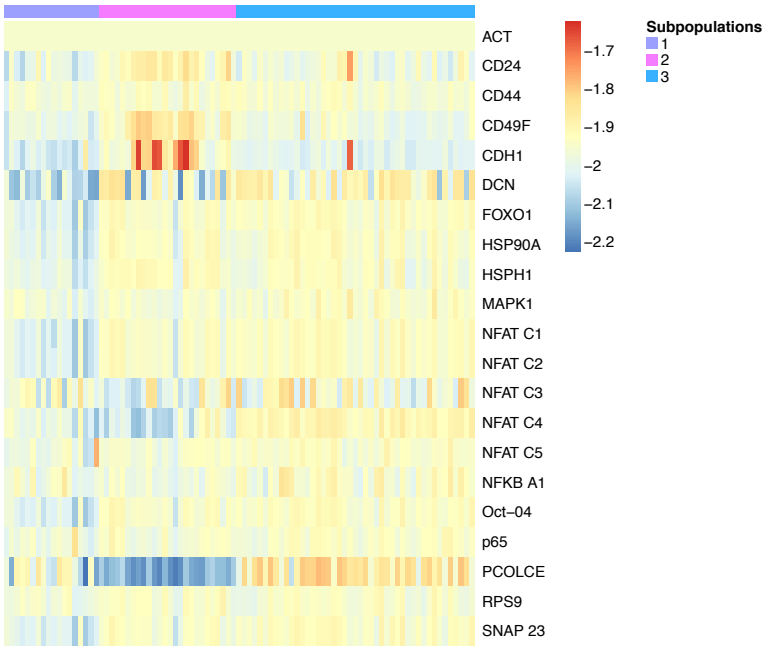


Figure 9. Unsupervised hierarchical clustered heatmap of HMLER single cell qPCR analysis. Epithelial cells represented by subpopulation 2 and mesenchymal cells by subpopulation 3. Ct values were generated by targeted real-time qPCR. Red colored cells represent low Ct and blue represents high Ct values, respectively. X-axis: genes, Y-axis: cells; analyses carried out using 80 cells.

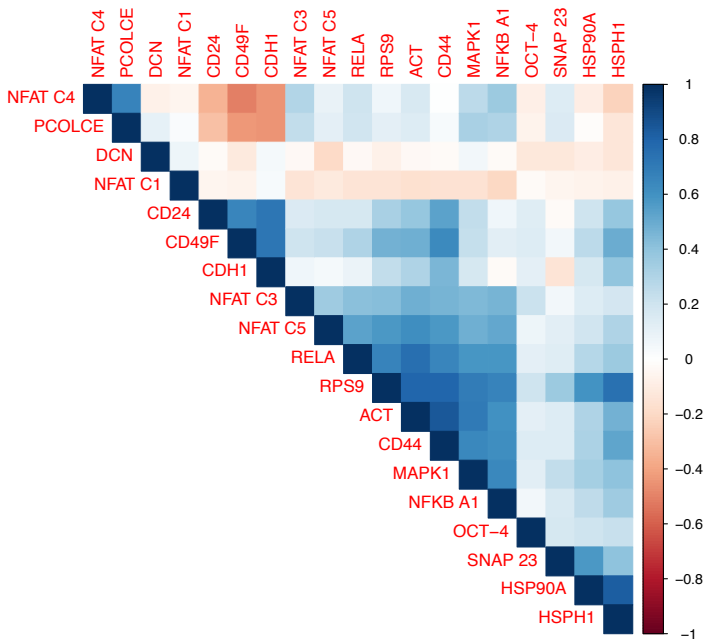


Figure 10. Clustered pairwise correlation matrix of Ct values generated from targeted real-time qPCR data; analyses carried out using 80 HMLER cells.

5.2 Breast cancer cell fate modulation by eATP dose response.

As mentioned above, extracellular ATP “eATP” is very often part of the cancer microenvironment as an important signaling regulator. The reasons for its release and diverse distribution in tissues are: inflammation and stress-related cell death, hypoxia, mechanical stress and non-targeted therapies. These conditions consequentially trigger series of cellular signaling events, which generate intracellular secondary messengers like high variable Ca^{2+} fluxes (Virgilio, Ben, Sarti, Giuliani, & Falzoni, 2017) (Kroemer, Galluzzi, Kepp, & Zitvogel, 2013) (Lohman, Billaud, & Isakson, 2012).

In order to investigate downstream changes in gene expression caused by spatiotemporal modulation of calcium dynamics triggered by eATP, we performed a first dose response experiment by applying medium with different levels of eATP (Section 4.4.2.1). To characterize the resulting cell fate, we generated single cell transcriptomics data as described in Section 4.5. The resulting DropSeq single cell data from 4 conditions are shown in **Figure 11A** and consist of 8400 cells with 33538 genes expressed. On the **Figure 11B** expression of gene *PCOLCE* is shown, which is associated with the mesenchymal state. This and other E-M state specific genes allowed us to identify mesenchymal “M” (*PCOLCE*, *VIM*, *S100A4*) and epithelial “E” (*CD24*, *CDH1*, *ITGB4*) cell populations.

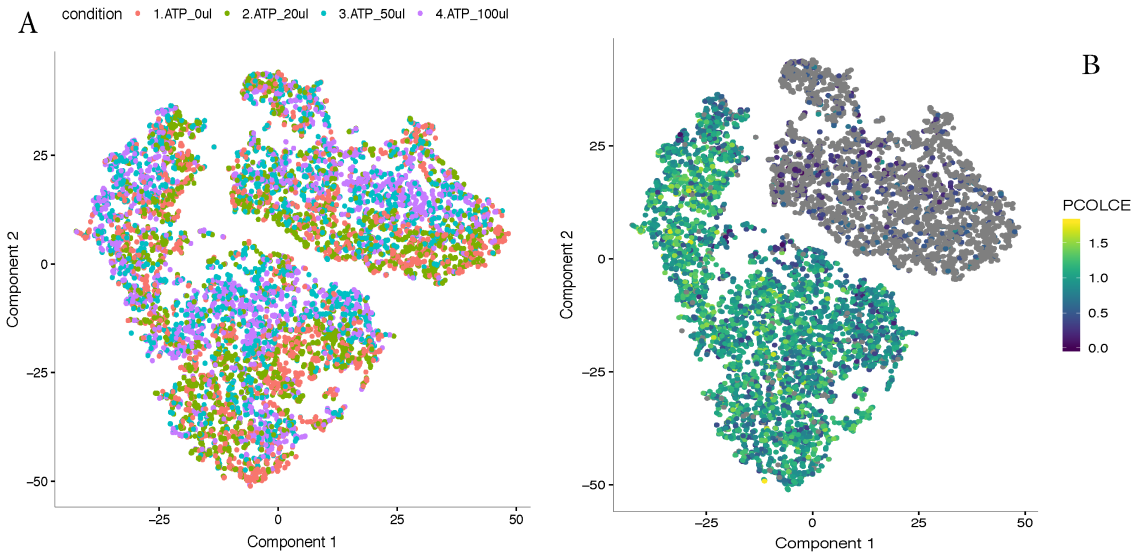


Figure 11. t-SNE plots showing 4 populations of cells, which were treated with 0 µM, 20 µM, 50 µM, 100 µM of eATP (Section 4.4.2.1). Each dot represents one cell. The closer the cells are to each other, the more similar their transcriptoms are. (A) The different applied ATP conditions indicated by color do not exhibit a very specific pattern in the t-SNE space. (B) PCOLCE expression values indicative for the mesenchymal state were normalized and presented as percentage of total cellular mRNA; analyses carried out using 2000 cells per condition (8000 cells).

On the **Figure 11A**, the distributions of cells from each condition within the subpopulations are shown by color-coding. To investigate shifts in the location of cells between different conditions on the tSNE plot in more detail, we next quantified changes in genes expression by performing the "*DifferentialGeneTest*" from our adapted Monocle pipeline. This approach generated a list of differentially expressed genes (DEGs). Applying a threshold of Q-val < 0.001 we acquired 2707 significantly expressed genes. The top 1000 genes can be found in the Supplementary Material (**Table S1**).

As expect, at least 2 subpopulations are visible in the data and we clustered cells according to cell-cell proximities visible on the tSNE plots (**Figure 12**). Higher cluster number on tSNE plot allowed us to track the differences of trends in genes between conditions in relation to the clustered subgroups. Additionally we were able to identify and exclude differences, which come from cell cycling genes, such as Aurora Kinase A (*AURKA*), Cyclin-dependent kinase 1 (*CDK1*) or Centromere Protein F (*CENPF*).

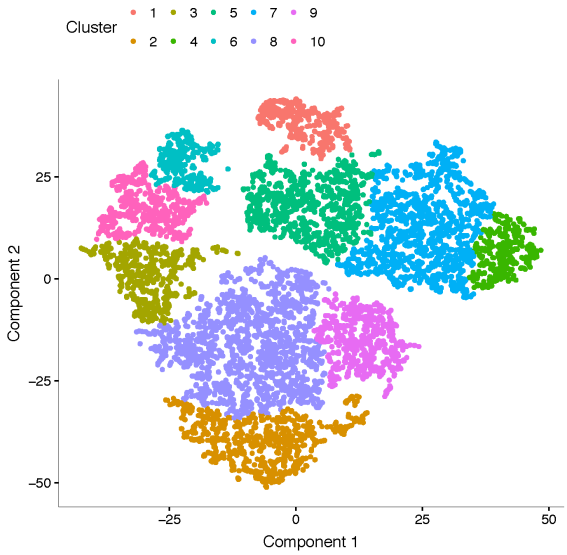


Figure 12. t-SNE plot of 4 different experimental conditions (**Figure 11**). Data have been divided into 10 clusters according to the differences in gene expression. Clusters associated with “E” subpopulation: 1,4,5,7, and clusters associated with “M” subpopulation: 2,3,6,8,9,10; analyses carried out using 2000 cells per condition (8000 cells).

For this purpose, we analyzed the expression dynamics from the top DEG list. Based on this list and in the literature reported genes (Lauren Averett Byers, Lixia Diao, Jing Wang, 2011) involved in motility and EMT, we first focused on the 8 genes shown in **Figure 13** which exhibited a Q-value smaller than 0.01.

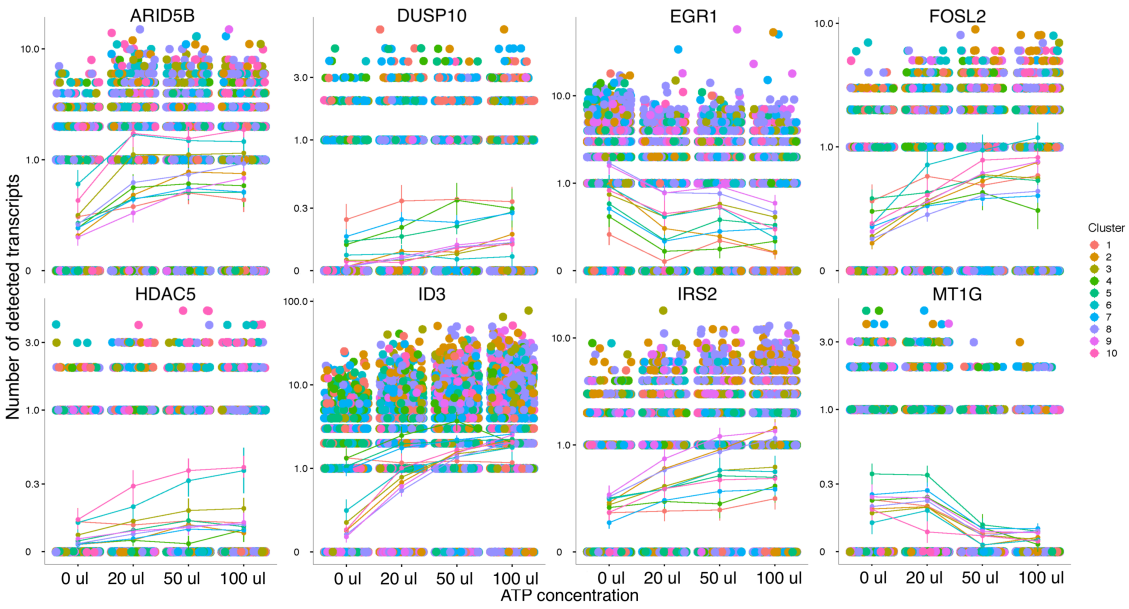


Figure 13. Jitter plots of the 4 eATP stimulated conditions exemplify 8 important genes, which are known to be involved in EMT process. Each dot represents a number of “true” captured RNA transcripts from a specific condition in a specific cluster (color-coded). Trendlines are tracking average expression of gene across the horizontal axis indicate a coherent dose-response behavior across all clusters; analyses carried out using 2000 cells per condition. (“E” subpopulation: clusters 1,4,5,7 and “M” subpopulation: clusters 2,3,6,8,9,10)

When analyzing gene expression trends we have often seen clusters belonging to subpopulations “E” and “M” being affected differentially, as we can see with AT-Rich Interactive Domain-Containing Protein 5B (*ARID5B*), Histone deacetylase 5 (*HDAC5*), DNA-binding protein inhibitor (*ID3*) or Insulin Receptor Substrate 2 (IRS2).

Another set of genes we wanted to evaluate, were genes involved in stress related responses. This would allow us to connect EMT to the potential burden of constant eATP treatment (**Figure 14**). We can see genes with steady dose response curve like complement decay-accelerating factor (*CD55)* or thioredoxin interacting protein (*TXNIP)*. Other genes like C-type lectin domain family 2 member D (*CLEC2D*) or Endonuclease G (*ENDOG*) seems to be more responsive with higher eATP concentration. We could also notice some genes having opposing expression trends like C-X-C motif chemokine ligand 1 (*CXCL1*).

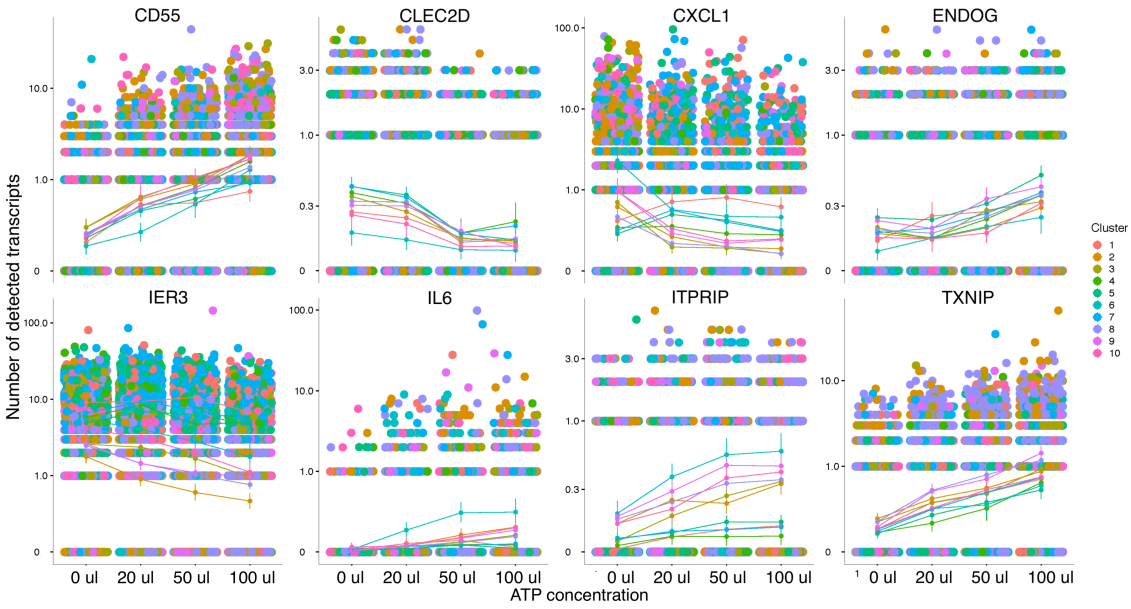


Figure 14. Jitter plot for 8 DEGs involved in stress related signaling for the 4 eATP stimulated conditions; analyses carried out using 2000 cells per condition.

5.3 Cell fate modulation by inducing distinct Ca^{2+} profiles by eATP

Based on these observations how ATP stimulation can induce EMT specific signaling and the central role Ca^{2+} may play for some key players, we were next investigating the activation pattern in dependence on specific eATP induced Ca^{2+} signals.

5.3.1 Oscillatory and stochastic Ca^{2+} profiles applied using perfusion system

Driven by the curiosity to unravel full the potential and capacity of signaling molecules such as the Ca^{2+} secondary messenger, we decided to perturb the signaling system in a well-controlled manner. Previous studies have highlighted that some genetic profiles can be significantly altered by a difference in the dynamics of the stimuli (Dolmetsch et al., 1998). For this purpose, we established a perfusion system as described in Section 4.2. This macrofluidics setup allowed us to robustly induce precise patterns of calcium dynamics to the entire population of cells. Experimental details are described in Section 4.1.2, while the visualization of perturb conditions are shown on **Figure 15**.

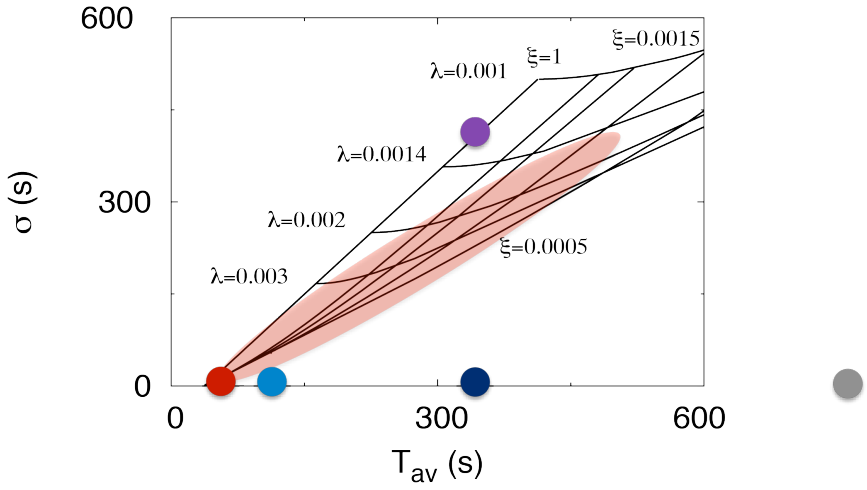


Figure 15. Plot exhibits the experimental setup of 5 conditions with different patterns of applied Ca^{2+} dynamics. T_{av} on X-axis represents average interspike intervall between calcium spikes, while σ on Y-axis is the standard deviation of the corresponding spike train. Red corresponds to deterministic oscillations with a 10 sec spike of ATP and a period of 1 min; light blue to deterministic oscillations with 10 sec spike and a period of 2 min; dark blue to oscillation with 10 sec spike and a period of 6 min; purple describe stochastic spiking with a 10 sec spike of ATP and an average period of 6 min; grey correspond to control condition without ATP stimulation.

While previous studies have focused on the frequency dependence of gene expression, the design of our experiment was inspired by previous investigations on the stochasticity of Ca^{2+} oscillation (Skupin et al., 2010), where potentially additional information could be encoded in the variability of spiking. In order to do so, we treated cells with 1,2 and 6 min of deterministic Ca^{2+} oscillation and a 6 min stochastic spiking pattern. Calcium traces of constant, 1 min and 2 min periods of ATP-induced Ca^{2+} spikes were shown on **Figure 7**. After treatment, cells were subsequently processed with our established Drop-seq pipeline (Section 4.4.1). The generated digital gene expression matrices (DGEM) were further analyzed using our bioinformatics pipeline (Section 4.6).

5.3.2 Single cell analyses of cells with different Ca^{2+}(eATP) imposed profiles

After generating the digital gene expression matrices, we evaluate the quality of the sequenced libraries by looking at the "knee plots" (**Figure 16A**) and the quantity of captured genes could be estimated from the heatmap (**Figure 16B**). For most of the downstream analyses, typically around 800 cells per condition passed the quality check with respect to total RNA content.

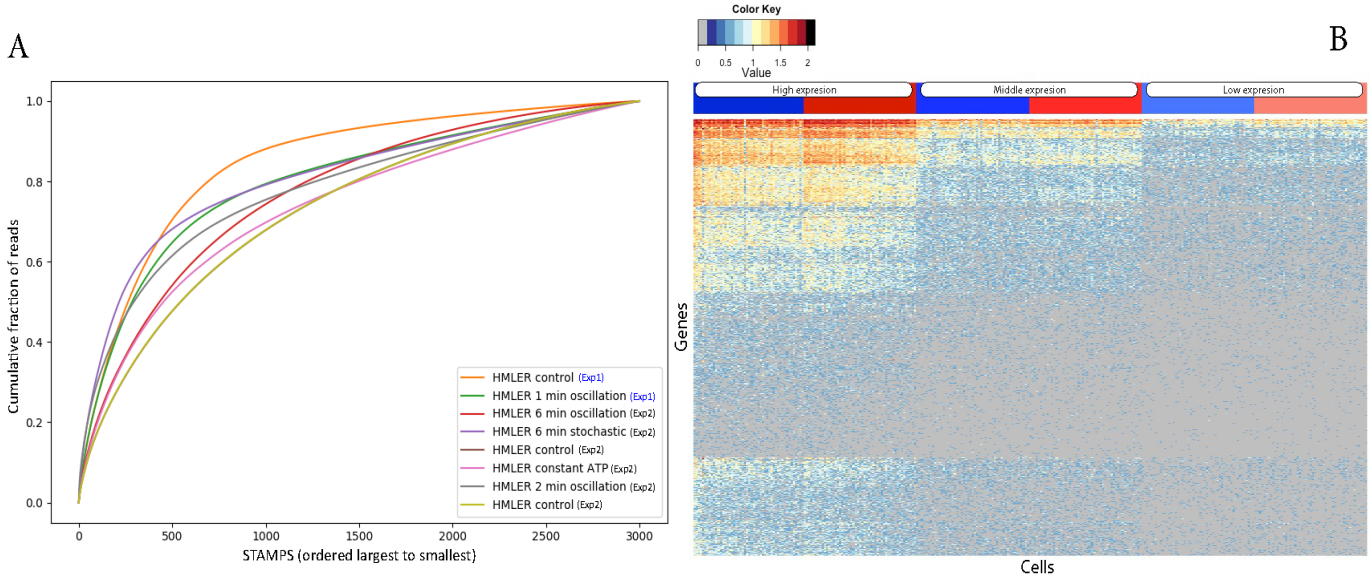


Figure 16. (**A**) Knee plot generated for all conditions by plotting the cumulative frequency and looking for an inflection point (knee). (**B**) Heatmap representation of DGEM from experiment 1 (Exp1 in Section 4.1.2). Blue bar represents control; red bar represents 1 min oscillations.

Next the digital gene expression matrices for all 6 conditions were used to perform DGE analysis by the "*differentialGeneTest*" of the Monocle package. For this purpose, each perturbation condition was first compared to the control condition without any activation stimuli. The numbers of DEGs are shown on **Figure 17.**

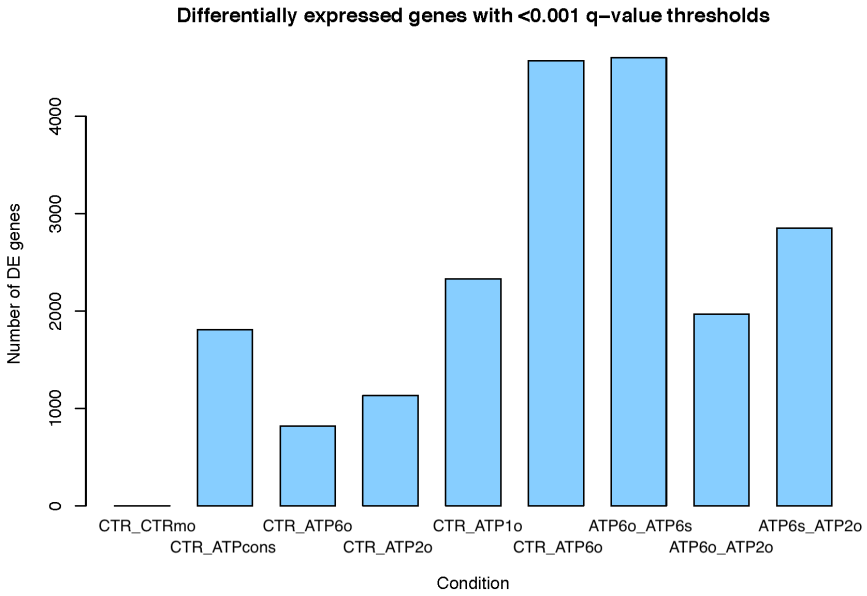


Figure 17. Bar plot showing the number of DEGs when compered between conditions. Samples from experiment 1: CTR – control, ATP1o – 1 min ATP oscillation. Experiment 2: CTRc, CTRmo – controls; ATPcons – constant ATP, ATP2o – 2 min ATP oscillations, ATP6o – 6 min ATP oscillations, ATP6s – 6 min ATP stochastic oscillations.

5.3.2.1 DGE analyses of data from cells with different calcium profiles

In the first experiment (Exp1) we wanted to evaluate first if we can observe similar differences in gene expression as those generated in the dose response experiment (Section 5.2). Jitter plots comparing control condition (no ATP stimulation) to 1 min oscillation of ATP are shown in **Figure 18**.

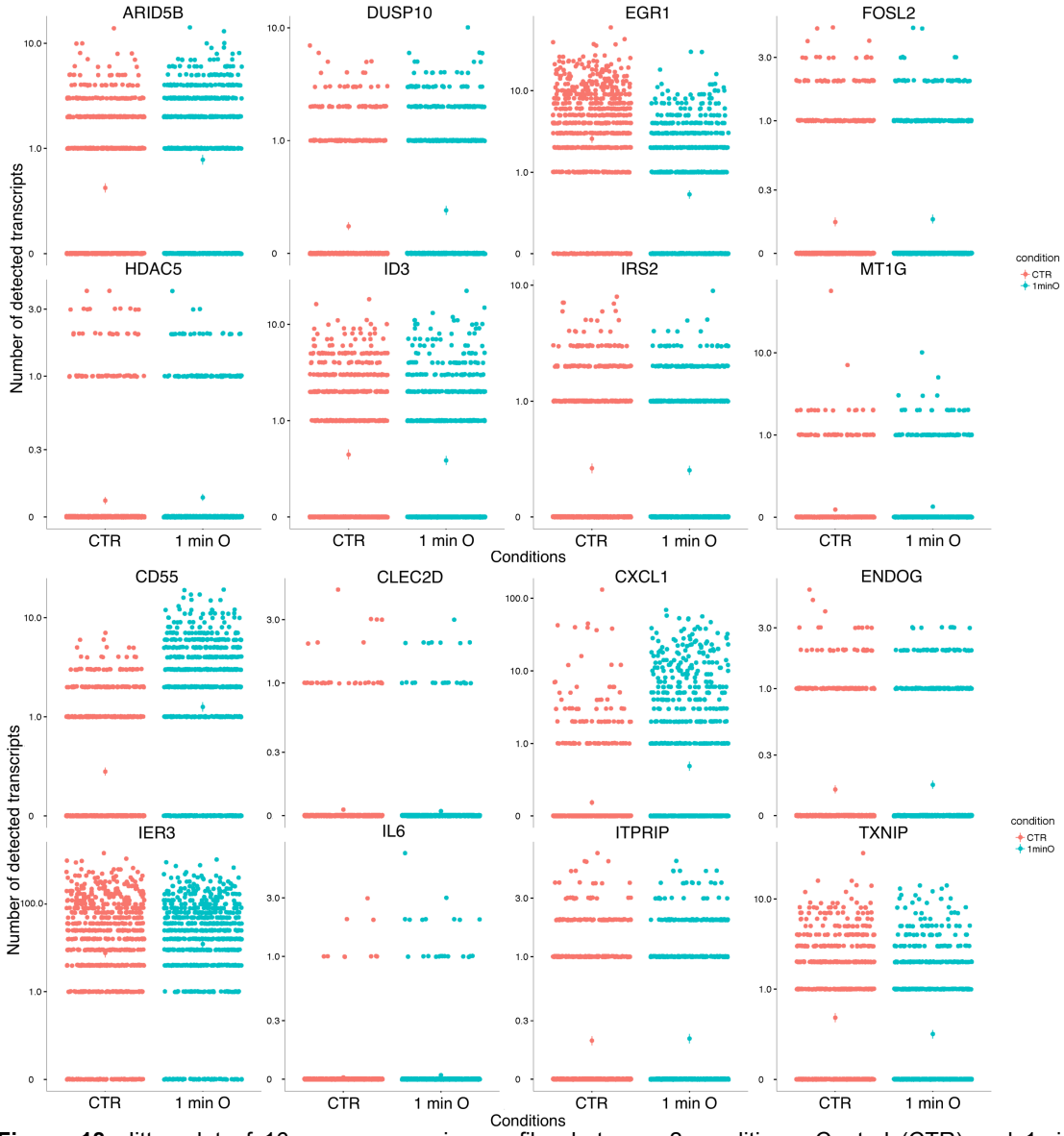


Figure 18. Jitter plot of 16 gene expression profiles between 2 conditions: Control (CTR) and 1min oscillatory eATP (1minO). The upper 8 genes are involved in EMT processes and the lower 8 genes are involved in stress response; analyses carried out using 800 cells per condition.

Expression of genes like *ARID5B*, *EGR1* and *DUSP10* seems to have similar trend when compered to constant ATP stimulation (**Figure 13**). Genes like *FOSL2*, *ID3*, *IRS2*, *MT1G* on the other hand seem not to be significantly affected when applying 1 min oscillations of eATP.

For genes related to stress responses we can also see same significant increase in *CD55* expression, while genes like *CLEC2D*, *ENDOG*, *IER3*, *IL6* or *ITPRIP* seems either not to be affected or the response is similar to the level of 20 μM ATP stimulation from the dose response experiment (**Figure 14**). Surprisingly *CXCL1* and *TXNIP* genes expression seems to have opposite trends as in had in dose response.

To investigate whether the signaling regulation by oscillation of stimuli can have a significant different effect on the cells, we next designed an additional experimental setup (Exp2) to quantify the effect of oscillation frequency and on variability of spiking. For this purpose, we tested two more oscillation frequencies (2min and 6 min) and one stochastic oscillation conditions of eATP as described in **Figure 17**. The resulting expression data for the previously highlighted genes are shown on **Figure 19**.

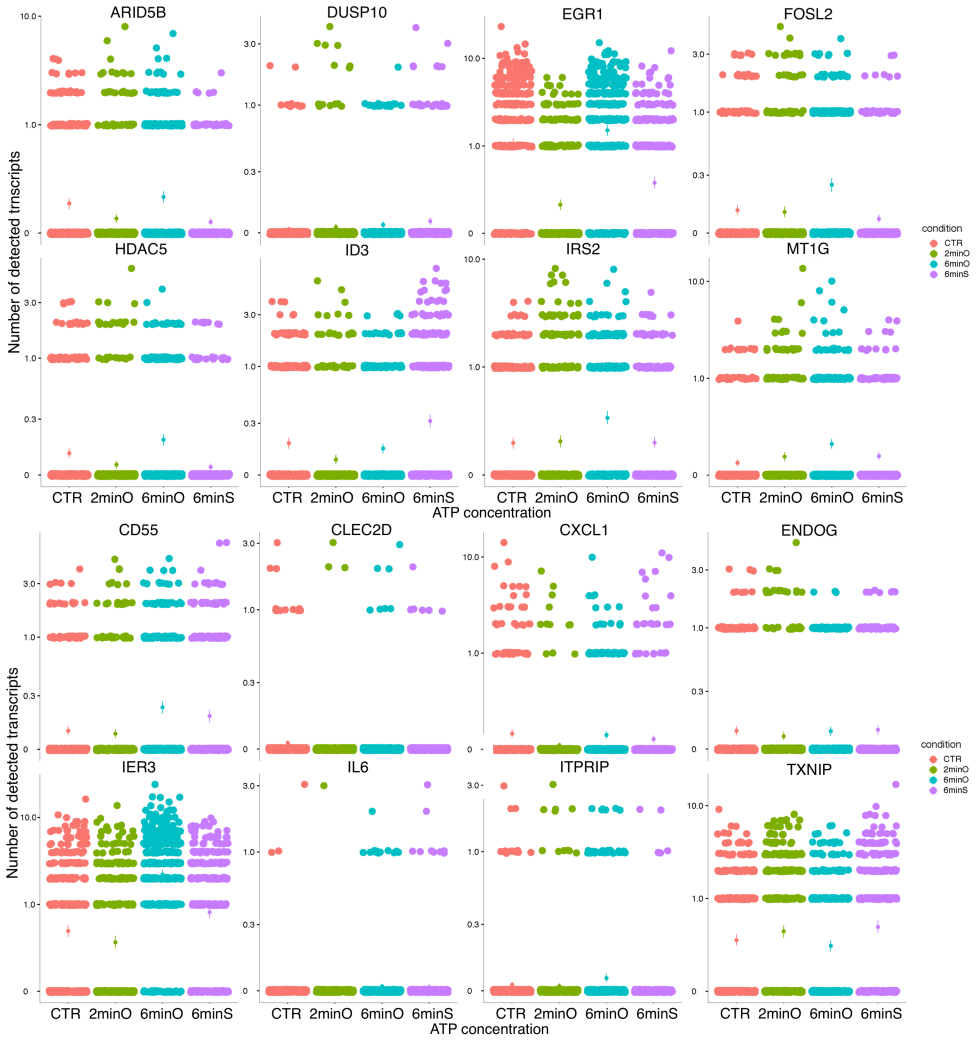


Figure 19. Jitter plot of the previously described 16 genes involved in EMT and stress response for the 4 additional conditions performed in experiment 2 with control (CTR), 2 min deterministic oscillations (2minO), 6 min oscillation (6minO) and 6 min of stochastic spiking (6minS). Dots with error bars represent average expression; analyses carried out using 700 cells per condition.

When analyzing gene expression data from these different ATP patterns, we observed some interesting properties for specific genes. For

instance, the expression of *ARID5B*, *HDAC5*, *FOSL2* and *ID3* behave similarly by decreasing expression for shorter stimuli periods and increasing expression for the longer period of 6 min. Interestingly, when we apply stochastic spiking with an average period of 6 min, the expression of these genes drops again, except for *ID3*, which is being upregulated. Analysis of the full gene sets has shown that there are a number of genes responding similarly as evaluated by DEG analysis (**Figure S1**). These types of dynamical regulation of gene expression could potentially lead to a completely new understanding of cell signaling.

When looking at the stress associated genes, we observed a similar trend for the shorter oscillation periods (1 or 2 min) and 6 min stochastic spiking with genes like *IER3*, but then we can see significant upregulation during 6 min oscillation. On the other hand, we found genes, which exhibited a completely opposite trend like *TXNIP* where expression is higher in constant eATP, then seems to be decreasing with increasing deterministic period, and finally increases in 6 min stochastic spiking.

5.3.2.2 Correlation analyses of E and M states after eATP stimulation

To investigate changes in expression profiles of the epithelial and mesenchymal subpopulations, we first used correlation analyses. By plotting values of Spearman correlation of all captured genes in the controls sample, we were able to extract genes correlated and anticorrelated with the “E” and “M” subpopulations (**Figure 20**).

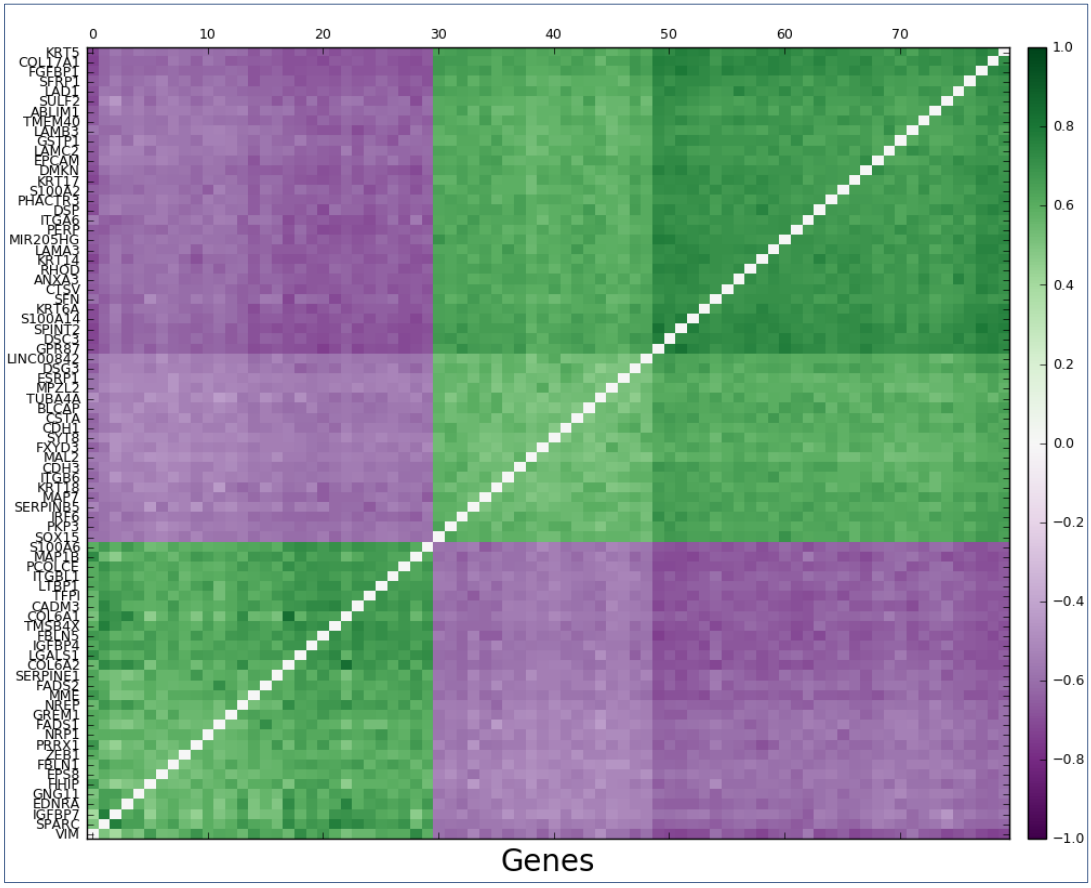


Figure 20. Zoom into highly correlated and anticorrelated gene clusters of HMLER cells, which contain E and M genes. Upper gene group correlates with E cells specific genes and lower group of genes correlates with M cells specific genes.

Because we suspect some level of heterogeneity and transition in the parental HMLER population, we perform analysis of the "pure" E and M subpopulations. For this analysis, we used the Principle Component Analysis (PCA) of the control condition and selected cells from the endpoints of the epithelial-mesenchymal spectrum (**Figure 21**) to separate pure E and M cells for the subsequent analyses (**Figure 23**). Additionally, we generated a correlation network from the correlation matrix with a threshold of 0.6 to identify core regulatory interactions (**Figure 22**).

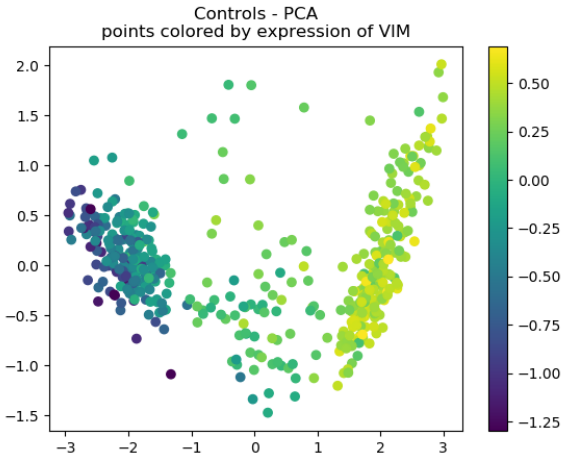


Figure 21. PCA plot generated with genes from the correlation cluster (**Figure 20**) for HMLER cell populations under control condition. For cell identity, the expression level of the mesenchymal marker VIM is color coded.

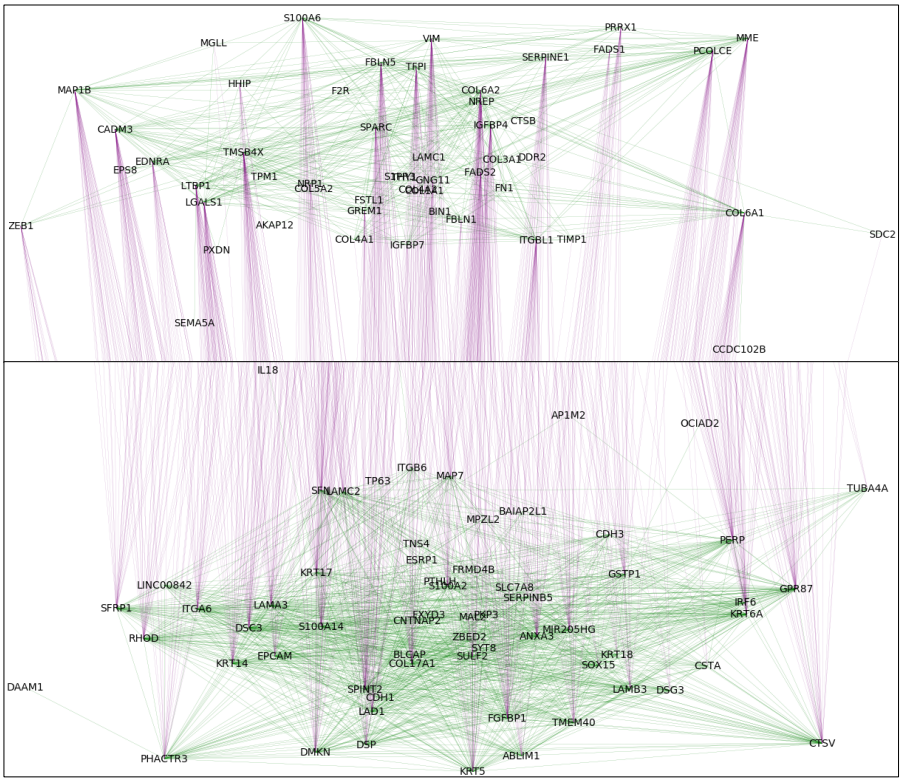


Figure 22. Correlation network analyses of E and M genes from the correlation matrix (X15). Top figure represents epithelial gene interactions, bottom represent mesenchymal genes. Green lines connect positively correlated genes and purple lines connect anticorrelated genes, respectively. Correlation cut-off was set to |0.6|.

Further, we investigated the differences in gene expression between control and stimulation condition of epithelial and mesenchymal subpopulations separately. By evaluating cells with the most E and M phenotype, we could point out most susceptible genes to treatment in a given subpopulation (**Figure 23**).

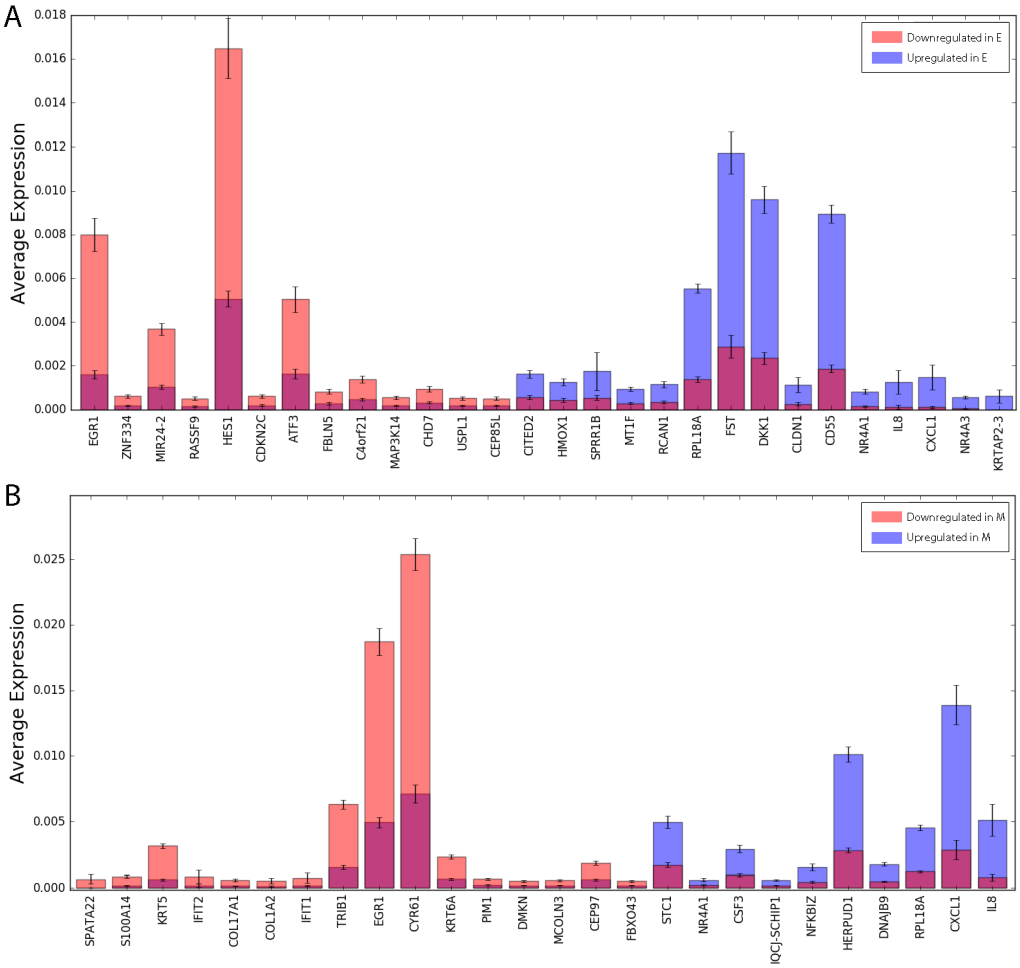


Figure 23. Comparison of average gene expression between untreated cells and after treatment with 1 min ATP oscillations. Plot (**A**) compares epithelial cells “E”, plot (**B**) compares mesenchymal cells “M”. Purple bar represent average of upregulated genes after stimulation; orange bar represent average of downregulated genes after stimulation.

The analysis exhibited a subpopulation-specific response to treatment. For example, the upregulation of the *CD55* gene due to treatment is mainly associated with pure E cells, while upregulation of the *CXCL1* gene is associated with M cells. We can also see significant decrease in *HES1* expression, coming mostly from E cells.

5.3.2.3 BEAM analyses and EMT "states" identification.

Besides the pure "E" and "M" populations shown in Section 5.3.2.2, we already know from the dose response cluster analyses (Section 5.2) that the cellular EMT spectrum is more complex in agreement with similar conclusions from recent papers on hybrid states in EMT (Grosse-Wilde et al., 2015). To investigate this theory, we employ branched expression analysis modeling (BEAM) analyses. This method tries to assign cells to a "dynamic *state*" on a transitioning state space (**Figure 24**).

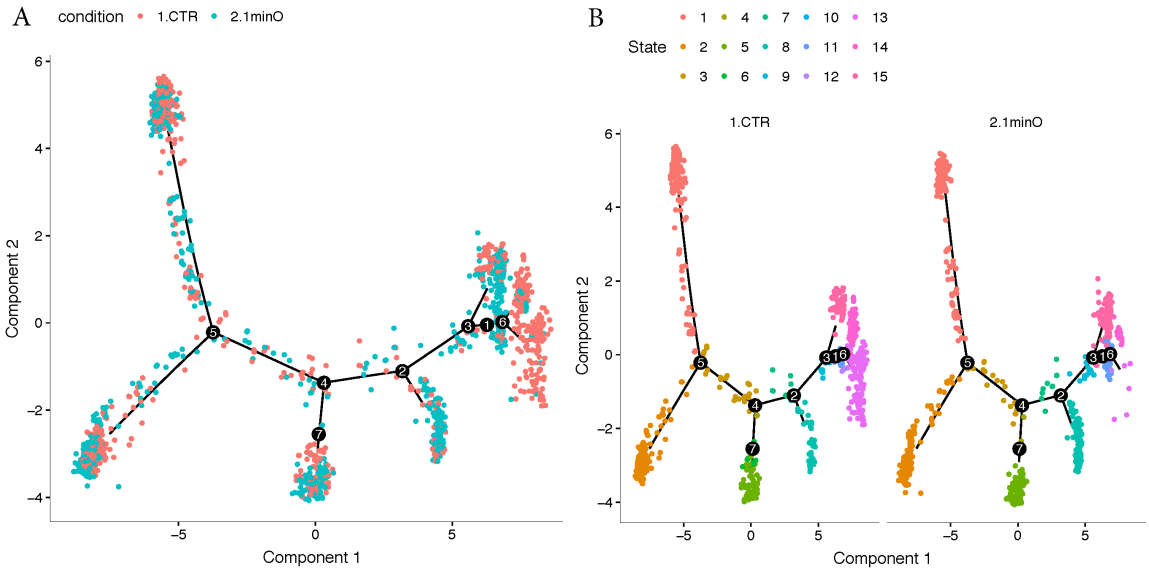


Figure 24. BEAM analysis graph showing HMLER cells from control and 1 min ATP oscillation condition (EXP1). Graph (**A**) exhibits involvement of cells from difference conditions into each dynamical state. Graph (**B**) shows the "state" identities on the transitioning state space. Numbers indicate the possible branching points of the process.

In the BEAM trajectory analyses, we observed some apparent differences in the cell state space occupation. Cell after stimulation tend to disappear from state 13 and 14 to populate states 8, 10 and 15. In order to characterize these states, we quantified the E-gene and M-gene scores for each state as shown in **Figure 25**. This analysis indicates that cells shifting between states originate from the mesenchymal subfractions. Next we determined the genes, which define the separate identity of states 13 and 14 from 8, 10 and 15 to be a high expression of Thymosin Beta 4 X-Linked (*TMSB4X*) (low in state 8 and 15), S100 Calcium Binding Protein A6 (*S100A6)*

(downregulated in state 8 and 15), Tissue Inhibitor Of Metalloproteinases 1 (*TIMP*) (downregulated in state 15), *EGR1* (downregulated in state 8 and 10), and Galectin-1 (*LGALS1)* (downregulated in state 15).

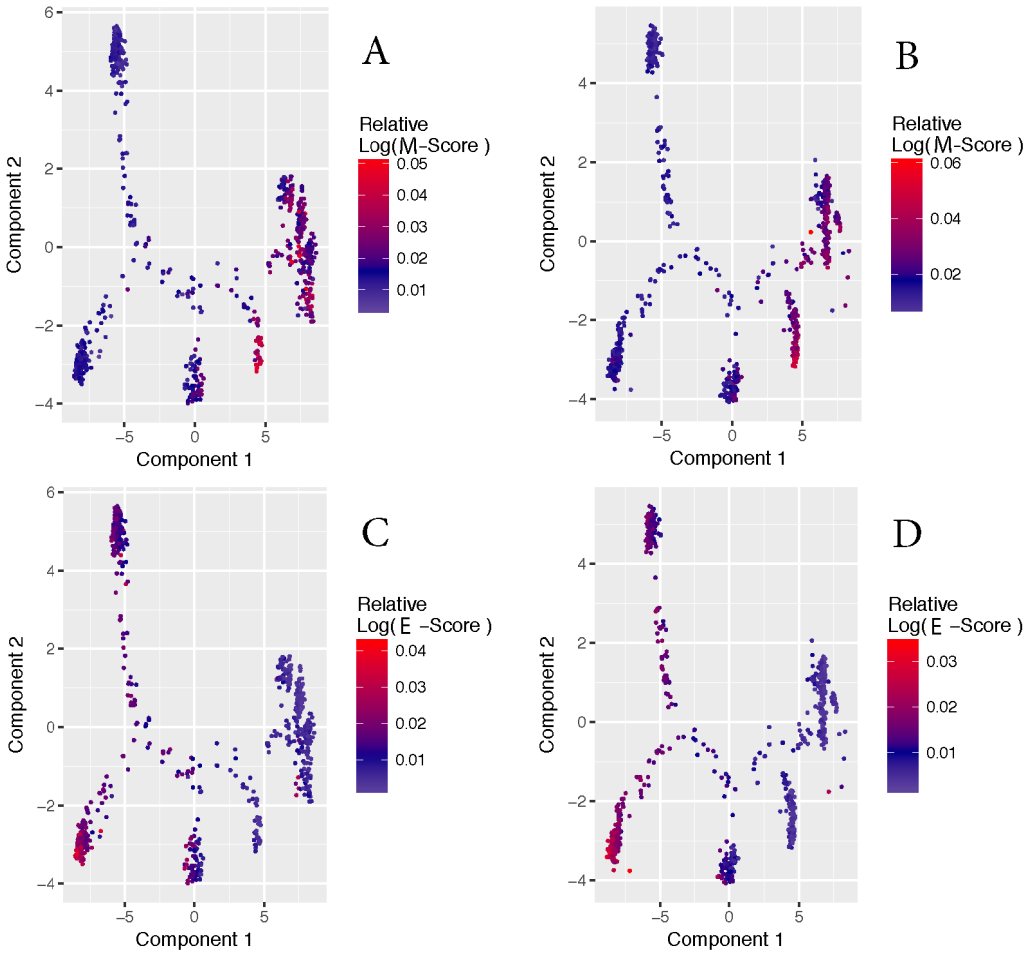


Figure 25. BEAM analysis graph showing scores of cumulative "M" and "E" genes from control (**A** and **C**) and 1 min eATP oscillation (**B** and **D**) condition. Genes used for the score were identified by the correlation analyses (**Figure 20**) and subsequent validation with literature reports.

Finally, we analyzed in more detail the differences in gene expression induced by 6 min deterministic oscillation or stochastic spiking with an average period of 6 min by comparing their "*dynamic states*" in the BEAM branching analyses. These different activation patterns clearly induce distinct cell states as shown in **Figure 26** and by the DEGs given in the Supplementary Material (**Figure S2**) since the stochasticity in eATP stimulation generates a separate branch for the 6 min stochastic oscillation. Most distinct genes between state 1 and 2 are e.g. *FTH1* (upregulation of ferritin heavy chain 1 in state 2), *EIF1*

(upregulation of Eukaryotic translation initiation factor in state 2), *MRPS6* (upregulation of 28S ribosomal protein S6 in state 2), *ZFAS1* (upregulation of ZNFX1 antisense RNA 1 in state 2).

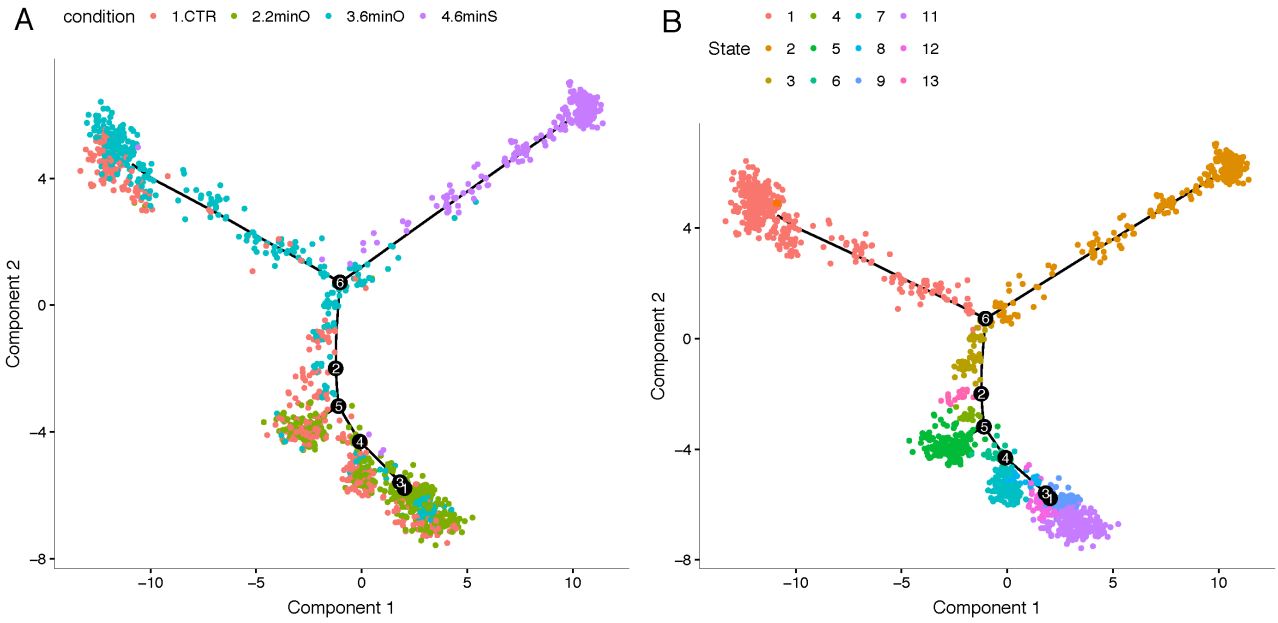


Figure 26. BEAM analysis graph showing eATP stimulated HMLER cells from control, 2 min oscillation, 6 min oscillation and 6 min stochastic oscillation condition (EXP2). Graph A exhibits involvement of cells from difference conditions into each dynamical state. Graph B shows the "state" identities on the transitioning state space. Numbers indicate the possible branching points of the process.

5.3.3 Analyses of biological processes

In order to better understand the biological implications of these changes in gene expression, we used the "Go Enrichment Analyses" tool (http://geneontology.org) considering separately up- and downregulated sets of DEGs (with their corresponding q-value) between conditions. This allowed us to extract lists of different biological processes with their significance scores. Obtained processes per condition are shown in Supplementary Material (**Table S2**).

When comparing all eATP stimulated samples to the control condition, we can observed high involvement of "cell cycle" (GO:0007049, 0022402, 1903047) and "chromosome and organelle organization" (GO: 0051276, 0006996) processes in each condition indicating that even with the 6 min intervals between spikes, we are able to maintain those functions on a

significant level (Erlinge, 1998). In similar fashion we observed downregulation of genes involved in “protein transport, metabolism and targeting” (GO: 0006810, 0070972, 0006614, 0072599, 0006613, 0045047, 0006518, 0006612). Additionally, we found downregulation of processes involved in “cell death” (GO:0008219, 0012501, 0010941, 0043067).

As further interesting observations when investigating “regulation of cell cycle arrest” (GO:0071156) and “positive regulation of cell cycle arrest” (GO: 0071158), we detected upregulation in constant, 1 min and 2 min eATP oscillations, but no significant difference for 6 min eATP oscillations. However, in 6 min stochastic spiking we found again significant upregulation. “Cellular component assembly” (GO:0022607) and “cellular response to stress” (GO:0033554) exhibited the same response pattern.

A number to processes are only upregulated in the 1 min oscillation and 6 min stochastic oscillation conditions, such as "protein acetylation", "protein acylation", "internal protein amino acid acetylation", "positive regulation of histone ubiquitination", “type I interferon production” (GO:0006473, 0043543, 0006475, 0033184, 0032479). Additionally, we notice that "protein autophosphorylation" (GO: 0046777) was present in cells from 2 min oscillations and 6 min stochastic spiking.

On top of that we noticed that some of the processes were uniquely upregulated in the 6 min stochastic spiking condition like: "androgen receptor signaling pathway", "histone exchange", "positive regulation of histone phosphorylation" (GO:0030521, 0043486, 0033129). Another interesting process is “microtubule-based movement” (GO:0007018), which is only present when we stimulate cells with slow oscillations of 2 min and 6 min periods and stochastic spiking with an average period of 6 min.

When investigating epithelial processes, we noticed downregulation of “epithelial cell differentiation” and “epithelium development” processes in all conditions after stimulation (GO:0030855, 0060429) with a high confidence p-value. Surprisingly, we found upregulation of “epithelial cell differentiation” and “response to epidermal growth factor” (GO:0009913) in for the 2 min oscillations. Other epithelial processes were present also in 1 min oscillation and 6 min stochastic oscillation conditions showing upregulation of

"endodermal cell differentiation" (GO:0035987), while no significant MET-related processes were detected.

For mesenchymal processes, the GO analysis identified upregulation of “mesenchymal cell proliferation” (GO:0060916) for constant eATP stimulation and upregulation of “mesenchymal cell differentiation” (GO: 0048762) for the 2 min oscillation condition.

Additionally, we noticed changes in the “Wnt signaling pathway” (GO:0016055), which is significantly upregulated for 2 min oscillation and 6 min stochastic spiking condition. Furthermore, the 6 min stochastic spiking has also activated a “non-canonical Wnt signaling pathway” (GO:0035567).

I have performed all laboratory experiments and data analyses presented in the result section (Section 5). Methods developed by me have been specified in the methods section (Section 4).

6 Discussion

Signal transduction is the key mechanism by which cells sense their environment and adapt to it. Hence it is not only a fundamental aspect of cellular function but also the foundation of multicellularity because it allows cells to develop into specialized cell types building organs and to coordinate a complex organism. For these epigenetic mechanisms, a plethora of spatiotemporal stimuli are interpreted and translated into orchestrated cell fates.

Single cell RNA-seq technology allows us now to decipher subtle cell signaling implications in a more untargeted way. We are able to evaluate changes in the whole transcriptome on a population level. Having this in mind we developed a perfusion setup, by which we have challenged cellular signaling system and engage in attempt to understand dynamics of those changes.

The goal of this thesis was to investigate the importance of concrete stimuli dynamics in information transduction. Since it is becoming more and more apparent that population averaged readouts tend to inadequately illuminate the complex dynamics and heterogeneity of cellular responses (Longo & Hasty, 2006), we investigated a specific signal transduction model of cell fate transition at the single-cell level. As a model system we used the HMLER cell line, as it accurately reflects the transition interplay between epithelial and mesenchymal cells in breast cancer. To perturb and study this trans-differentiation process, we investigated the effect of well-controlled extracellular ATP-driven Ca^{2+} signaling on cell fate dynamics by single-cell transcriptome measurements. From this high-dimensional data, we were able to define in detail the “dynamical states” in the spectrum of the epithelial and mesenchymal subpopulations (Grosse-Wilde et al., 2015). Interestingly, current findings indicate that cells undergoing partial EMT, which express stem markers in an epithelial context, are the major contributors to cancer metastasis (Saitoh, 2018). Therefore, we focused our analysis particularly on genes and pathways related to EMT, MET, stress, immunity and cell cycle, as

these are often connected in cell signaling of developing cancer (Suarez-carmona, Lesage, Cataldo, & Gilles, 2017; Wesley, Bove, Mccarthy, & Der, 2007; Y. Yang, Pan, Lei, Wang, & Song, 2006).

By investigating changes of the HMLER cell line gene expression pattern after perturbations, we first confirmed the stability of the E and M subpopulations, and the recovery of the missing subpopulation after separation by measuring the expression of the CD44 receptor (Section 5.1.1). Although we have observed some variation in the balance between E and M subpopulations in cell culture, the 1:1 ratio ration tends to be recovered in the used condition. Furthermore, the recovery dynamics of the subpopulations could be explained by the paracrine signaling interplay between E and M cells.

Many publications describe ATP as a life-death signal (Valladares et al., 2013). Under normal conditions, ATP is present at high concentrations (5–10 mM) within cells and at very low concentrations in the extracellular healthy tissue (10–100 nM). However, within tumor microenvironments, extracellular ATP (eATP) concentrations can reach hundreds of micromoles and this is being read by cells as a “danger signal” (Allard, Longhi, & John, 2017).

When evaluating the effect of eATP in HMLER cells after 48 h, we observed a higher ration of CD44+ fraction. Surprisingly, when cells were treated with periodically transient eATP, we noticed a lower ratio of the CD44+ fraction (Section 5.1.2). This finding indicates that epithelial subpopulation is more sensitive to longer eATP treatment. This is further supported by the observation of longer duration of Ca^{2+} spikes in epithelial cells after each eATP pulse (Section 5.1.3).

An important pathway regulated by Ca^{2+} dynamics is the P2X/P2Y-Ca^{2+}-calmodulin-calcineurin pathway, which consequentially activates proteins of the NFAT family. By using our targeted singe-cell approach (Section 5.1.4), we were able to evaluate the presence of *NFATc4* transcription variant and its association to the mesenchymal fraction by its correlation to the *PCOLCE* gene and the anti-correlation to *CDH1*. Gene expression of the Protein Phosphatase 5 (*PPP5C*) is one of the downstream targets of *NFATc4*, which has been shown to participate in the response to hormones and cellular stress. Elevated

levels of this protein seem to be associated with hypertrophy, breast cancer development and modulation of TGFβ responses (Bruce, Macartney, Yong, Shou, & Sapkota, 2012). In our data, the expression levels of *PPP5C* (**Figure S1B**) are higher in the M subpopulations in a dose response dependent manner, as we observed its downregulation in 20 µM eATP and significant upregulation at 100 µM. Expression of *NFATc4* is also controlled by *CITED2*, which governs migration and invasiveness (Jayaraman, Doucet, Lau, & Kominsky, 2016; Qiang Li, Diana L. Ramírez-Bergeron, Sally L. Dunwoodie, 2012), and we detected a corresponding upregulation in the M subpopulations (especially in clusters 6 and 10 in **Figure S1B**) for 20 µM and 50 µM constant eATP stimulation.

We further tested expression of other genes significantly changed by various constant concentrations of eATP in the medium (Section 4.2). From these genes, the *ARID5B,* which is a novel transcriptional co-regulator for *Sox9* (Hata et al., 2013), exhibits a consistent increase with increasing eATP concentration (**Figure 13**). Knockdown of *SOX9* seems to inhibits proliferation, invasion and EMT (Huang & Guo, 2019) whereas the increase of *ARID5B* (**Figure 13**, Cluster 6 and 10) together with increased *SOX9* expression could lead to Notch1-induced mesenchymal features of cells. *DUSP10* is another gene identified as a critical factor involved in the metastatic progression through phosphatase-mediated activation of the ERK pathway (Ng et al., 2017).

When expression of Early Growth Response 1 (ERG1) protein drops, it has been reported that non-small-cell lung cancer tissue cells acquire mesenchymal phenotype and migration capabilities (Shan et al., 2015). Gene *FOSL2* seems to positively regulate EMT, inducing TGF-β1 pathway in the same lung cancer type (Junfeng Wang et al., 2014). Our data shows highest expression and expression increase in Clusters 6 and 10.

Next we identified the *HDAC5* gene, which seems to be upregulated in dependence on eATP, and according to literature promotes malignancy through a *miRNA-589*/*HDAC5* pathway (Liu, Lv, Li, & Zhang, 2017). Similar to *ARID5B*, the highest response is visible in Clusters 6 and 10. *ID3* is a particularly interesting gene in EMT as it defines the potency of cell

differentiation and proliferation. Knockdown of *ID3* in epithelial cells is sensitizing cells to BMP, which consequently leads to robust growth inhibition and induction of transdifferentiation (Kowanetz, Valcourt, Bergstro, & Heldin, 2004). In our study, *ID3* expression seems to be steadily growing with increasing eATP concentration (especially in M subpopulations, **Figure 13**), which could lower M cell migration and the probability of EMT.

IRS2 interacts with DVL2 and stabilizes it by suppressing its degradation, leading to promotion of Wnt/β-catenin-mediated EMT and cell proliferation (Geng et al., 2014).

It was recently documented that Metallothionein-1G (MT1G) suppressed tumor invasion and EMT through regulating the expression of matrix metalloproteinase family (MMP) (Zeng et al., 2018). In our case eATP seems to downregulate *MT1G*, and consequentially could promote EMT.

We also focused on DEG, which could contribute to cellular oxidative stress, apoptosis or are involved in immunological responses. We noticed that stimulation with eATP causes expression of Interleukin 6 (*IL-6*) gene in a concentration-dependent manner (**Figure 14**) in agreement with findings in the literature (Ihara, Hirukawa, Goto, & Togari, 2005). Consequentially IL-6 drives expression of *CD55*. Translation of this protein prevents excess complement activation and is a way to protect cells from damage (Dho, Lim, Kim, & Kim, 2018). Gene *CLEC2D* encodes for the receptors for KLRB1 protein, and protects against natural killer cell-mediated lysis. *CLEC2D* downregulation in our data would make cells susceptible to NK-cells (Mathew, Chaudhary, Powers, Jamboor, & Mathew, 2016). Another factor, which triggers immune cells to tumor microenvironment is CXCL1, a protein that exhibits neutrophil chemoattractant activity and additionally is also associated with migration inhibition (Wen et al., 1997). Interestingly, already at intermediate eATP concentration, we observe that the M population having this gene downregulated whereas E cells seems to have opposite trend.

We further detected many genes, which are more directly involved in apoptosis regulation, such as *ENDOG*, *IER3*, *ITRIP* or *TXNIP*. In case of *ENDOG*, it induces caspase-independent apoptosis via DNA degradation or oxidative stress. It is believed to be an important constituent implicated in cancer, aging, and neurodegenerative diseases such as Parkinson's disease

(Büttner et al., 2013; Pote, 2012). In our data we can see significant upregulation only when we apply 50 or 100 µM eATP treatment. Radiation-inducible immediate-early IEX-1 gene (*IER3*) on the other hand protects cells from induced apoptosis caused by Fas or tumor necrosis factor type alpha. Inositol 1,4,5-Trisphosphate Receptor Interacting (*ITPRIP*) is another gene involved in cell death when downregulated. This mechanism is performed by enhancing Ca^{2+}-mediated inhibition of Ca^{2+} release form IP_3R (Kwon et al., 1978; Simino et al., 2017). In our data, we observed upregulation in all cells, especially in all E clusters and Cluster 3 from the M population. Another important protein, which regulates cellular redox signaling and protects cells from oxidative stress, is TXNIP (G. Xu, Chen, Jing, & Shalev, 2012). Expression of this gene strongly influences cytoplasmic Ca^{2+} increase (Gab Seok Kim, Joo Eun Jung, Purnima Narasimhan, Hiroyuki Sakata, 2013). In our data, upregulation of *TXNIP* expression strongly correlates with an increase of eATP concentration (**Figure 14**), as well as with shortening of ISI for oscillatory treatment. This downregulation in gene expression with longer ISI in deterministic oscillations (6mO) is opposed by eATP stochastic spiking (6mS) (**Figure 19**).

When imposing different calcium profiles on HMLER cells (**Figure 15**), we observed an increasing number of DEGs compared to the control conditions for decreasing oscillatory periods of Ca^{2+} spikes. This might have been expected because cells can interact with more stimuli in the same treatment period (**Figure 17**) (Zhu et al., 2011). It has also been reported that with different periods different signaling pathways can be activated (Smedler & Uhlén, 2014) and that some pathways are more precisely activated by oscillations (Dolmetsch et al., 1998; Hogan, Hogan, Chen, & Chen, 2003; Nelson, 2004).

Interestingly, we found dramatic changes in the number of DEGs when changing from a deterministic oscillation pattern to a stochastic spiking behavior with the same average period of eATP activation. This finding suggests an additional layer of information encoding in the dynamics of signaling molecules like Ca^{2+} (Skupin et al., 2010). Although there are many interesting genes and pathways modulated by this stochastic dynamics (**Table**

S2), the focus was put on those related to breast cancer development and EMT. The gene *ID3* is a tumor suppressor, which promotes cell adhesion (Nair, Teo, Mittal, & Swarbrick, 2014). In our data, we found that *ID3* expression is steadily increasing with higher persistent concentration of eATP. This tendency seems to be abolished or even expression downregulated when applying 1, 2 or 6 min oscillatory stimulation (**Figure 18, 19**). Surprisingly, for 6 min stochastic stimulation, we observed a recovery of *ID3* expression. It is further interesting that some genes like IER3 have the highest expression with long oscillatory ISI periods (6minO) and a similar trend can be observed for *HDAC5*, *IRS2* and *CD55* genes.

By comparing pure E and M populations for 1 min deterministic oscillations, we identified that the upregulation of *CD55* expression is mainly coming from the enriched E fraction (**Figure 23**), while upregulation of the *CXCL1* chemoattractant gene is induced mostly from the enriched M fraction. Another interesting gene strongly downregulated in the E fraction is the Hes Family BHLH Transcription Factor 1 (*HES1*). HES1 is a transcription repressor (downstream of the Notch pathway) and also inhibits proliferation and migration under oxidative stress (L. Xu et al., 2017). Surprisingly, the eATP dose response had no effect on its expression, but when we triggered 1 min deterministic oscillations, we found a significant downregulation in the E fraction. This type of stimuli dynamic could potentially contribute to EMT phenotype under stress. Another gene strongly downregulated in the 1 min oscillatory condition in M cells is the Cellular Communication Network Factor 1 (*CYR61*). This protein promotes adhesion, matrix deposition, stemness, but also promotes EMT by Raf-1/MEK/ERK/Elk-1/TWIST-1 signaling (Hou, Lin, Hou, & Liu, 2014). In dose response experiments, we observed a consistent decrease in *CYR61* expression when eATP constant concentration was increasing. A significant downregulation is also visible in 1, 2 min oscillatory and 6 min stochastic oscillation conditions (**Figure S3A**) whereas 6 min oscillation seems not to suffer from downregulation. Another highly upregulated protein in the E subpopulation in 1 min oscillation condition is Follistantin (*FST*), which is hindering proliferation as an Activin antagonist (Antsiferova et al., 2009). Again, dose response did not affect significantly *FST* expression,

but for increasing oscillation periods we identified a dramatic increase in *FST* expression, which could consequentially slow down proliferation of E cells (Figure S3B).

Similar increases in expression levels in dependence on increasing ISI periods were found for other genes as shown in the Supplementary Material including the bone morphogenetic protein receptor type 2 (BMPR2), which promotes metastasis by RhoA-ROCK-LIMK2 pathway (S. Wang, Ren, Jiao, Huang, & Bao, 2017). The Tight Junction Protein 1 (TJP1) also follows exactly the same trend, and its upregulation is associated with TGF-β induced migration (Yoon, Kim, Lee, & You, 2015). Also, the Transducer Of ErbB-2 1 (TOB1) as a proliferation inhibitor (Jiao et al., 2011) exhibited a similar trend, even if the dose response experiments showed a steady increase with eATP concentrations.

In the branching analyses of 1 min deterministic oscillation (**Figure 24, 25**), we notice a change in the distribution of mesenchymal cells between different “dynamical states”. Characterizations of those states were based on the “*differentialGeneTest*”, and we found downregulation of genes, such as TIMP, which is a inhibitor of the matrix metalloproteinases (MMPs), a group of peptidases involved in degradation of the extracellular matrix. Also downregulation of TMSB4X would potentially slow down proliferation and migration. Additionally, we observed downregulation of S100A6, which is a Ca^{2+} binding dependent protein promoting proliferation and migration of tumors by β-catenin signaling (X. Chen et al., 2015). Those observations would suggest that 1 min oscillation with eATP could carry some potential protective processes slowing down metastatic development.

Another interesting difference of expression profiles were identified between the 6 min deterministic oscillatory and 6 min stochastic eATP stimulations. The shift between state 1 and 3 (mostly in the 6 min oscillation condition) and state 2 (mostly in the 6 min stochastic oscillation condition) can be characterized by expression of genes such as *DST*, which governs assembly of hemidesmosomes of epithelial cells (downregulated in state 2).

Downregulation of *FTH1* seem to be associated with state 2 and has been linked in the past to inhibition of apoptosis (Y. Chen et al., 2016). *ZFAS1* is a lncRNA upregulated in state 2, it promotes tumor development through regulation of miR-150 (He, He, Li, & Zhou, 2019). Additionally, many ribosomal-related genes seem to be upregulated in state 2 (**Figure S1**).

For a more systematic investigation, we then used GO pathway analyses to integrate the different DEGs into a coherent perspective (Section 5.3.3). In particular, we observed distorted signaling in histone modifications and in the canonical and non-canonical Wnt signaling pathways for the stochastic spiking with 6 min average period compare to other conditions. We also observed significant upregulation of pathway involved in androgen receptor signaling (GO:0030521), which in clinical breast tumor studied is often associated with motility and progression of the diseases (Giovannelli, Donato, Galasso, Zazzo, & Bilancio, 2018). Hence, stochastic eATP-induced Ca^{2+} signaling seems to be harmful in breast cancer if our HMLER model system reflects the *in vivo* physiology.

As we can see from this data, timing does matter when constant, oscillatory or stochastic stimulation with eATP is applied. Additionally, we could also notice that EMT related genes are uniquely modulated with those different dynamic setting. Cells associated with a particular state or cluster have been defined as risk genes. Oscillatory treatment seems to partially lift the expression burden of stress related genes by decreasing expression of some genes like *ENDOG* or by upregulating protective genes like *IER3*. But on the other hand, 6 min stochastic spiking induces larger diversification of the cell when compare to 6 min deterministic oscillation. Stochastic dynamics seems to induce larger diversification of responses and expresses 80% more DEG than 6 min deterministic oscillations when compared to the control condition.

I believe that 6 min deterministic oscillation with its eATP induced Ca^{2+} profile would be interesting conditions to test for tumor initiating potential. The reasoning for this hypothesis would be based on the observation of a lower number of upregulated apoptotic genes, and the upregulation of some key stemness and EMT genes such as e.g. CYR61. On the other hand, 6 min

stochastic oscillation with its eATP induced Ca^{2+} profile induce wide range of genes expressed, and might promote cells to become a melting pot in tumor microevolution processes such as immune evasion.

7 Outlook

Cell signaling is a way to control epigenetic modifications, which are responsible for the establishment, maintenance and reversal of transcriptional states. Epigenetic modifications are fundamental for the development of multicellularity, adjustments to external environment or the cell's ability to "remember" past events. They have been reported in many disorders related to behavior plasticity, immunity, memory, cancer, addictions as well as psychological and neurodegenerative disorders (Moosavi & Ardekani, 2016). Hence, cellular signaling is a complex system which is not only governed by the number of components moving towards one pathway, but also by timing at which each of these components are interacting with one another.

As future steps, I would focus more on de-convoluting input signals by using stimuli that trigger a narrower downstream signal (such as specific high K_d (Dissociation constant) receptor antagonist, or modulating membrane action potential). This would allow for a better definition of the input-output relationship. Additionally, it would allow me to better describe the interactions between the components throughout the signaling pathways.

Although investigating transcriptomes offers enormous amount of information we need to keep in mind that not all genes will be translated into functional proteins. Having this in mind we plan to link gene expression profiles with measurement of cellular surface protein markers by using recently established Cite-seq technology in our lab (Mimitou et al., 2018). I believe that surface protein information will allow us to add additional dimension in understanding differentiation and transition processes. With the protein information we could get much better understanding of the state of the cell required for some transition processes to occur.

Generated stimuli-response data in this thesis could be used to highlight and link "dangerous states" of cancerous tissue, which are at risk of EMT in a particular environmental condition. Further, this knowledge could be evaluated in vivo (e.g. mouse model) by targeting or blocking those "dynamic states". Guiding transcription in a more refined manner could potentially also contribute to improvements in protocols used in iPSCs differentiation or transdifferentiation. By involving stochastic or oscillatory dynamics in cell

simulation by potentially modulating pathway responses of critical factors like e.g. c-Myc, Oct-3/4, SOX2 or KLF4.

Although there is still a lot of effort needed in order to understand and decode this dense machinery of cellular signaling, I believe that the result of this thesis on the specific EMT model demonstrates that this is a promising approach to take if one wants to tackle complex diseases like breast cancer or neurodegenerative diseases.

Appendix

Supplement table S1.

(Top 1000 DEG in eATP dose response experiment)

Gene short name	P-val	Q-val	Number cells expressed
AREG	>1xE-350	>1xE-350	8232
AVPI1	>1xE-350	>1xE-350	5232
CD55	>1xE-350	>1xE-350	5052
CHMP1B	>1xE-350	>1xE-350	6280
CTGF	>1xE-350	>1xE-350	6069
CXCL1	>1xE-350	>1xE-350	3128
DUSP1	>1xE-350	>1xE-350	6336
DUSP6	>1xE-350	>1xE-350	6285
ID3	>1xE-350	>1xE-350	5742
NBEAL1	>1xE-350	>1xE-350	8160
NR4A1	>1xE-350	>1xE-350	2297
SFN	>1xE-350	>1xE-350	7660
STC1	>1xE-350	>1xE-350	3749
TSC22D1	>1xE-350	>1xE-350	7885
TXNIP	>1xE-350	>1xE-350	4251
ZNF90	>1xE-350	>1xE-350	7878
AL136454.1	>1xE-350	>1xE-350	5676
PDE4D	2,18E-319	4,06E-316	3900
UQCRHL	3,62E-294	6,39E-291	4172
ETS2	3,18E-284	5,32E-281	6109
CEBPB	7,36E-279	1,18E-275	7964
NACA2	1,27E-270	1,93E-267	3802
NHSL2	1,41E-267	2,06E-264	2806
PTX3	2,11E-248	2,95E-245	4570
HAS2	1,09E-242	1,46E-239	3004
TOB1	5,85E-237	7,54E-234	5125
CEBPD	1,75E-213	2,18E-210	5575
GADD45A	6,17E-209	7,39E-206	7142
ACTB	1,61E-207	1,86E-204	8321
EGR1	5,72E-198	6,39E-195	4180
IL11	5,30E-195	5,73E-192	2215
IER3	1,42E-191	1,49E-188	7138
ZFP36L1	1,92E-190	1,96E-187	7650
RPL36	6,13E-185	6,05E-182	8321
ARID5B	6,79E-184	6,50E-181	4943
CDC42EP3	5,21E-183	4,85E-180	7633
CYR61	5,95E-177	5,39E-174	7795
PHLDA1	3,44E-172	3,04E-169	7903
SLC7A2	5,26E-170	4,52E-167	3560
MALAT1	7,36E-169	6,17E-166	8321
NEAT1	3,14E-167	2,57E-164	8142
HOXB2	3,01E-150	2,41E-147	5815
ATP5F1D	7,71E-148	6,01E-145	8314
LY6E	4,88E-145	3,72E-142	8278
IGFBP4	9,09E-144	6,78E-141	5659
JUN	1,10E-142	8,01E-140	6100
IL6	4,47E-142	3,19E-139	771
IRS2	5,93E-141	4,15E-138	4581
IER2	9,41E-141	6,44E-138	7035
CLEC2D	1,53E-139	1,03E-136	2801
MT1G	2,23E-137	1,47E-134	1903
KLF6	6,63E-136	4,28E-133	7846
FST	3,18E-135	2,01E-132	3031
MYC	5,54E-135	3,44E-132	7156
MIR222HG	5,11E-123	3,11E-120	3897
BCL7A	3,14E-122	1,88E-119	3463
RGS4	9,63E-117	5,67E-114	1508
AKAP12	4,09E-114	2,37E-111	6583
RGS2	2,90E-113	1,65E-110	1088
HMGA2	3,51E-113	1,96E-110	8078
UQCRC1	4,34E-113	2,39E-110	8135
RPS26	5,94E-108	3,21E-105	8321
TSC22D3	1,94E-107	1,03E-104	4792
FOSL2	2,63E-106	1,38E-103	4273
FNDC3A	7,82E-104	4,03E-101	6906
SLC26A2	3,15E-100	1,60E-97	7589
FOXS1	1,15E-99	5,75E-97	1325
NR4A2	4,11E-98	2,03E-95	548
TGIF1	6,17E-96	3,00E-93	5801
AP1S1	6,12E-89	2,93E-86	7666
ELOB	4,02E-88	1,90E-85	8320
B3GNT5	1,74E-87	8,11E-85	6222
GAPDH	2,68E-87	1,23E-84	8321
PABPC3	9,48E-84	4,30E-81	1395
DUSP4	5,05E-82	2,26E-79	7174
CXCL8	3,34E-80	1,47E-77	839
KRT14	2,82E-79	1,23E-76	7801
CLIC1	2,76E-78	1,19E-75	8321
KRT17	9,93E-78	4,22E-75	8000
SRM	2,31E-77	9,70E-75	8191
FRMD6	2,63E-77	1,09E-74	6963
NR4A3	4,50E-77	1,84E-74	437
DRAP1	6,22E-77	2,51E-74	8296
AL161421.1	1,53E-75	6,11E-73	2592
B4GALT1	5,73E-75	2,26E-72	5439
ZFP36L2	9,37E-75	3,65E-72	8261
IRX3	8,92E-74	3,44E-71	2298
RPL28	6,11E-73	2,33E-70	8321
BRI3	5,43E-71	2,05E-68	7613
PNRC1	1,94E-70	7,23E-68	5527
NDUFS2	6,99E-70	2,58E-67	5683
CITED2	5,34E-69	1,95E-66	3374
ITPRIP	2,07E-68	7,45E-66	2472
PTOV1	3,49E-68	1,25E-65	4538
CCNB1	7,16E-68	2,53E-65	7001
PTP4A1	1,04E-67	3,64E-65	7755
SOWAHC	1,83E-67	6,32E-65	4770
IRX2	3,18E-67	1,09E-64	5767
WDR66	3,60E-67	1,22E-64	2918
SETSIP	9,84E-67	3,30E-64	722
BANF1	3,09E-66	1,03E-63	8072
RPS29	3,32E-66	1,09E-63	8321
PFN1	6,18E-66	2,01E-63	8321
BRIX1	8,77E-66	2,83E-63	6855
PER1	9,57E-66	3,06E-63	2963
ATF4	2,52E-65	7,99E-63	8214
S100A7	2,89E-65	9,06E-63	196
AL161431.1	3,30E-64	1,03E-61	4315
FIS1	4,79E-64	1,47E-61	8173
FKBP8	6,79E-64	2,07E-61	6911
CDCA4	1,14E-63	3,44E-61	6679
ID1	4,09E-63	1,22E-60	5499

FAM83D	4,98E-63	1,48E-60	3517
SOCS3	2,29E-62	6,74E-60	2187
AURKA	4,67E-62	1,36E-59	6041
ARHGAP29	4,79E-62	1,39E-59	7974
HSPA8	1,05E-61	3,01E-59	8320
MED24	1,29E-61	3,66E-59	3184
CAV1	1,62E-61	4,56E-59	8321
INHBA	4,07E-61	1,14E-58	5669
ENDOG	5,34E-61	1,48E-58	3005
RSRP1	7,89E-61	2,17E-58	6353
ELL2	8,42E-61	2,30E-58	6923
SERPINE2	1,78E-60	4,81E-58	8201
MIDN	3,89E-60	1,04E-57	4183
PPP1R14B	5,40E-60	1,44E-57	8277
EMP1	7,76E-60	2,05E-57	7446
EREG	1,26E-59	3,29E-57	3996
CREM	4,36E-59	1,13E-56	5956
SGK1	2,75E-58	7,08E-56	6219
CALM2	4,86E-58	1,24E-55	8321
RHOB	1,12E-57	2,84E-55	5124
BDNF	1,57E-56	3,95E-54	1698
PLPP3	2,72E-56	6,82E-54	998
SNHG25	3,13E-56	7,77E-54	5183
AC006058.1	5,42E-56	1,34E-53	3234
RAB5C	7,00E-56	1,71E-53	7793
CENPA	2,32E-55	5,63E-53	4793
SERPINB2	2,92E-55	7,05E-53	433
ZNF428	3,28E-55	7,81E-53	6421
FOS	3,28E-55	7,81E-53	4040
S100A13	8,42E-55	1,99E-52	8310
STUB1	1,48E-54	3,48E-52	8223
VAMP2	3,16E-54	7,37E-52	4718
FGF5	7,18E-54	1,66E-51	3934
PHF20	8,26E-54	1,90E-51	7688
CREB5	1,10E-53	2,50E-51	3097
IGFBP2	6,63E-53	1,50E-50	3346
ARF5	7,04E-53	1,58E-50	3459
POLR2L	1,38E-52	3,09E-50	8320
BAX	1,69E-51	3,76E-49	8181
CRCT1	2,96E-51	6,54E-49	171
RGCC	4,36E-51	9,56E-49	1114
TIPARP	1,42E-50	3,09E-48	5258
RPS28	1,63E-50	3,54E-48	8321
ARL6IP4	1,93E-50	4,14E-48	8321
RPS10	4,36E-50	9,31E-48	8321
CAPG	6,80E-50	1,44E-47	6490
ATG101	1,45E-49	3,05E-47	7370
IL24	1,18E-48	2,47E-46	716
BCL7C	1,67E-48	3,48E-46	7489
ANKRD37	1,73E-48	3,57E-46	2465
ZBTB38	2,86E-48	5,89E-46	7177
KPNA2	2,96E-48	6,06E-46	7612
MT.CO2	4,26E-48	8,66E-46	8321
DDIT4	5,07E-48	1,02E-45	7880
HERPUD1	6,01E-48	1,21E-45	7278
MRPL2	1,03E-47	2,06E-45	5072
CTSZ	2,01E-47	3,99E-45	7863
TKT	2,21E-47	4,35E-45	8317
MT.CO1	2,59E-47	5,08E-45	8321
AL355596.1	3,40E-47	6,64E-45	477
SPHK1	1,38E-46	2,67E-44	8026
NFIL3	4,76E-46	9,17E-44	1773
RPS3	7,93E-46	1,52E-43	8321
OSBP2	1,90E-45	3,61E-43	1282
CARHSP1	5,46E-45	1,03E-42	8013
INSIG1	1,67E-44	3,14E-42	8134
PKM	2,43E-44	4,56E-42	8321
CXCL3	4,62E-44	8,61E-42	1666
ATP5MF	7,28E-44	1,35E-41	8308
AC004817.3	9,52E-44	1,75E-41	565
UBE2S	1,01E-43	1,84E-41	8041
HIST1H4C	2,24E-43	4,09E-41	7515
PGM2L1	2,52E-43	4,56E-41	3317
ANXA1	3,82E-43	6,89E-41	8309
PIK3R1	6,08E-43	1,09E-40	6008
PPP1R3B	7,21E-43	1,29E-40	1204
KLF5	1,52E-42	2,71E-40	3276
HJURP	3,02E-42	5,33E-40	2493
MT2A	3,50E-41	6,14E-39	8321
PLAU	4,79E-41	8,37E-39	6372
DUSP10	4,96E-41	8,63E-39	1744
SFRP1	5,48E-41	9,47E-39	3052
EVA1C	1,57E-40	2,70E-38	4105
ZBTB16	3,30E-40	5,64E-38	2531
HSP90AA1	5,20E-40	8,85E-38	8320
ADPRHL1	5,59E-40	9,47E-38	765
LDLR	9,44E-40	1,59E-37	6637
MCL1	1,48E-39	2,48E-37	7965
CDCA8	2,44E-39	4,07E-37	3612
SLC2A3	3,17E-39	5,26E-37	2331
ATP1A1	3,23E-39	5,33E-37	7056
LDHB	4,28E-39	7,03E-37	8321
MT1E	4,51E-39	7,37E-37	8314
NNMT	8,85E-39	1,44E-36	8256
PID1	1,23E-38	1,99E-36	3000
KIF23	1,94E-38	3,13E-36	4887
ADIRF	2,48E-38	3,98E-36	7779
NOV	2,94E-38	4,69E-36	2866
TUBA1C	2,97E-38	4,73E-36	8298
PAXX	3,92E-38	6,19E-36	6309
GRAMD1B	6,65E-38	1,05E-35	210
ERF	8,13E-38	1,27E-35	2975
PLK2	9,15E-38	1,43E-35	3545
NPTX1	1,72E-37	2,67E-35	131
MGST1	1,90E-37	2,94E-35	8319
TFAP2C	2,14E-37	3,30E-35	2812
MFGE8	2,39E-37	3,66E-35	5537
VMP1	3,51E-37	5,35E-35	8078
ADAMTS1	4,73E-37	7,18E-35	1057
BSG	7,50E-37	1,13E-34	8288
STIP1	8,98E-37	1,35E-34	7463
ATP5ME	1,08E-36	1,62E-34	8280
NR3C1	1,18E-36	1,76E-34	7444
ARHGDIA	1,76E-36	2,61E-34	8134
HHIP.AS1	2,13E-36	3,15E-34	3864
THUMPD3.AS1	3,33E-36	4,89E-34	7317
NDUFA3	5,13E-36	7,51E-34	6710
EDARADD	5,29E-36	7,72E-34	1115
ARL4D	6,36E-36	9,24E-34	3269
HDAC5	9,99E-36	1,44E-33	1401
ASPM	1,06E-35	1,53E-33	5220
YWHAH	1,09E-35	1,57E-33	8201
PSRC1	2,34E-35	3,34E-33	2750
CHD9	3,15E-35	4,48E-33	7145
PDIA3	3,54E-35	5,01E-33	8294
RGS17	8,98E-35	1,27E-32	5329
USP53	9,72E-35	1,36E-32	4530
SMURF2	1,00E-34	1,40E-32	4734
HIPK2	1,25E-34	1,74E-32	5836

FHL3	1,73E-34	2,40E-32	6679
DGCR6L	2,06E-34	2,84E-32	6840
PDE7B	2,24E-34	3,08E-32	1220
LAMB3	2,86E-34	3,92E-32	5807
MRPL23	2,98E-34	4,06E-32	7707
TRAF4	5,54E-34	7,52E-32	6294
NUPR1	9,53E-34	1,29E-31	3798
EPN1	9,69E-34	1,30E-31	5527
PFDN2	1,06E-33	1,43E-31	8283
YTHDF2	1,20E-33	1,61E-31	7291
CENPE	1,31E-33	1,74E-31	4722
PGK1	1,39E-33	1,84E-31	8292
C19ORF33	1,63E-33	2,15E-31	8118
KRT7	1,91E-33	2,51E-31	8318
G6PD	2,25E-33	2,95E-31	6432
SDF2L1	2,49E-33	3,25E-31	8160
RPL10	2,50E-33	3,25E-31	8321
BCL3	3,95E-33	5,12E-31	990
F3	8,26E-33	1,06E-30	7015
DEPDC1	8,31E-33	1,06E-30	3901
ATP2B1	8,32E-33	1,06E-30	8275
ZEB1	8,88E-33	1,13E-30	3629
SGO2	8,93E-33	1,13E-30	4290
PSMA3	9,33E-33	1,18E-30	8233
JUND	9,52E-33	1,20E-30	1892
TPX2	1,06E-32	1,33E-30	6869
IRX1	1,28E-32	1,61E-30	1255
RIN2	1,55E-32	1,93E-30	4372
KLF9	1,72E-32	2,13E-30	1571
TUBB2A	2,54E-32	3,14E-30	7428
RGMB	3,82E-32	4,72E-30	2886
H1FX	7,26E-32	8,92E-30	5176
TRIB1	9,11E-32	1,11E-29	2185
ALDOA	9,28E-32	1,13E-29	4782
RPS9	1,39E-31	1,69E-29	8321
TFPT	2,54E-31	3,08E-29	4405
FN1	3,11E-31	3,76E-29	8319
KIF20B	3,26E-31	3,92E-29	6168
CD99	4,97E-31	5,95E-29	8066
ZNF331	5,01E-31	5,98E-29	1554
OTUB1	7,32E-31	8,71E-29	6299
CKS2	1,43E-30	1,70E-28	8284
FOSL1	1,96E-30	2,31E-28	5327
S100A4	2,64E-30	3,10E-28	6385
MDH1	3,26E-30	3,82E-28	8067
PRDX1	3,61E-30	4,22E-28	8321
GADD45B	4,12E-30	4,80E-28	5833
NAA20	6,41E-30	7,44E-28	8287
CD63	7,44E-30	8,60E-28	8321
RAN	9,53E-30	1,10E-27	8321
MAD2L1	1,30E-29	1,49E-27	6664
SRSF2	2,01E-29	2,30E-27	8282
HMGCS1	2,06E-29	2,35E-27	7100
SERPINE1	2,59E-29	2,94E-27	7943
LINC00707	3,50E-29	3,97E-27	3284
SCAND1	3,73E-29	4,21E-27	8269
HMMR	3,98E-29	4,48E-27	4430
PRDX2	4,00E-29	4,49E-27	8227
PRSS23	4,90E-29	5,48E-27	8264
EMD	9,76E-29	1,09E-26	7631
SLC3A2	1,08E-28	1,20E-26	7874
TNS4	1,51E-28	1,67E-26	3537
EEF1E1	1,72E-28	1,90E-26	8091
PPAN	2,96E-28	3,26E-26	5856
DMBT1	3,73E-28	4,09E-26	375
REL	4,99E-28	5,45E-26	3397
NME4	6,09E-28	6,63E-26	6346
SDC4	8,13E-28	8,82E-26	5136
AC068491.3	8,89E-28	9,62E-26	2722
THBS1	9,01E-28	9,71E-26	8059
PSMC3	1,54E-27	1,66E-25	8140
ERGIC3	1,64E-27	1,75E-25	8178
PRRX1	1,86E-27	1,99E-25	4770
NDUFS8	1,93E-27	2,05E-25	8307
WDR43	2,18E-27	2,31E-25	7200
MARCKS	2,53E-27	2,68E-25	6226
DCAF13	2,94E-27	3,10E-25	7754
MKI67	3,11E-27	3,27E-25	6712
ERGIC1	3,12E-27	3,27E-25	7047
TECR	3,55E-27	3,70E-25	7942
SMOX	3,65E-27	3,80E-25	1116
RAB31	4,92E-27	5,11E-25	6154
TIMP1	5,24E-27	5,42E-25	8316
DCXR	5,31E-27	5,48E-25	7236
GPX4	5,36E-27	5,51E-25	8279
BNC1	6,76E-27	6,93E-25	4863
JARID2	7,04E-27	7,20E-25	3919
KLF3	7,07E-27	7,21E-25	4927
KRT8	7,19E-27	7,30E-25	5027
PLAUR	8,51E-27	8,62E-25	5951
KRTCAP2	8,73E-27	8,82E-25	5747
IL1R1	1,09E-26	1,10E-24	1467
HHIP	1,13E-26	1,13E-24	5313
MT.CYB	1,45E-26	1,45E-24	8321
GDF15	1,91E-26	1,90E-24	1113
MFSD2B	2,12E-26	2,11E-24	1269
MRPL50	2,17E-26	2,16E-24	7923
NDUFB9	2,23E-26	2,20E-24	8321
AC006480.2	2,29E-26	2,26E-24	1618
KNSTRN	2,90E-26	2,85E-24	6084
ATP5MGL	3,16E-26	3,10E-24	1408
CREB3L2	3,79E-26	3,71E-24	4232
TOMM5	4,39E-26	4,28E-24	5939
TPGS1	4,76E-26	4,63E-24	4055
ATP1B3	6,10E-26	5,91E-24	8256
IRF1	7,04E-26	6,80E-24	2946
RCE1	7,40E-26	7,13E-24	2291
CADM3	8,75E-26	8,40E-24	5257
MAZ	9,95E-26	9,53E-24	4365
TOB2	1,01E-25	9,64E-24	5068
ARF4	1,02E-25	9,75E-24	8153
ASNA1	1,18E-25	1,12E-23	7281
TRAPPC1	1,69E-25	1,60E-23	7944
TIPIN	1,80E-25	1,70E-23	5242
PRR15	1,94E-25	1,83E-23	1180
SLC25A3	2,16E-25	2,03E-23	8321
HM13	2,26E-25	2,11E-23	7483
MRPL13	2,26E-25	2,11E-23	8272
RPL36A	3,06E-25	2,85E-23	8320
PRSS3	4,44E-25	4,13E-23	8278
DUSP5	4,58E-25	4,24E-23	2633
PTPN1	5,58E-25	5,16E-23	7871
APOE	6,56E-25	6,04E-23	675
RALY	8,55E-25	7,86E-23	8157
TRMT10C	8,98E-25	8,22E-23	6817
KLF4	9,72E-25	8,89E-23	3265
COL4A2	1,05E-24	9,55E-23	7250
IDI1	1,22E-24	1,11E-22	8114
SERPINB6	1,41E-24	1,28E-22	6759

ATP5PB	1,58E-24	1,43E-22	8318
MCAM	1,79E-24	1,61E-22	885
CSRP1	1,84E-24	1,65E-22	6930
SPDL1	1,98E-24	1,77E-22	6481
RPL22L1	2,12E-24	1,89E-22	8307
SLC30A1	2,19E-24	1,95E-22	2548
ERCC6	2,44E-24	2,17E-22	5460
PTMS	2,44E-24	2,17E-22	8264
HNRNPA1L2	2,51E-24	2,23E-22	1256
UBA1	3,35E-24	2,96E-22	6132
SF3B6	3,52E-24	3,10E-22	8320
CDA	3,70E-24	3,25E-22	6436
ANKRD1	3,85E-24	3,37E-22	818
AES	3,90E-24	3,41E-22	6662
C20ORF27	6,27E-24	5,46E-22	7743
SNHG9	8,34E-24	7,24E-22	2551
CPNE7	8,67E-24	7,52E-22	1833
CAPNS1	9,83E-24	8,49E-22	7100
MYL12A	1,12E-23	9,68E-22	8316
E2F1	1,18E-23	1,01E-21	2330
PIP4P1	1,35E-23	1,16E-21	3905
ODC1	1,36E-23	1,17E-21	8193
S100A11	1,47E-23	1,26E-21	8321
TUBA1B	1,57E-23	1,33E-21	8320
SRP19	2,14E-23	1,82E-21	8262
PSMA2	2,76E-23	2,34E-21	8281
PYURF	3,32E-23	2,80E-21	8239
UBE2T	4,21E-23	3,55E-21	6792
GRINA	4,32E-23	3,63E-21	5333
PTP4A2	4,71E-23	3,95E-21	7629
SERTAD1	4,85E-23	4,05E-21	4645
KDELR1	4,99E-23	4,16E-21	8084
SNRNP70	7,14E-23	5,94E-21	7768
HSP90AB1	8,00E-23	6,65E-21	8321
MT.ND4L	9,01E-23	7,46E-21	5934
EIF3E	9,57E-23	7,90E-21	8321
CCL20	9,78E-23	8,06E-21	750
ZWINT	9,90E-23	8,14E-21	6960
RNF145	1,34E-22	1,10E-20	7462
C11ORF96	1,51E-22	1,24E-20	125
YTHDC1	1,76E-22	1,44E-20	6177
LAPTM4A	2,46E-22	2,00E-20	8252
KCNQ1OT1	2,55E-22	2,07E-20	3151
CSF3	2,79E-22	2,26E-20	2188
PNN	3,52E-22	2,85E-20	7870
NAB2	3,73E-22	3,01E-20	3658
MEG3	3,82E-22	3,07E-20	1136
PA2G4	4,07E-22	3,26E-20	8279
CD151	4,62E-22	3,69E-20	8267
MT.ND6	4,75E-22	3,79E-20	7951
DBF4	4,78E-22	3,81E-20	6329
SNHG15	5,79E-22	4,60E-20	6362
ROMO1	6,28E-22	4,98E-20	8250
ZC3H12C	7,69E-22	6,08E-20	2231
DKK1	8,11E-22	6,40E-20	7361
CFL1	9,49E-22	7,47E-20	8321
CBX8	1,02E-21	7,98E-20	1301
CEP170	1,07E-21	8,36E-20	4876
HIST1H1D	1,08E-21	8,45E-20	3972
LSM6	1,14E-21	8,89E-20	7852
PHLDA3	1,15E-21	8,98E-20	6318
SIGMAR1	1,18E-21	9,14E-20	6652
PUF60	1,18E-21	9,15E-20	8018
ANKRD11	1,33E-21	1,03E-19	7869
FOXF1	1,59E-21	1,22E-19	304
COL6A2	1,59E-21	1,22E-19	4746
PPDPF	1,61E-21	1,24E-19	8320
HIVEP3	1,66E-21	1,27E-19	1934
AP2B1	1,71E-21	1,30E-19	7091
PRKCSH	1,71E-21	1,31E-19	5431
DENND3	1,86E-21	1,41E-19	1664
CBLB	1,91E-21	1,45E-19	1135
H2AFZ	2,01E-21	1,52E-19	8321
ARRDC4	2,02E-21	1,53E-19	656
RAC1	2,17E-21	1,63E-19	8321
ESD	2,44E-21	1,83E-19	8161
STXBP2	2,45E-21	1,84E-19	1731
TIMM17A	2,88E-21	2,16E-19	8280
CDK2AP2	3,29E-21	2,46E-19	6245
CALML5	3,38E-21	2,52E-19	75
DCTN6	3,60E-21	2,68E-19	7072
C16ORF74	3,66E-21	2,71E-19	6734
NIFK	4,00E-21	2,95E-19	7918
NAXE	4,00E-21	2,95E-19	7591
HGSNAT	4,37E-21	3,22E-19	2467
BCAS4	4,48E-21	3,30E-19	5938
CNBP	4,66E-21	3,42E-19	8307
GPRC5A	5,14E-21	3,76E-19	1024
B2M	5,41E-21	3,96E-19	8321
FBLN5	5,69E-21	4,15E-19	6278
EMP3	5,85E-21	4,26E-19	8305
EIF2S1	6,02E-21	4,37E-19	7900
FRMD4A	6,65E-21	4,81E-19	4897
RNF167	6,82E-21	4,93E-19	5973
PSMA1	7,27E-21	5,24E-19	8309
SPRY2	8,78E-21	6,32E-19	2480
LBH	1,25E-20	8,97E-19	550
RPS15	1,26E-20	9,04E-19	8321
ZNF580	1,35E-20	9,62E-19	6286
JUNB	1,36E-20	9,68E-19	7119
MLXIP	1,63E-20	1,16E-18	4673
FSTL3	1,82E-20	1,29E-18	6713
LMF2	1,96E-20	1,39E-18	4158
NQO1	2,02E-20	1,43E-18	8293
RHOV	2,03E-20	1,44E-18	324
REEP4	2,31E-20	1,63E-18	5000
TAGLN2	2,45E-20	1,73E-18	8321
THY1	2,60E-20	1,82E-18	6719
LDHA	2,73E-20	1,91E-18	8321
EEF1D	2,74E-20	1,92E-18	8321
BCAP31	2,81E-20	1,96E-18	8165
FZD8	2,85E-20	1,98E-18	1391
UQCRFS1	2,96E-20	2,05E-18	8317
ASS1	3,23E-20	2,24E-18	2020
PAICS	3,35E-20	2,31E-18	8054
FOXC2	3,59E-20	2,48E-18	3612
MED30	4,23E-20	2,91E-18	5571
CCDC88C	4,53E-20	3,12E-18	475
TSTA3	5,08E-20	3,49E-18	8005
IRF6	5,93E-20	4,06E-18	2463
SMC4	6,02E-20	4,11E-18	7624
DYNLT1	6,03E-20	4,11E-18	8288
C12ORF75	6,11E-20	4,15E-18	8290
FABP5	6,27E-20	4,26E-18	8198
PCNA	7,17E-20	4,85E-18	6971
SLC25A39	8,05E-20	5,45E-18	7756
ARPC3	9,43E-20	6,37E-18	8321
FADS2	9,54E-20	6,42E-18	4703
BPGM	9,62E-20	6,47E-18	5672

EXOSC3	1,15E-19	7,72E-18	7549
DDX5	1,27E-19	8,51E-18	8311
PRPF31	1,28E-19	8,55E-18	7559
FKBP1A	1,35E-19	9,03E-18	8318
C5AR1	1,37E-19	9,11E-18	252
PRDX3	1,45E-19	9,62E-18	8105
BAK1	1,69E-19	1,12E-17	4228
SSBP1	1,74E-19	1,15E-17	8317
SKP1	1,79E-19	1,18E-17	8321
CSNK2B	1,87E-19	1,23E-17	8213
CCT2	1,93E-19	1,27E-17	8266
HMGB2	2,01E-19	1,32E-17	7072
LRWD1	2,12E-19	1,39E-17	2420
PYGB	2,32E-19	1,52E-17	6088
PELI1	2,71E-19	1,77E-17	1768
UAP1	2,78E-19	1,81E-17	7916
PHGDH	2,84E-19	1,85E-17	6183
RRBP1	3,67E-19	2,38E-17	8205
SELENOW	3,91E-19	2,53E-17	8305
LUZP1	3,98E-19	2,57E-17	7965
CDK17	4,26E-19	2,75E-17	3458
POLR2F	4,28E-19	2,76E-17	8260
TUBA1A	4,56E-19	2,93E-17	6853
EIF4E	4,81E-19	3,08E-17	7828
RCAN1	5,42E-19	3,47E-17	2363
HNRNPA2B1	6,00E-19	3,83E-17	8321
SPCS2	6,47E-19	4,13E-17	8224
IGF1R	6,53E-19	4,16E-17	3197
TUBB4B	7,90E-19	5,02E-17	8279
CPM	9,22E-19	5,84E-17	732
CCT5	1,00E-18	6,34E-17	8247
MTRNR2L1	1,02E-18	6,45E-17	371
DEPP1	1,07E-18	6,77E-17	481
CYP51A1	1,12E-18	7,07E-17	2060
KLC3	1,16E-18	7,26E-17	2316
MIF	1,19E-18	7,48E-17	8294
RPS17	1,24E-18	7,75E-17	8321
FADS3	1,27E-18	7,93E-17	6937
MZT1	1,49E-18	9,28E-17	7222
MCRIP1	1,63E-18	1,02E-16	6046
PSMC4	1,64E-18	1,02E-16	7695
MAP2K3	1,72E-18	1,06E-16	6120
SUB1	1,74E-18	1,08E-16	8321
CCT8	1,78E-18	1,10E-16	8267
LEPROT	1,81E-18	1,11E-16	7985
NCL	1,84E-18	1,13E-16	8311
TMPO	1,88E-18	1,15E-16	7070
SPRR2D	2,05E-18	1,25E-16	96
CCND1	2,24E-18	1,37E-16	8052
SSB	2,24E-18	1,37E-16	8273
UGP2	2,41E-18	1,47E-16	8047
C7ORF50	2,99E-18	1,82E-16	7878
PSMC2	3,29E-18	2,00E-16	7388
YDJC	3,75E-18	2,27E-16	7467
C1ORF216	4,23E-18	2,56E-16	2369
AC006064.4	4,33E-18	2,62E-16	1275
KRT10	4,52E-18	2,72E-16	8319
SELENOF	5,06E-18	3,04E-16	8184
CSTB	5,09E-18	3,06E-16	8320
KLF7	5,51E-18	3,31E-16	2340
PHAX	5,72E-18	3,43E-16	7989
RRAGA	6,41E-18	3,83E-16	7536
CD68	6,68E-18	3,99E-16	1674
LAMTOR2	6,99E-18	4,16E-16	8049
RCN1	7,66E-18	4,55E-16	7107
TRPV3	7,73E-18	4,59E-16	491
NDC80	8,10E-18	4,80E-16	3894
B3GNT2	8,19E-18	4,85E-16	3668
ZNF703	8,24E-18	4,86E-16	1263
C1QBP	8,46E-18	4,99E-16	8319
AC016831.1	8,50E-18	5,00E-16	916
VPS29	1,13E-17	6,63E-16	8289
NDUFS6	1,13E-17	6,63E-16	8316
TAF7	1,19E-17	6,95E-16	8107
PLAT	1,20E-17	7,02E-16	3507
RING1	1,25E-17	7,31E-16	3304
SRSF7	1,40E-17	8,16E-16	8224
IFI27L2	1,43E-17	8,29E-16	6682
AC011603.2	1,46E-17	8,49E-16	1448
OSR1	1,64E-17	9,49E-16	715
PPP1R10	1,66E-17	9,62E-16	4783
CD82	1,75E-17	1,01E-15	6710
MRFAP1	1,90E-17	1,09E-15	8310
BGN	2,05E-17	1,18E-15	1916
RPS27L	2,36E-17	1,35E-15	8309
B3GAT3	2,37E-17	1,36E-15	4393
MT.CO3	2,40E-17	1,37E-15	8321
ATP5MC2	2,45E-17	1,40E-15	8319
CAV2	2,48E-17	1,42E-15	8215
SNU13	2,49E-17	1,42E-15	8320
BEST1	2,66E-17	1,51E-15	2007
EIF4A3	2,96E-17	1,68E-15	7078
EIF1B	3,04E-17	1,72E-15	7447
HSPE1	3,05E-17	1,73E-15	8320
EID1	3,18E-17	1,80E-15	8305
PSMA4	3,29E-17	1,85E-15	8299
PIM3	3,36E-17	1,89E-15	3170
PSMC6	3,55E-17	1,99E-15	7756
SHISA4	3,93E-17	2,20E-15	2504
PMAIP1	3,99E-17	2,24E-15	6382
UBE2C	4,03E-17	2,25E-15	6806
KIF2C	4,21E-17	2,35E-15	3667
GTPBP4	4,42E-17	2,46E-15	7296
TGFB1	4,45E-17	2,47E-15	6437
LAMP1	4,71E-17	2,62E-15	7466
EIF3A	5,18E-17	2,87E-15	8290
AJUBA	5,35E-17	2,96E-15	4221
F2R	5,79E-17	3,20E-15	5754
TMEM219	6,01E-17	3,32E-15	7036
TUBB	9,04E-17	4,98E-15	8319
RPL15	9,33E-17	5,13E-15	8321
PSAT1	9,57E-17	5,25E-15	6325
CSNK1E	1,06E-16	5,81E-15	5216
KRT5	1,06E-16	5,81E-15	5927
MRPS30	1,10E-16	6,02E-15	6158
MEDAG	1,17E-16	6,39E-15	80
GNAI2	1,19E-16	6,50E-15	8104
PTTG2	1,22E-16	6,63E-15	358
DCN	1,29E-16	7,02E-15	3116
GRN	1,30E-16	7,05E-15	6948
NUF2	1,45E-16	7,83E-15	4402
AKR1B1	1,47E-16	7,92E-15	8263
FAM50A	1,48E-16	7,95E-15	6963
UBE2V1	1,59E-16	8,54E-15	1899
NOL11	1,67E-16	8,95E-15	5027
TSPO	1,69E-16	9,05E-15	8321
IGFBP6	1,71E-16	9,17E-15	5120
ARL6IP1	1,82E-16	9,73E-15	6173
FMNL1	2,00E-16	1,07E-14	1205

CCM2	2,03E-16	1,08E-14	7380
BRI3BP	2,04E-16	1,09E-14	4249
NUSAP1	2,27E-16	1,21E-14	6243
SNAPC1	2,34E-16	1,24E-14	4624
SRI	2,83E-16	1,50E-14	8243
UBC	3,10E-16	1,64E-14	8315
ABCA1	3,33E-16	1,75E-14	2560
ACTN4	3,38E-16	1,78E-14	7681
AXL	3,68E-16	1,93E-14	7178
KHDRBS1	3,94E-16	2,07E-14	8280
SH2B3	4,05E-16	2,12E-14	3994
GASAL1	4,14E-16	2,16E-14	1923
ZNF205	4,42E-16	2,31E-14	1549
POLR2I	4,50E-16	2,35E-14	8149
GSTP1	4,66E-16	2,43E-14	8321
ATP5F1A	5,15E-16	2,68E-14	8317
CHCHD5	5,56E-16	2,89E-14	6870
HAT1	5,60E-16	2,90E-14	6909
TXNDC9	6,01E-16	3,11E-14	7917
EIF4A1	6,24E-16	3,23E-14	8292
MAP1LC3A	6,34E-16	3,27E-14	1753
TANK	6,46E-16	3,33E-14	6367
AL049629.2	7,10E-16	3,65E-14	2363
CBX4	7,26E-16	3,73E-14	1372
IRF2BP1	7,75E-16	3,97E-14	751
DYNLRB1	8,02E-16	4,11E-14	8276
IRF3	8,04E-16	4,11E-14	5049
ARHGAP11A	9,11E-16	4,65E-14	4625
CHPT1	9,32E-16	4,75E-14	6538
MRPL14	9,79E-16	4,98E-14	8314
PHACTR3	1,05E-15	5,33E-14	2884
FAM89B	1,07E-15	5,42E-14	3369
AC006262.2	1,12E-15	5,66E-14	621
LCE3D	1,33E-15	6,72E-14	262
RBM39	1,52E-15	7,65E-14	8309
CCNL1	1,56E-15	7,86E-14	5839
AP1S3	1,62E-15	8,17E-14	4020
ARL6IP5	1,66E-15	8,36E-14	7932
LAMA3	1,85E-15	9,27E-14	4095
LTB	1,85E-15	9,27E-14	501
MRPS6	1,97E-15	9,85E-14	8231
SCAMP3	2,02E-15	1,01E-13	5074
PRMT2	2,05E-15	1,02E-13	7858
TIMM13	2,19E-15	1,09E-13	8317
COX8A	2,25E-15	1,12E-13	8321
CENPF	2,34E-15	1,16E-13	5826
CERCAM	2,35E-15	1,17E-13	2622
SMARCE1	2,49E-15	1,23E-13	4314
KRTAP2.3	2,71E-15	1,34E-13	433
PPA1	2,76E-15	1,36E-13	8318
IKBIP	2,81E-15	1,39E-13	8055
C19ORF53	2,95E-15	1,45E-13	8320
PSMC5	3,17E-15	1,56E-13	8294
KRT81	3,32E-15	1,63E-13	4702
EBP	3,32E-15	1,63E-13	8190
LRRC59	3,33E-15	1,63E-13	8279
PRMT1	3,49E-15	1,71E-13	8016
CDCA2	3,73E-15	1,82E-13	3506
CDKN3	3,81E-15	1,86E-13	7289
C5AR2	4,49E-15	2,18E-13	314
SLC9A3R2	4,54E-15	2,21E-13	1559
UBE2V2	4,55E-15	2,21E-13	8178
SPCS1	4,59E-15	2,23E-13	8321
ZFAND5	4,67E-15	2,26E-13	5990
ELK3	5,00E-15	2,41E-13	6635
PSMA5	5,01E-15	2,42E-13	8238
ZFP36	5,08E-15	2,45E-13	4820
RHBDD2	5,59E-15	2,69E-13	4360
TRMT1	6,10E-15	2,93E-13	3775
NAA38	6,54E-15	3,14E-13	8129
TLE1	6,74E-15	3,23E-13	2924
OSTC	7,35E-15	3,51E-13	8312
ILF2	7,67E-15	3,67E-13	8163
RPL37A	7,69E-15	3,67E-13	8321
GADD45GIP1	8,05E-15	3,84E-13	8320
ANKRD9	8,34E-15	3,97E-13	2051
RPL41	8,36E-15	3,97E-13	8321
NMT1	9,09E-15	4,31E-13	5370
PRR34.AS1	9,17E-15	4,34E-13	6403
SLC1A5	9,53E-15	4,51E-13	5960
ISG20	9,69E-15	4,58E-13	3557
NIP7	1,01E-14	4,75E-13	7034
CTSB	1,09E-14	5,13E-13	8253
RBM26	1,12E-14	5,27E-13	6050
SNHG7	1,14E-14	5,35E-13	7878
TMSB10	1,21E-14	5,67E-13	8321
BOP1	1,23E-14	5,78E-13	7164
CLPTM1	1,25E-14	5,86E-13	5234
MIR4435.2HG	1,28E-14	5,96E-13	8220
METRNL	1,36E-14	6,34E-13	905
SERPINF1	1,44E-14	6,73E-13	1390
LCE1B	1,53E-14	7,14E-13	53
PHB2	1,67E-14	7,74E-13	8203
SLC25A5	1,73E-14	8,04E-13	8319
SHARPIN	1,79E-14	8,30E-13	6991
MINOS1	1,80E-14	8,35E-13	8321
BCAM	1,83E-14	8,43E-13	2612
TPBG	1,86E-14	8,59E-13	7883
GABARAP	1,98E-14	9,11E-13	1825
EPN3	2,13E-14	9,82E-13	2517
CLDN4	2,17E-14	9,96E-13	128
YRDC	2,24E-14	1,03E-12	3001
SETD1B	2,44E-14	1,12E-12	1394
MCOLN1	2,61E-14	1,20E-12	2585
CDKN1A	2,71E-14	1,24E-12	6672
CXCL2	2,80E-14	1,28E-12	1197
ILK	3,12E-14	1,42E-12	7713
IL6R	3,24E-14	1,47E-12	2622
SC5D	3,26E-14	1,48E-12	6157
AP2A1	3,32E-14	1,51E-12	3592
TM4SF1	3,35E-14	1,52E-12	8041
ATP5MC3	3,58E-14	1,62E-12	8320
MED28	3,60E-14	1,63E-12	7797
SLC27A5	3,73E-14	1,68E-12	5263
TYMS	4,13E-14	1,86E-12	7544
FKBP10	4,24E-14	1,91E-12	5907
GTSE1	4,42E-14	1,99E-12	4998
GAS6	4,56E-14	2,05E-12	7159
GAS1	4,67E-14	2,09E-12	182
GDI1	4,73E-14	2,12E-12	3770
TCF25	5,19E-14	2,32E-12	7687
UBE2L3	5,29E-14	2,36E-12	8318
DDX21	5,41E-14	2,41E-12	8170
KLK5	5,70E-14	2,54E-12	1366
COL7A1	6,16E-14	2,74E-12	4924
CKAP2	6,30E-14	2,80E-12	6124
RACGAP1	6,60E-14	2,93E-12	3725
PCLAF	6,75E-14	2,99E-12	7853
ASAP1	7,28E-14	3,22E-12	7697

GSK3A	7,28E-14	3,22E-12	3635
YIF1A	7,29E-14	3,22E-12	8160
RABGGTB	7,32E-14	3,23E-12	7736
TRIR	7,75E-14	3,41E-12	8306
SDHC	8,34E-14	3,66E-12	8253
DUSP11	8,66E-14	3,80E-12	6399
C19ORF48	8,71E-14	3,82E-12	7979
ADAM15	8,82E-14	3,86E-12	5822
CCDC124	8,85E-14	3,87E-12	7717
ANXA2	9,19E-14	4,01E-12	8321
KCNJ15	9,53E-14	4,16E-12	1593
XAB2	9,70E-14	4,23E-12	1077
ZNF207	9,72E-14	4,23E-12	7958
TMED10	9,93E-14	4,31E-12	8127
ARL2	1,01E-13	4,36E-12	7469
ICAM3	1,01E-13	4,36E-12	4350
ITGA2	1,02E-13	4,41E-12	3427
RPL27A	1,02E-13	4,42E-12	8321
HNRNPF	1,06E-13	4,58E-12	8144
SEMA7A	1,13E-13	4,89E-12	1786
ATP1B1	1,15E-13	4,97E-12	6999
PCBP1	1,17E-13	5,03E-12	8300
H3F3A	1,18E-13	5,05E-12	8319
SLC38A2	1,24E-13	5,32E-12	7517
EBNA1BP2	1,25E-13	5,37E-12	8286
ANAPC10	1,26E-13	5,38E-12	4882
EEF1A1	1,26E-13	5,38E-12	8321
SINHCAF	1,27E-13	5,42E-12	5327
CYCS	1,33E-13	5,65E-12	8317
SOCS2	1,33E-13	5,68E-12	5624
PEG10	1,38E-13	5,88E-12	5879
RPL34	1,51E-13	6,40E-12	8321
LY6K	1,53E-13	6,48E-12	6481
ADAMTSL4	1,54E-13	6,51E-12	566
CDK16	1,62E-13	6,83E-12	5977
ADRB2	1,71E-13	7,22E-12	2856
IRX4	1,72E-13	7,25E-12	2223
FKBP3	1,77E-13	7,46E-12	8221
NFKBID	1,82E-13	7,64E-12	1153
OAT	1,87E-13	7,84E-12	7755
VPS4A	1,95E-13	8,15E-12	6783
SNX3	1,97E-13	8,26E-12	8320
C17ORF53	2,01E-13	8,39E-12	923
PRPSAP1	2,12E-13	8,83E-12	6104
FADS1	2,12E-13	8,83E-12	7826
PPP1R15A	2,17E-13	9,03E-12	4904
NDUFB6	2,33E-13	9,71E-12	8275
N4BP2L2	2,51E-13	1,04E-11	7475
HIST2H2AC	2,60E-13	1,08E-11	4519
PKMYT1	2,64E-13	1,09E-11	4812
MAP1S	2,69E-13	1,11E-11	1661
WRAP53	2,73E-13	1,13E-11	2864
DNAJA1	2,80E-13	1,16E-11	8266
CYP1B1	2,82E-13	1,16E-11	1103
PKP3	2,91E-13	1,20E-11	3698
PARVB	3,23E-13	1,33E-11	2339
ZNF706	3,24E-13	1,33E-11	8317
PLP2	3,42E-13	1,40E-11	8318
SUSD6	3,42E-13	1,40E-11	1719
RPL8	3,59E-13	1,47E-11	8321
ISCA2	3,67E-13	1,50E-11	6979
RAB1A	3,73E-13	1,52E-11	8285
RPS4X	3,96E-13	1,61E-11	8321
SAP18	4,09E-13	1,67E-11	8315
C8ORF82	4,56E-13	1,86E-11	3655
DNASE2	4,68E-13	1,90E-11	4130
PCDH9	4,92E-13	2,00E-11	2446
CDKN2B	5,00E-13	2,03E-11	2614
PCOLCE	5,15E-13	2,09E-11	5315
UXS1	5,34E-13	2,16E-11	4775
TXNRD2	5,55E-13	2,24E-11	5961
S100A8	5,79E-13	2,34E-11	1231
S100A2	6,08E-13	2,45E-11	8321
MDFI	6,29E-13	2,53E-11	3446
ATP6AP2	6,51E-13	2,62E-11	6817
POLR2K	6,74E-13	2,71E-11	8276
SFXN5	6,80E-13	2,73E-11	3659
GNPDA1	6,98E-13	2,80E-11	6880
HIVEP2	7,10E-13	2,84E-11	1494
SMARCB1	7,38E-13	2,95E-11	7691
RAB11A	7,53E-13	3,01E-11	8049
CDCA3	7,94E-13	3,16E-11	5285
H3F3C	8,12E-13	3,24E-11	687
TAF10	8,18E-13	3,26E-11	6696
ANGPTL4	8,41E-13	3,34E-11	5667
COPS8	8,54E-13	3,39E-11	8259
BAG3	8,76E-13	3,47E-11	6101
SARS	8,80E-13	3,49E-11	7769
RPL35	9,19E-13	3,64E-11	8321
PGAM1	9,44E-13	3,73E-11	8321
UMPS	9,73E-13	3,84E-11	5547
ANP32A	1,01E-12	3,96E-11	6628
CCPG1	1,04E-12	4,07E-11	4376
ZC3H12A	1,04E-12	4,07E-11	2018
ANXA5	1,04E-12	4,08E-11	8320
FLNA	1,06E-12	4,16E-11	7722
UBB	1,08E-12	4,24E-11	8321
CYC1	1,15E-12	4,49E-11	8318
ZSWIM6	1,16E-12	4,52E-11	2519
SERPINA1	1,16E-12	4,55E-11	740
MED31	1,22E-12	4,76E-11	6940
CSF2	1,23E-12	4,81E-11	824
OXSR1	1,24E-12	4,81E-11	6308
SDHB	1,29E-12	5,00E-11	8266
NECTIN2	1,31E-12	5,08E-11	4292
MVD	1,33E-12	5,14E-11	7267
ADH5	1,38E-12	5,35E-11	7995
TRAPPC4	1,41E-12	5,46E-11	7725
CHID1	1,51E-12	5,84E-11	4621
FDPS	1,53E-12	5,90E-11	8311
VGLL3	1,62E-12	6,26E-11	520
PNPLA2	1,65E-12	6,34E-11	2293
SAR1B	1,68E-12	6,47E-11	7807
C12ORF45	1,74E-12	6,68E-11	7148
GTF3C6	1,78E-12	6,82E-11	8306
GHITM	1,78E-12	6,83E-11	8276
SNHG8	1,84E-12	7,04E-11	8102
EIF5	1,85E-12	7,08E-11	8295
SMS	1,98E-12	7,57E-11	8286
NUDCD1	2,00E-12	7,64E-11	6604
QTRT1	2,01E-12	7,67E-11	4754
NUP37	2,03E-12	7,75E-11	6306
DSP	2,06E-12	7,83E-11	3849
MRPS23	2,25E-12	8,54E-11	8083
NOP53	2,27E-12	8,61E-11	8108
GPCPD1	2,30E-12	8,73E-11	1644
USP5	2,42E-12	9,17E-11	1720
STX1A	2,47E-12	9,34E-11	1090
OTUD1	2,54E-12	9,60E-11	428

PI3	2,72E-12	1,03E-10	316
MRPL3	2,73E-12	1,03E-10	8188
COMMD1	2,94E-12	1,11E-10	6939
SFXN3	3,08E-12	1,16E-10	2885
SLC19A2	3,09E-12	1,16E-10	1318
SLC25A10	3,11E-12	1,17E-10	3576
ARGLU1	3,12E-12	1,17E-10	8074
HPCAL1	3,14E-12	1,18E-10	7442
RPL30	3,31E-12	1,24E-10	8321
LINC02043	3,34E-12	1,25E-10	229
ZBTB21	3,65E-12	1,36E-10	2377
PLA2R1	3,65E-12	1,36E-10	1867
GABARAPL1	3,65E-12	1,36E-10	967
ZNF217	3,73E-12	1,39E-10	3515
TMEM60	3,77E-12	1,40E-10	5711
AC004816.1	3,92E-12	1,45E-10	3587
METTL23	3,94E-12	1,46E-10	7222
PMEPA1	4,14E-12	1,53E-10	5438
EIF4H	4,16E-12	1,54E-10	8198
WDR61	4,28E-12	1,58E-10	6353
IGF2BP2	4,34E-12	1,60E-10	7951
PITPNA	4,52E-12	1,67E-10	4327
ZMYND19	4,56E-12	1,68E-10	1882
BUB1	4,59E-12	1,69E-10	3848
NDRG1	4,68E-12	1,72E-10	4617
NOB1	4,86E-12	1,78E-10	7406
BCAS2	4,94E-12	1,81E-10	7476
CHTOP	5,17E-12	1,89E-10	6996
CKS1B	5,19E-12	1,90E-10	8154
EEF1B2	5,21E-12	1,90E-10	8321
VIM	5,22E-12	1,90E-10	8309
SMC3	5,33E-12	1,94E-10	7720
DDX17	5,54E-12	2,02E-10	7727
AL133453.1	5,68E-12	2,07E-10	3693
PITPNB	5,80E-12	2,11E-10	7200
ARPC5	5,90E-12	2,14E-10	8308
CHMP5	6,02E-12	2,18E-10	7830
TTK	6,08E-12	2,20E-10	2456
PTPN12	6,23E-12	2,25E-10	6699
MTMR14	6,64E-12	2,40E-10	3438
TMEM126B	6,70E-12	2,42E-10	7692
CPEB4	6,71E-12	2,42E-10	2884
DLGAP1.AS1	6,79E-12	2,45E-10	1202
GSN	6,83E-12	2,46E-10	6149
ZBED2	6,87E-12	2,47E-10	3206
NDUFB11	7,08E-12	2,54E-10	8292
GABARAPL2	7,19E-12	2,58E-10	8271
SPARC	7,22E-12	2,59E-10	8242
SUMO1	7,42E-12	2,65E-10	8319
MAFF	7,66E-12	2,74E-10	3338
AUP1	7,76E-12	2,77E-10	8119
ARHGAP21	7,81E-12	2,79E-10	4751
ATP13A2	8,19E-12	2,92E-10	4236
RHOG	8,40E-12	2,99E-10	7039
SYMPK	8,59E-12	3,05E-10	2502
CDKN2A	8,64E-12	3,07E-10	8239
GPC1	8,73E-12	3,10E-10	4567
DNMBP	8,82E-12	3,13E-10	2179
S100A10	8,93E-12	3,16E-10	8321
ACAT2	9,94E-12	3,52E-10	8099
NDUFA4	1,03E-11	3,65E-10	8321
DYRK2	1,04E-11	3,66E-10	2956
SIK1	1,07E-11	3,76E-10	229
CTSL	1,07E-11	3,78E-10	7211
HACD3	1,08E-11	3,79E-10	7237
C1ORF116	1,09E-11	3,84E-10	1516
DTYMK	1,15E-11	4,02E-10	8143
PGP	1,18E-11	4,14E-10	8182
TMEM141	1,25E-11	4,37E-10	7748
SCD	1,27E-11	4,43E-10	8291
HMOX2	1,27E-11	4,46E-10	6948
RTN4	1,32E-11	4,61E-10	8320
PLIN3	1,46E-11	5,10E-10	7798
RFC2	1,47E-11	5,12E-10	5989
IL32	1,51E-11	5,25E-10	985
PNRC2	1,51E-11	5,25E-10	7316
CXORF40B	1,54E-11	5,36E-10	2385
OST4	1,55E-11	5,39E-10	8320
WAPL	1,56E-11	5,40E-10	7101
DNAJC1	1,58E-11	5,47E-10	7664
CHPF2	1,68E-11	5,81E-10	2978
UCHL1	1,68E-11	5,81E-10	203
PTGES3	1,69E-11	5,85E-10	8316
SNRPA	1,71E-11	5,90E-10	6233
MRPL36	1,74E-11	5,99E-10	8294
PCMT1	1,74E-11	6,00E-10	8288
MTRNR2L3	1,81E-11	6,24E-10	269
TOMM7	1,83E-11	6,29E-10	8321
FAM3A	1,93E-11	6,63E-10	3948
CCNE2	1,95E-11	6,70E-10	2260
MVK	2,02E-11	6,91E-10	4874
HIST1H1B	2,02E-11	6,92E-10	3370
LSM5	2,05E-11	7,01E-10	8312
SNX9	2,09E-11	7,15E-10	6360
CHRNA9	2,10E-11	7,15E-10	130
CHAC2	2,20E-11	7,48E-10	4564
ELOF1	2,21E-11	7,52E-10	7671
CDK6	2,31E-11	7,86E-10	6850
SEC61B	2,31E-11	7,86E-10	8321
VAC14	2,32E-11	7,86E-10	1771
ZMYM4	2,43E-11	8,23E-10	5672
MYL12B	2,49E-11	8,43E-10	8320
SIL1	2,50E-11	8,48E-10	6048
TCEAL4	2,55E-11	8,62E-10	8118
RPL3	2,62E-11	8,86E-10	8321
HGH1	2,66E-11	8,97E-10	2227
PARK7	2,68E-11	9,03E-10	8321
CCDC107	2,70E-11	9,08E-10	6901
ATP5PF	2,74E-11	9,21E-10	8321
CSTF3	2,79E-11	9,37E-10	6556
ZRANB2	2,80E-11	9,38E-10	7479

Supplement table S2.

(Significantly downregulated biological pathways in 1 min oscillatory condition).

Category	Overrepresented p-value	numDEInCat	Term
GO:0007049	6.55353292145036e-33	283	cell cycle
GO:0000278	6.74562388019394e-31	185	mitotic cell cycle
GO:1903047	4.04784203269682e-29	164	mitotic cell cycle process
GO:0022402	6.07450615059027e-29	221	cell cycle process
GO:0051276	2.44155362566763e-26	202	chromosome organization
GO:0010564	5.78324830586916e-26	144	regulation of cell cycle process
GO:0090304	2.26961790443797e-23	543	nucleic acid metabolic process
GO:0051726	3.37424289734685e-23	188	regulation of cell cycle
GO:0007346	5.32096264804285e-23	122	regulation of mitotic cell cycle
GO:0007059	3.03225770379425e-21	81	chromosome segregation
GO:0098813	2.60887813084557e-20	71	nuclear chromosome segregation
GO:0080090	6.71336337328417e-20	598	regulation of primary metabolic process
GO:0000819	1.12420116818081e-19	59	sister chromatid segregation
GO:1901987	1.20833399847538e-19	87	regulation of cell cycle phase transition
GO:1901990	1.71289241986604e-19	83	regulation of mitotic cell cycle phase transition
GO:0043170	2.25531528164928e-19	827	macromolecule metabolic process
GO:0044772	4.91542778977299e-19	101	mitotic cell cycle phase transition
GO:0044770	7.8438916730491e-19	105	cell cycle phase transition
GO:0051171	8.61198720814212e-19	580	regulation of nitrogen compound metabolic process
GO:0006139	1.0408547916832e-18	565	nucleobase-containing compound metabolic process
GO:0046483	2.137719111115469e-18	573	heterocycle metabolic process
GO:0031323	2.585073737340063e-18	600	regulation of cellular metabolic process
GO:0140014	2.675158437163934e-18	73	mitotic nuclear division
GO:1901360	3.45238229480322e-18	588	organic cyclic compound metabolic process
GO:0006996	3.9988761745249e-18	436	organelle organization
GO:0016070	4.98963900368372e-18	478	RNA metabolic process
GO:0000280	5.7230961256347e-18	89	nuclear division
GO:0019222	1.42415636952134e-17	633	regulation of metabolic process
GO:0010467	1.60724687534794e-17	536	gene expression
GO:0006725	1.999210136565534e-17	572	cellular aromatic compound metabolic process
GO:0044260	2.41466578898426e-17	745	cellular macromolecule metabolic process
GO:0034641	3.5889751530572e-17	602	cellular nitrogen compound metabolic process
GO:0050794	6.068628201886644e-17	888	regulation of cellular process
GO:0060255	9.4237273662998e-17	593	regulation of macromolecule metabolic process
GO:0051301	1.093717472275545e-16	109	cell division
GO:0048285	1.26985001885028e-16	92	organelle fission
GO:0044237	5.558112083283777e-16	882	cellular metabolic process
GO:0019219	6.88375379939769e-16	430	regulation of nucleobase-containing compound metabolic process
GO:0016071	7.330139747463666e-16	118	mRNA metabolic process
GO:0000070	8.02743367658327e-16	49	mitotic sister chromatid segregation
GO:0006807	1.035358065256484e-15	843	nitrogen compound metabolic process
GO:0008380	1.05374364036256e-15	80	RNA splicing
GO:0006397	3.310437249771731e-15	87	mRNA processing
GO:0006974	1.51883880509515e-14	128	cellular response to DNA damage stimulus
GO:0000075	1.62722886144538e-14	54	cell cycle checkpoint
GO:0051252	1.66561995492441e-14	401	regulation of RNA metabolic process
GO:0044238	1.71298667281671e-14	866	primary metabolic process
GO:0071840	2.045908330166055e-14	634	cellular component organization or biogenesis
GO:0007052	2.806181167432655e-14	39	mitotic spindle organization
GO:0050789	4.352423252031384e-14	915	regulation of biological process
GO:0016043	4.6209723297402e-14	621	cellular component organization
GO:1902850	5.762775154773334e-14	43	microtubule cytoskeleton organization involved in mitosis
GO:0010468	6.73869594645416e-14	452	regulation of gene expression
GO:1902749	1.213525463795664e-13	47	regulation of cell cycle G2/M phase transition
GO:0009889	1.249726124587884e-13	433	regulation of biosynthetic process
GO:1901991	1.458938063064455e-13	46	negative regulation of mitotic cell cycle phase transition
GO:0044839	1.796208092940134e-13	54	cell cycle G2/M phase transition
GO:0006259	1.818198510945974e-13	139	DNA metabolic process
GO:0000226	2.259664779488964e-13	103	microtubule cytoskeleton organization
GO:0033044	2.529708680569414e-13	71	regulation of chromosome organization
GO:0007093	2.604261788028754e-13	44	mitotic cell cycle checkpoint
GO:0008152	3.015656039624474e-13	914	metabolic process
GO:0033043	3.277618608312644e-13	178	regulation of organelle organization
GO:0009987	3.762514961557824e-13	1158	cellular process
GO:0010605	3.940636760882564e-13	295	negative regulation of macromolecule metabolic process
GO:2000112	4.911357281092134e-13	406	regulation of cellular macromolecule biosynthetic process
GO:0007017	5.042161933320474e-13	128	microtubule-based process
GO:1901988	5.130755567122164e-13	47	negative regulation of cell cycle phase transition
GO:0071704	5.490859648212294e-13	884	organic substance metabolic process
GO:0007051	5.562874146026724e-13	47	spindle organization
GO:0000375	6.069660312186964e-13	63	RNA splicing, via transesterification reactions
GO:0009892	6.081533166609054e-13	313	negative regulation of metabolic process
GO:0010556	1.1129890477154904e-12	413	regulation of macromolecule biosynthetic process
GO:0033554	1.177326492257484e-12	228	cellular response to stress
GO:0000377	1.380793812029014e-12	62	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile
GO:0000398	1.380793812029014e-12	62	mRNA splicing, via spliceosome
GO:0031326	1.556313500822944e-12	421	regulation of cellular biosynthetic process
GO:0010389	1.625644931936434e-12	43	regulation of G2/M transition of mitotic cell cycle
GO:0000086	1.637023100470334e-12	50	G2/M transition of mitotic cell cycle
GO:0010948	2.504617641494134e-12	59	negative regulation of cell cycle process
GO:0006325	2.559525548833374e-12	120	chromatin organization
GO:0000077	3.166685240931294e-12	40	DNA damage checkpoint
GO:0031570	3.208742701021094e-12	42	DNA integrity checkpoint
GO:0045786	3.398337889074434e-12	93	negative regulation of cell cycle
GO:0051172	3.704667965402634e-12	265	negative regulation of nitrogen compound metabolic process
GO:0031324	3.855289985246864e-12	278	negative regulation of cellular metabolic process
GO:0010629	4.010806151643094e-12	217	negative regulation of gene expression
GO:0006396	8.0100306806849e-12	121	RNA processing
GO:1901362	8.469332331388234e-12	428	organic cyclic compound biosynthetic process
GO:0051983	9.33300730500772e-12	34	regulation of chromosome segregation
GO:0034645	1.024838642898914e-11	466	cellular macromolecule biosynthetic process
GO:0044267	1.0501158582061e-11	481	cellular protein metabolic process
GO:0044271	1.330517864027154e-11	459	cellular nitrogen compound biosynthetic process
GO:0051128	1.526305370893314e-11	291	regulation of cellular component organization
GO:0007062	1.733827165151264e-11	23	sister chromatid cohesion
GO:0044403	1.947235027004194e-11	111	symbiont process
GO:0048523	2.161460168397294e-11	453	negative regulation of cellular process
GO:0045930	2.241464972755114e-11	54	negative regulation of mitotic cell cycle
GO:0006351	2.248877701260114e-11	371	transcription, DNA-templated
GO:0097659	2.353986985631774e-11	374	nucleic acid-templated transcription
GO:0009059	2.944506951113334e-11	474	macromolecule biosynthetic process
GO:0016032	3.697586173546974e-11	105	viral process
GO:0032774	3.700601280610624e-11	374	RNA biosynthetic process
GO:0018130	4.52676853678594e-11	415	heterocycle biosynthetic process
GO:0044419	4.965393668589724e-11	111	interspecies interaction between organisms
GO:0048522	5.199389071515334e-11	494	positive regulation of cellular process
GO:2001251	5.222464649873984e-11	39	negative regulation of chromosome organization
GO:0045787	6.800514474679324e-11	68	positive regulation of cell cycle
GO:0019438	9.193325434456174e-11	414	aromatic compound biosynthetic process
GO:0010558	1.006285528705264e-10	183	negative regulation of macromolecule biosynthetic process
GO:0034654	1.014633364879554e-10	409	nucleobase-containing compound biosynthetic process
GO:0048519	1.052885530858624e-10	490	negative regulation of biological process
GO:2000113	1.275300782751324e-10	176	negative regulation of cellular macromolecule biosynthetic process
GO:1903311	1.944223120915584e-10	54	regulation of mRNA metabolic process
GO:0006355	2.043106026771344e-10	354	regulation of transcription, DNA-templated
GO:1903506	2.113608320013824e-10	358	regulation of nucleic acid-templated transcription
GO:2001141	2.428562860831394e-10	358	regulation of RNA biosynthetic process
GO:0048518	2.489138929166944e-10	538	positive regulation of biological process
GO:0007088	2.737224653723074e-10	43	regulation of mitotic nuclear division

GO:0045934	3.10611091347499e-10	178	negative regulation of nucleobase-containing compound metabolic process
GO:0009890	3.15587554438368e-10	187	negative regulation of biosynthetic process
GO:0031327	3.56189273622718e-10	185	negative regulation of cellular biosynthetic process
GO:0065007	3.79415802879704e-10	938	biological regulation
GO:0090068	3.8743269089432e-10	54	positive regulation of cell cycle process
GO:0010604	4.193600135334 43e-10	334	positive regulation of macromolecule metabolic process
GO:0051173	6.211304212346 75e-10	318	positive regulation of nitrogen compound metabolic process
GO:0006281	9.480596500119 39e-10	81	DNA repair
GO:0016569	1.323934850214 94e-09	82	covalent chromatin modification
GO:0042770	1.326476391759 47e-09	34	signal transduction in response to DNA damage
GO:0044265	2.050407957174 02e-09	137	cellular macromolecule catabolic process
GO:0031325	3.278156234372e-09	325	positive regulation of cellular metabolic process
GO:0006950	3.344925858625 14e-09	344	response to stress
GO:0043412	3.53893281427 52e-09	413	macromolecule modification
GO:1901576	3.553553831250 41e-09	534	organic substance biosynthetic process
GO:0016570	3.625906957152 44e-09	80	histone modification
GO:0033045	3.779776564811 54e-09	26	regulation of sister chromatid segregation
GO:0044774	4.280892198555 82e-09	29	mitotic DNA integrity checkpoint
GO:0006464	5.208214537225 55e-09	399	cellular protein modification process
GO:0036211	5.208214537225 55e-09	399	protein modification process
GO:0033047	5.961065975602 91e-09	24	regulation of mitotic sister chromatid segregation
GO:0051783	7.716291962886 11e-09	43	regulation of nuclear division
GO:0007010	8.144143351052 58e-09	180	cytoskeleton organization
GO:0044773	8.747076828513 77e-09	27	mitotic DNA damage checkpoint
GO:0019538	8.959039257539 09e-09	502	protein metabolic process
GO:0009893	1.064521423419 37e-08	347	positive regulation of metabolic process
GO:0010628	1.234881086749 67e-08	215	positive regulation of gene expression
GO:0007098	1.26548728991111e-08	33	centrosome cycle
GO:0033046	1.338972476356 44e-08	18	negative regulation of sister chromatid segregation
GO:0051985	1.338972476356 44e-08	18	negative regulation of chromosome segregation
GO:0031023	1.352608159689 44e-08	35	microtubule organizing center organization
GO:0008283	1.360818939389 57e-08	207	cell proliferation
GO:0009058	1.384268775379 97e-08	535	biosynthetic process
GO:0019884	1.538709994455 83e-08	29	antigen processing and presentation of exogenous antigen
GO:0044249	1.898285014099 68e-08	522	cellular biosynthetic process
GO:0051641	1.988471232725 31e-08	303	cellular localization
GO:0009057	2.269017575261 35e-08	155	macromolecule catabolic process
GO:0071103	2.335450347450 23e-08	45	DNA conformation change
GO:0033048	3.318854440747 73e-08	17	negative regulation of mitotic sister chromatid segregation
GO:0070727	3.519889802720 91e-08	208	cellular macromolecule localization
GO:0072401	4.266771623706 84e-08	22	signal transduction involved in DNA integrity checkpoint
GO:0072422	4.266771623706 84e-08	22	signal transduction involved in DNA damage checkpoint
GO:0032268	4.555062888461 64e-08	255	regulation of cellular protein metabolic process
GO:0045935	4.862037090974 85e-08	206	positive regulation of nucleobase-containing compound metabolic process
GO:0071310	5.283719603787 48e-08	254	cellular response to organic substance
GO:0034613	5.625657940504 98e-08	206	cellular protein localization
GO:0051246	6.696847458229 08e-08	269	regulation of protein metabolic process
GO:0051304	7.252972316543 03e-08	25	chromosome separation
GO:0051254	7.872621337359 65e-08	190	positive regulation of RNA metabolic process
GO:0006366	8.150672383127 35e-08	286	transcription by RNA polymerase II
GO:0072395	8.340629300733 05e-08	22	signal transduction involved in cell cycle checkpoint
GO:0051253	9.057200222754 71e-08	155	negative regulation of RNA metabolic process
GO:1905818	9.314054144003 87e-08	20	regulation of chromosome separation
GO:0002478	9.3411892308601e-08	27	antigen processing and presentation of exogenous peptide antigen
GO:0045841	1.067943482825 83e-07	15	negative regulation of mitotic metaphase/anaphase transition
GO:1902100	1.067943482825 83e-07	15	negative regulation of metaphase/anaphase transition of cell cycle
GO:2000045	1.113349364863e-07	31	regulation of G1/S transition of mitotic cell cycle
GO:1902806	1.151884208705 43e-07	33	regulation of cell cycle G1/S phase transition
GO:0070647	1.295802416766 58e-07	129	protein modification by small protein conjugation or removal
GO:0031571	1.329325984391 14e-07	20	mitotic G1 DNA damage checkpoint
GO:0044819	1.329325984391 14e-07	20	mitotic G1/S transition checkpoint
GO:0044085	1.427363111735 748e-07	320	cellular component biogenesis
GO:0044843	1.453414802566 9e-07	45	cell cycle G1/S phase transition
GO:1905819	1.599781925505 03e-07	15	negative regulation of chromosome separation
GO:2000816	1.599781925505 03e-07	15	negative regulation of mitotic sister chromatid separation
GO:0000082	1.655983731229 16e-07	43	G1/S transition of mitotic cell cycle
GO:0044783	1.776851072948 86e-07	20	G1 DNA damage checkpoint
GO:2000134	2.033402451936 77e-07	25	negative regulation of G1/S transition of mitotic cell cycle
GO:0070507	2.209978141749 87e-07	40	regulation of microtubule cytoskeleton organization
GO:0009719	2.242352120516 71e-07	179	response to endogenous stimulus
GO:0051310	2.282970132576 56e-07	18	metaphase plate congression
GO:0008608	2.984188100920 03e-07	13	attachment of spindle microtubules to kinetochore
GO:1902807	3.459250187233 33e-07	25	negative regulation of cell cycle G1/S phase transition
GO:0044257	3.610325260861 99e-07	96	cellular protein catabolic process
GO:0030330	3.654258405066 74e-07	26	DNA damage response, signal transduction by p53 class mediator
GO:0007094	3.852338653111 39e-07	14	mitotic spindle assembly checkpoint
GO:0031577	3.852338653111 39e-07	14	spindle checkpoint
GO:0071173	3.852338653111 39e-07	14	spindle assembly checkpoint
GO:0071174	3.852338653111 39e-07	14	mitotic spindle checkpoint
GO:0051225	4.067868940045 84e-07	27	spindle assembly
GO:0045132	5.032374426061 68e-07	21	meiotic chromosome segregation
GO:0045839	5.483580849811 63e-07	17	negative regulation of mitotic nuclear division
GO:0006260	6.061162533917 08e-07	47	DNA replication
GO:1902275	6.169379487851 81e-07	37	regulation of chromatin organization
GO:0007091	6.208772698490 13e-07	18	metaphase/anaphase transition of mitotic cell cycle
GO:0032886	6.498246659112 28e-07	43	regulation of microtubule-based process
GO:0045893	7.045278023222 85e-07	170	positive regulation of transcription, DNA-templated
GO:0044784	7.393027354919 87e-07	18	metaphase/anaphase transition of cell cycle
GO:0030163	7.509637014119 05e-07	110	protein catabolic process
GO:0048002	7.793032696190 69e-07	27	antigen processing and presentation of peptide antigen
GO:0010965	7.988805991380 65e-07	18	regulation of mitotic sister chromatid separation
GO:0022607	8.483987016887 12e-07	301	cellular component assembly
GO:1903508	9.336077149731 85e-07	177	positive regulation of nucleic acid-templated transcription
GO:1902680	9.665099294424 28e-07	177	positive regulation of RNA biosynthetic process
GO:0007080	1.134016752072 85e-06	14	mitotic metaphase plate congression
GO:1903507	1.158688790655 36e-06	143	negative regulation of nucleic acid-templated transcription
GO:1902679	1.189255631806 51e-06	143	negative regulation of RNA biosynthetic process
GO:0051493	1.196896899486 67e-06	79	regulation of cytoskeleton organization
GO:0010033	1.502628227645 93e-06	288	response to organic substance
GO:0051306	1.507321093939 66e-06	18	mitotic sister chromatid separation
GO:0071495	1.590729001401 97e-06	157	cellular response to endogenous stimulus
GO:0045892	1.615709901564 96e-06	138	negative regulation of transcription, DNA-templated
GO:0006333	1.627060620847 45e-06	28	chromatin assembly or disassembly
GO:0051303	1.631134127897 02e-06	19	establishment of chromosome localization
GO:0019882	1.689826539457 21e-06	30	antigen processing and presentation
GO:0140013	1.800000296116 69e-06	30	meiotic nuclear division
GO:0033365	1.837797820439 15e-06	107	protein localization to organelle
GO:0031056	1.848291703053 51e-06	31	regulation of histone modification
GO:0000910	2.119185741175e-06	33	cytokinesis
GO:0050000	2.314199558719 89e-06	19	chromosome localization
GO:0051129	2.366151853859 7e-06	92	negative regulation of cellular component organization
GO:0051236	2.378292788403 19e-06	38	establishment of RNA localization
GO:0050684	2.446763179018 69e-06	27	regulation of mRNA processing
GO:0006403	2.548278914305 49e-06	41	RNA localization
GO:0051784	2.639510154447 77e-06	17	negative regulation of nuclear division
GO:0043484	2.736988608625 69e-06	28	regulation of RNA splicing
GO:1903046	2.834296600395 55e-06	32	meiotic cell cycle process
GO:0032446	2.954440635865 37e-06	102	protein modification by small protein conjugation
GO:0034502	3.212750685871 66e-06	20	protein localization to chromosome
GO:0010638	3.429861462053 41e-06	83	positive regulation of organelle organization
GO:0090307	3.445744973183 17e-06	18	mitotic spindle assembly
GO:0043933	3.706268737108 05e-06	215	protein-containing complex subunit organization
GO:0006357	3.770882535585 47e-06	267	regulation of transcription by RNA polymerase II
GO:0070887	4.413586966952 85e-06	282	cellular response to chemical stimulus
GO:0031124	4.447175095772 54e-06	21	mRNA 3'-end processing
GO:0071156	4.455971665459 63e-06	22	regulation of cell cycle arrest
GO:0006302	4.706473813549 97e-06	39	double-strand break repair
GO:0006323	4.762801810615 32e-06	30	DNA packaging
GO:0030071	4.965171630233 12e-06	16	regulation of mitotic metaphase/anaphase transition

GO:0018205	5.63806672568273e-06	55	peptidyl-lysine modification
GO:1902099	5.82873800405362e-06	16	regulation of metaphase/anaphase transition of cell cycle
GO:0010639	6.04120343312335e-06	57	negative regulation of organelle organization
GO:0019886	6.82906535977699e-06	21	antigen processing and presentation of exogenous peptide antigen via MHC class II
GO:0051603	7.09346546991038e-06	87	proteolysis involved in cellular protein catabolic process
GO:0051298	7.15326848667932e-06	19	centrosome duplication
GO:0050657	7.32374922967023e-06	36	nucleic acid transport
GO:0050658	7.32374922967023e-06	36	RNA transport
GO:0043488	7.3671285883509e-06	26	regulation of mRNA stability
GO:0071824	7.54039871640603e-06	38	protein-DNA complex subunit organization
GO:0071158	7.92531731302359e-06	19	positive regulation of cell cycle arrest
GO:0097711	8.05763343911413e-06	24	ciliary basal body-plasma membrane docking
GO:0001944	8.41902079069703e-06	93	vasculature development
GO:0010608	9.16989546201959e-06	70	posttranscriptional regulation of gene expression
GO:0045944	9.538426103242663e-06	134	positive regulation of transcription by RNA polymerase II
GO:0051169	9.9274414868692e-06	55	nuclear transport
GO:0051321	9.952060757770174e-06	38	meiotic cell cycle
GO:0032269	1.0003574319800 8e-05	114	negative regulation of cellular protein metabolic process
GO:0002495	1.0231103995881e-05	21	antigen processing and presentation of peptide antigen via MHC class II
GO:0072331	1.056323910170 04e-05	36	signal transduction by p53 class mediator
GO:0000079	1.068047961988 14e-05	18	regulation of cyclin-dependent protein serine/threonine kinase activity
GO:0051248	1.0940965126884e-05	120	negative regulation of protein metabolic process
GO:0006303	1.115996201667 84e-05	19	double-strand break repair via nonhomologous end joining
GO:0001568	1.189970215997 14e-05	90	blood vessel development
GO:0072431	1.227204712212 41e-05	16	signal transduction involved in mitotic G1 DNA damage checkpoint
GO:1902400	1.227204712212 41e-05	16	intracellular signal transduction involved in G1 DNA damage checkpoint
GO:0019941	1.368755404784 45e-05	77	modification-dependent protein catabolic process
GO:0006915	1.371637592304 59e-05	187	apoptotic process
GO:0002504	1.379274020242 04e-05	21	antigen processing and presentation of peptide or polysaccharide antigen via MHC class II
GO:0009725	1.425949611783 79e-05	107	response to hormone
GO:0072358	1.514393919408 61e-05	93	cardiovascular system development
GO:0072413	1.530680344518 56e-05	16	signal transduction involved in mitotic cell cycle checkpoint
GO:1902402	1.530680344518 56e-05	16	signal transduction involved in mitotic DNA damage checkpoint
GO:1902403	1.530680344518 56e-05	16	signal transduction involved in mitotic DNA integrity checkpoint
GO:0034249	1.562038374024 56e-05	31	negative regulation of cellular amide metabolic process
GO:0031328	1.582107969061e-05	197	positive regulation of cellular biosynthetic process
GO:0009891	1.585096692684 98e-05	199	positive regulation of biosynthetic process
GO:0032465	1.722610725834 54e-05	20	regulation of cytokinesis
GO:0042127	1.736440447076 09e-05	156	regulation of cell proliferation
GO:0006913	1.761854917139 44e-05	54	nucleocytoplasmic transport
GO:0032508	1.778417571071 62e-05	18	DNA duplex unwinding
GO:0006511	1.799372052794 24e-05	76	ubiquitin-dependent protein catabolic process
GO:0016567	1.942198488079 05e-05	94	protein ubiquitination
GO:0043632	1.946893177612 53e-05	77	modification-dependent macromolecule catabolic process
GO:0065004	1.959075680130 73e-05	32	protein-DNA complex assembly
GO:0048024	2.083803096361 77e-05	20	regulation of mRNA splicing, via spliceosome
GO:0051052	2.213654553662 65e-05	57	regulation of DNA metabolic process
GO:0006977	2.214278901857 98e-05	15	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest
GO:0010557	2.30963411700 35e-05	190	positive regulation of macromolecule biosynthetic process
GO:0043487	2.401231797289 32e-05	26	regulation of RNA stability
GO:0046605	2.463902597817 83e-05	16	regulation of centrosome cycle
GO:1904029	2.664521147135 36e-05	18	regulation of cyclin-dependent protein kinase activity
GO:0000209	2.829260945843 84e-05	44	protein polyubiquitination
GO:0032392	2.848321804413 08e-05	19	DNA geometric change
GO:0018193	2.857055471656 79e-05	134	peptidyl-amino acid modification
GO:0017148	2.914865932034 32e-05	28	negative regulation of translation
GO:0000726	2.98740520288197e-05	19	non-recombinational repair
GO:0065003	2.995203080066 81e-05	185	protein-containing complex assembly
GO:0006310	3.137143182883 08e-05	41	DNA recombination
GO:0002475	3.146763226208 74e-05	6	antigen processing and presentation via MHC class Ib
GO:0000122	3.157204765545 63e-05	102	negative regulation of transcription by RNA polymerase II
GO:0008150	3.424290750958 67e-05	1204	biological_process
GO:0090224	3.607301952985 67e-05	14	regulation of spindle organization
GO:0015931	3.785138507386 91e-05	38	nucleobase-containing compound transport
GO:0045931	3.981804277781 68e-05	28	positive regulation of mitotic cell cycle
GO:0031399	3.998660302078 89e-05	180	regulation of protein modification process
GO:0051053	4.084910387430 11e-05	27	negative regulation of DNA metabolic process
GO:0008104	4.576773617866 21e-05	264	protein localization
GO:0051716	4.593170684208 94e-05	569	cellular response to stimulus
GO:0007064	4.612692255872 47e-05	10	mitotic sister chromatid cohesion
GO:2001020	4.871299329350 24e-05	33	regulation of response to DNA damage stimulus
GO:0051383	5.023814770413 86e-05	9	kinetochore organization
GO:0001101	5.030116947348 88e-05	46	response to acid chemical
GO:0051168	5.134119380479 63e-05	34	nuclear export
GO:0060236	5.385321391197 74e-05	13	regulation of mitotic spindle organization
GO:0051028	5.488246108093 45e-05	29	mRNA transport
GO:0006473	5.493836152486 66e-05	33	protein acetylation
GO:1901564	5.580169755264 54e-05	538	organonitrogen compound metabolic process
GO:0051130	5.657152863258 84e-05	140	positive regulation of cellular component organization
GO:0032270	5.672886377304 23e-05	154	positive regulation of cellular protein metabolic process
GO:0006338	5.704741003441 23e-05	29	chromatin remodeling
GO:0061013	5.744545041923 68e-05	28	regulation of mRNA catabolic process
GO:0008219	5.846711055593 22e-05	203	cell death
GO:0071230	6.823994148060 32e-05	17	cellular response to amino acid stimulus
GO:0022406	7.664147326503 35e-05	32	membrane docking
GO:0012501	7.668309003819 76e-05	191	programmed cell death
GO:0031329	8.480415827713 17e-05	93	regulation of cellular catabolic process
GO:0006611	8.541220615985e-05	31	protein export from nucleus
GO:0009894	8.898248273651 93e-05	104	regulation of catabolic process
GO:0000380	9.999604690707 63e-05	16	alternative mRNA splicing, via spliceosome
GO:0034622	0.000100108527580688	114	cellular protein-containing complex assembly
GO:0002376	0.000106242222677036	233	immune system process
GO:0050793	0.000106680345280364	250	regulation of developmental process
GO:0010212	0.000106739301159573	26	response to ionizing radiation
GO:0043200	0.000108873375115343	22	response to amino acid
GO:0070192	0.000110624703513661	14	chromosome organization involved in meiotic cell cycle
GO:0000281	0.000111193533730051	19	mitotic cytokinesis
GO:0044248	0.000114057127242024	202	cellular catabolic process
GO:0070848	0.000117496302360817	86	response to growth factor
GO:0071426	0.000123548883392438	24	ribonucleoprotein complex export from nucleus
GO:0070925	0.000124409497755283	103	organelle assembly
GO:1905508	0.000125793661429964	12	protein localization to microtubule organizing center
GO:0051247	0.000130975655471179	160	positive regulation of protein metabolic process
GO:0071166	0.000134405005697858	24	ribonucleoprotein complex localization
GO:0006406	0.000137370157844131	22	mRNA export from nucleus
GO:0071427	0.000137370157844131	22	mRNA-containing ribonucleoprotein complex export from nucleus
GO:0071478	0.000146021933604916	29	cellular response to radiation
GO:0006405	0.00015174413783297	25	RNA export from nucleus
GO:2001252	0.000157612848887437	29	positive regulation of chromosome organization
GO:0071897	0.000163228048448993	30	DNA biosynthetic process
GO:0072359	0.00017377822738294	127	circulatory system development
GO:0007099	0.000173881127336506	11	centriole replication
GO:0140056	0.000179870039992866	30	organelle localization by membrane tethering
GO:0033036	0.000181868084064232	287	macromolecule localization
GO:0061640	0.000187171550134835	20	cytoskeleton-dependent cytokinesis
GO:0007063	0.00019301470287498	9	regulation of sister chromatid cohesion
GO:0032870	0.000196105178024187	80	cellular response to hormone stimulus
GO:0002476	0.000196313745109504	4	antigen processing and presentation of endogenous peptide antigen via MHC class Ib
GO:0030198	0.000197518144627081	54	extracellular matrix organization
GO:0043967	0.000199034070679956	16	histone H4 acetylation
GO:0044380	0.000203969013442645	16	protein localization to cytoskeleton
GO:0010824	0.000212971050305769	12	regulation of centrosome duplication
GO:0016573	0.000213727073731331	27	histone acetylation
GO:1901698	0.00021570775948605	110	response to nitrogen compound
GO:1902750	0.000216754353370595	13	negative regulation of cell cycle G2/M phase transition
GO:0034728	0.000229852648293785	22	nucleosome organization
GO:1901700	0.00023253533625837	150	response to oxygen-containing compound
GO:0071459	0.000241437128008931	7	protein localization to chromosome, centromeric region
GO:0031123	0.000250152231062823	21	RNA 3'-end processing

GO:0072698	0.0002566654888856693	15	protein localization to microtubule cytoskeleton
GO:0051495	0.0002576710573517 17	34	positive regulation of cytoskeleton organization
GO:2000026	0.0002582161681755 33	201	regulation of multicellular organismal development
GO:0034501	0.0002589443279460 04	6	protein localization to kinetochore
GO:0006261	0.0002595813797617 17	25	DNA-dependent DNA replication
GO:0071363	0.0002636095549613 95	81	cellular response to growth factor stimulus
GO:0044319	0.0002636707408510 23	10	wound healing, spreading of cells
GO:0090505	0.0002636707408510 23	10	epiboly involved in wound healing
GO:0046907	0.0002710480220446 08	183	intracellular transport
GO:0002428	0.0002712398178608 48	4	antigen processing and presentation of peptide antigen via MHC class Ib
GO:0030518	0.0002778374703436 21	26	intracellular steroid hormone receptor signaling pathway
GO:0018393	0.0002784366526313 49	27	internal peptidyl-lysine acetylation
GO:0051704	0.0002843124892192 51	202	multi-organism process
GO:0044087	0.0002880120193702 53	110	regulation of cellular component biogenesis
GO:0098534	0.0002929271633851 333	11	centriole assembly
GO:0002480	0.0002948380328224 46	4	antigen processing and presentation of exogenous peptide antigen via MHC class I, TAP-independent
GO:0031497	0.0002972242949300 42	19	chromatin assembly
GO:0006886	0.0003006388691761 92	115	intracellular protein transport
GO:0034340	0.0003056372997559 14	15	response to type I interferon
GO:0051315	0.0003074171718098 38	6	attachment of mitotic spindle microtubules to kinetochore
GO:0070482	0.0003217045025083 01	46	response to oxygen levels
GO:0048514	0.0003229462754274 96	74	blood vessel morphogenesis
GO:0018394	0.0003280498874837 04	28	peptidyl-lysine acetylation
GO:1901565	0.0003283102111964 06	124	organonitrogen compound catabolic process
GO:0006508	0.0003368257739122 82	158	proteolysis
GO:0051649	0.0003370160375177 08	216	establishment of localization in cell
GO:1901699	0.0003471064255658 36	76	cellular response to nitrogen compound
GO:0048545	0.0003491613044333 53	49	response to steroid hormone
GO:0018023	0.0003501266864772 77	12	peptidyl-lysine trimethylation
GO:0031058	0.0003515227239451 04	18	positive regulation of histone modification
GO:0010243	0.0003610792503645 84	103	response to organonitrogen compound
GO:0071539	0.0003666278282052 129	11	protein localization to centrosome
GO:0032502	0.0003745904411110 37	521	developmental process
GO:0019080	0.0003837896224120 25	14	viral gene expression
GO:0046890	0.0003880510733712 05	26	regulation of lipid biosynthetic process
GO:0051302	0.0003929251888383 67	26	regulation of cell division
GO:0031334	0.0003951906031614 37	37	positive regulation of protein complex assembly
GO:0006475	0.0003963102721181 86	27	internal protein amino acid acetylation
GO:1902905	0.0004075279463628 46	31	positive regulation of supramolecular fiber organization
GO:0031401	0.0004078233796525 036	120	positive regulation of protein modification process
GO:1901701	0.0004078568312871 68	113	cellular response to oxygen-containing compound
GO:1903827	0.0004093982077492 47	66	regulation of cellular protein localization
GO:0048856	0.000410385056124	492	anatomical structure development
GO:0080135	0.0004109897669179 28	77	regulation of cellular response to stress
GO:0042176	0.0004155041040634 99	49	regulation of protein catabolic process
GO:0009314	0.0004174747183483 45	54	response to radiation
GO:0050792	0.0004603721301610 97	25	regulation of viral process
GO:0006268	0.000460544957528 58	5	DNA unwinding involved in DNA replication
GO:0043062	0.0004626797445721 11	57	extracellular structure organization
GO:0002520	0.0004767628362851 95	93	immune system development
GO:1905269	0.0004921996404750 99	19	positive regulation of chromatin organization
GO:0010972	0.0005010753526428 45	11	negative regulation of G2/M transition of mitotic cell cycle
GO:1903312	0.0005039114380940 65	15	negative regulation of mRNA metabolic process
GO:0071214	0.0005068104560021 37	41	cellular response to abiotic stimulus
GO:0104004	0.0005068104560021 37	41	cellular response to environmental stimulus
GO:0002011	0.0005073140462840 21	15	morphogenesis of an epithelial sheet
GO:0034097	0.0005211386324347 48	101	response to cytokine
GO:0009628	0.0005228794006857 05	117	response to abiotic stimulus
GO:0034248	0.0005329598037166 87	51	regulation of cellular amide metabolic process
GO:0043254	0.0005345855856171 84	57	regulation of protein complex assembly
GO:0042981	0.0005437660670516 58	144	regulation of apoptotic process
GO:0010498	0.0005500137873015 86	54	proteasomal protein catabolic process
GO:0048869	0.0005501675530680 47	373	cellular developmental process
GO:0036293	0.0005615603510814 28	43	response to decreased oxygen levels
GO:0090504	0.0005779419016621 58	10	epiboly
GO:0043044	0.0005804200031638 16	15	ATP-dependent chromatin remodeling
GO:0016579	0.0005856573154573 68	37	protein deubiquitination
GO:0006418	0.0005878871803871 86	10	tRNA aminoacylation for protein translation
GO:0006417	0.0005953999302860 59	45	regulation of translation
GO:0043067	0.0006031174055654 02	145	regulation of programmed cell death
GO:0030261	0.0006070871673023 63	11	chromosome condensation
GO:0050896	0.0006140558256875 12	656	response to stimulus
GO:0051101	0.0006206022694577 59	20	regulation of DNA binding
GO:0070601	0.0006373927999751 68	5	centromeric sister chromatid cohesion
GO:0032479	0.0006425762254563 32	20	regulation of type I interferon production
GO:0051338	0.0006433918095292 83	100	regulation of transferase activity
GO:0007569	0.0006628916878765 25	19	cell aging
GO:0032606	0.0006770107665930 42	20	type I interferon production
GO:0007050	0.0006774108071683 03	34	cell cycle arrest
GO:0006378	0.0006787697039712 01	11	mRNA polyadenylation
GO:0043631	0.0006787697039712 01	11	RNA polyadenylation
GO:0034968	0.0006872050826870 99	22	histone lysine methylation
GO:0007044	0.0006967473996265 76	23	cell-substrate junction assembly
GO:0050810	0.0006992829134954 09	16	regulation of steroid biosynthetic process
GO:0018022	0.0007254054516444 53	23	peptidyl-lysine methylation
GO:0032467	0.0007345578777226 08	9	positive regulation of cytokinesis
GO:0030097	0.0007439438472974 1	84	hemopoiesis
GO:0000381	0.0007490511153935 373	13	regulation of alternative mRNA splicing, via spliceosome
GO:0010941	0.0007594389332073 15	154	regulation of cell death
GO:0071453	0.0007712472271804 41	28	cellular response to oxygen levels
GO:0097435	0.0007769147102843 71	84	supramolecular fiber organization
GO:0071496	0.0008029584511928 9	42	cellular response to external stimulus
GO:1902903	0.0008127443558488 12	47	regulation of supramolecular fiber organization
GO:0071407	0.0008128051604295 77	66	cellular response to organic cyclic compound
GO:0031572	0.0008239442148983 47	9	G2 DNA damage checkpoint
GO:0031503	0.0008456973634284 22	40	protein-containing complex localization
GO:0031060	0.0008611411203938 87	15	regulation of histone methylation
GO:0001706	0.0008811846315722 39	13	endoderm formation
GO:0071774	0.000888835437344977	23	response to fibroblast growth factor
GO:0070646	0.0008979074278556 22	38	protein modification by small protein removal
GO:0032436	0.0009414339670130 46	15	positive regulation of proteasomal ubiquitin-dependent protein catabolic process
GO:0019218	0.0009451767460495 28	18	regulation of steroid metabolic process
GO:0043543	0.0009537188697732 84	34	protein acylation
GO:0043039	0.0009547222169934 51	10	tRNA aminoacylation
GO:0018105	0.0009703541973183 33	41	peptidyl-serine phosphorylation
GO:0043903	0.000975939197467 81	26	regulation of symbiosis, encompassing mutualism through parasitism
GO:0030952	0.0009883500143837 568	6	establishment or maintenance of cytoskeleton polarity
GO:0031057	0.0010178733169399 6	11	negative regulation of histone modification
GO:0031145	0.0010222788606849 4	8	anaphase-promoting complex-dependent catabolic process
GO:0006412	0.0010296981995620 7	60	translation
GO:0090169	0.001030345039809 7	9	regulation of spindle assembly
GO:0071417	0.0010320636576966 5	69	cellular response to organonitrogen compound
GO:0046599	0.0010485006870088 8	7	regulation of centriole replication
GO:0033157	0.0010715806932295 4	35	regulation of intracellular protein transport
GO:1905288	0.0010886911443278 3	5	vascular associated smooth muscle cell apoptotic process
GO:1905459	0.0010886911443278 3	5	regulation of vascular associated smooth muscle cell apoptotic process
GO:1902115	0.0010922069543112 3	31	regulation of organelle assembly
GO:0014070	0.0011103596654732 2	93	response to organic cyclic compound
GO:0048731	0.0011209860267494 7	414	system development
GO:1905268	0.0011232657587320 5	13	negative regulation of chromatin organization
GO:0042221	0.0011240352356302 9	344	response to chemical
GO:0045595	0.0011311251407488 3	176	regulation of cell differentiation
GO:0036294	0.0011357936453604 2	26	cellular response to decreased oxygen levels
GO:0006402	0.0011413312020589 9	36	mRNA catabolic process
GO:0016571	0.001157953069994 07	24	histone methylation
GO:0001932	0.0011674771519597 6	135	regulation of protein phosphorylation
GO:0034086	0.0011762302278829 8	6	maintenance of sister chromatid cohesion
GO:0034088	0.0011762302278829 8	6	maintenance of mitotic sister chromatid cohesion
GO:0043038	0.0011877754173890 6	10	amino acid activation

GO:0060548	0.00119174810238984	99	negative regulation of cell death
GO:0040029	0.0011938791247338	43	regulation of gene expression, epigenetic
GO:0035987	0.0012177038057661	12	endodermal cell differentiation
GO:0043161	0.00122162531929346	46	proteasome-mediated ubiquitin-dependent protein catabolic process
GO:0044344	0.00124084651202513	22	cellular response to fibroblast growth factor stimulus
GO:0030522	0.0012467777716363	39	intracellular receptor signaling pathway
GO:0060337	0.00124974844196043	13	type I interferon signaling pathway
GO:0071357	0.00124974844196043	13	cellular response to type I interferon
GO:0030705	0.00125773393268702	31	cytoskeleton-dependent intracellular transport
GO:0071383	0.00130736112078497	36	cellular response to steroid hormone stimulus
GO:0019083	0.00131464256712164	11	viral transcription
GO:0007275	0.00132956085881453	454	multicellular organism development
GO:0006334	0.00139292925479726	15	nucleosome assembly
GO:0006695	0.00143904404601761	14	cholesterol biosynthetic process
GO:1902653	0.00143904404601761	14	secondary alcohol biosynthetic process
GO:0035295	0.00144160942644616	114	tube development
GO:0034508	0.00145009468660131	10	centromere complex assembly
GO:0007127	0.00145329936705858	17	meiosis I
GO:0051640	0.00152426806284364	83	organelle localization
GO:1905461	0.00152701730649123	4	positive regulation of vascular associated smooth muscle cell apoptotic process
GO:0031062	0.00156806188713023	10	positive regulation of histone methylation
GO:0006468	0.00158538330673482	184	protein phosphorylation
GO:0043687	0.00159448613738264	41	post-translational protein modification
GO:0071229	0.00161066785086599	30	cellular response to acid chemical
GO:1901800	0.00164037794889439	17	positive regulation of proteasomal protein catabolic process
GO:0022618	0.00165928374542523	32	ribonucleoprotein complex assembly
GO:0051754	0.00166866618176663	3	meiotic sister chromatid cohesion, centromeric
GO:0051701	0.00167952332854568	28	interaction with host
GO:0048193	0.00168281245207105	49	Golgi vesicle transport

(Significantly upregulated biological pathways in 1 min oscillatory condition).

Category	Overrepresented p-value	numDEInCat	Term
GO:0006614	3.015158916805 28e-39	61	SRP-dependent cotranslational protein targeting to membrane
GO:0006613	2.01407774823939e-38	61	cotranslational protein targeting to membrane
GO:0045047	1.08981605108091e-37	62	protein targeting to ER
GO:0072599	3.47543626728856e-37	62	establishment of protein localization to endoplasmic reticulum
GO:0000184	9.36112598880462e-37	61	nuclear-transcribed mRNA catabolic process, nonsense-mediated decay
GO:0070972	1.68623137511771e-35	63	protein localization to endoplasmic reticulum
GO:0006402	7.60706223183375e-32	72	mRNA catabolic process
GO:0000956	8.94981270843565e-32	66	nuclear-transcribed mRNA catabolic process
GO:0006413	2.55640283003708e-31	64	translational initiation
GO:0006401	3.90913891113886e-31	73	RNA catabolic process
GO:0006612	6.23668808638686e-30	62	protein targeting to membrane
GO:0090150	6.39634665099975e-29	70	establishment of protein localization to membrane
GO:0044265	7.7396874600926 14e-28	109	cellular macromolecule catabolic process
GO:0006412	1.06278306130156e-26	97	translation
GO:0043043	1.27244960035784e-26	98	peptide biosynthetic process
GO:0006518	8.12380964152126e-26	104	peptide metabolic process
GO:0009057	1.83326606732697e-25	113	macromolecule catabolic process
GO:0043604	1.29709126359466e-24	100	amide biosynthetic process
GO:0034655	2.32473669970438e-24	77	nucleobase-containing compound catabolic process
GO:0072657	7.04748482224167e-24	78	protein localization to membrane
GO:0072594	1.93739356688381e-23	77	establishment of protein localization to organelle
GO:0046700	3.23562425008563e-23	78	heterocycle catabolic process
GO:0044270	3.5251817955561e-23	78	cellular nitrogen compound catabolic process
GO:0016071	5.19357255628974e-23	88	mRNA metabolic process
GO:0019439	8.38025737013012e-23	78	aromatic compound catabolic process
GO:0006605	1.11261432260123e-22	70	protein targeting
GO:1901361	1.10953404420864e-21	78	organic cyclic compound catabolic process
GO:0043603	2.73681718273444e-21	106	cellular amide metabolic process
GO:0044271	9.25015485269217e-21	222	cellular nitrogen compound biosynthetic process
GO:0033365	2.14829837610596e-20	85	protein localization to organelle
GO:0034645	1.01564684603617e-19	215	cellular macromolecule biosynthetic process
GO:0044267	1.02287845956682e-19	235	cellular protein metabolic process
GO:0046907	1.49841072136092e-19	121	intracellular transport
GO:1901564	2.11916668399597e-19	282	organonitrogen compound metabolic process
GO:0044260	4.13202123899259e-19	304	cellular macromolecule metabolic process
GO:0009059	6.79981615156944e-19	217	macromolecule biosynthetic process
GO:1901566	8.37798765760509e-19	128	organonitrogen compound biosynthetic process
GO:0048519	1.25015536638109e-18	234	negative regulation of biological process
GO:0009892	1.94793687010574e-18	167	negative regulation of metabolic process
GO:0010605	2.50749368290942e-18	160	negative regulation of macromolecule metabolic process
GO:0019538	6.56301640023567e-18	245	protein metabolic process
GO:0051649	2.83609479419973e-17	127	establishment of localization in cell
GO:0044249	3.29585083156961e-17	242	cellular biosynthetic process
GO:0006886	3.55607261297996e-17	91	intracellular protein transport
GO:0051179	4.06553591855603e-17	246	localization
GO:0034613	4.90372191932284e-17	114	cellular protein localization
GO:0070727	7.16201767556797e-17	114	cellular macromolecule localization
GO:1901576	1.14851897035306e-16	243	organic substance biosynthetic process
GO:0009058	1.18862600271048e-16	245	biosynthetic process
GO:0044248	1.77034498502021e-16	129	cellular catabolic process
GO:0051641	1.81106220482141e-16	144	cellular localization
GO:0060255	2.35610143907666e-16	243	regulation of macromolecule metabolic process
GO:0019222	5.00794019125885e-16	256	regulation of metabolic process
GO:0010629	6.65110041201858e-16	126	negative regulation of gene expression
GO:0015031	1.52420619474238e-15	118	protein transport
GO:0015833	1.80314647240233e-15	119	peptide transport
GO:0006810	2.33844906549978e-15	202	transport
GO:0051234	4.01806345490776e-15	204	establishment of localization
GO:0042886	4.19447357890297e-15	119	amide transport
GO:0045184	4.49390703841542e-15	120	establishment of protein localization
GO:0009056	2.28691782177951e-14	132	catabolic process
GO:0008104	2.83767724099799e-14	135	protein localization
GO:1901575	2.90628919813921e-14	117	organic substance catabolic process
GO:0010468	5.07331363564006e-14	190	regulation of gene expression
GO:0034641	1.81614084879842e-13	270	cellular nitrogen compound metabolic process
GO:0010033	2.21426632186986e-13	143	response to organic substance
GO:0071705	3.53038356839701e-13	122	nitrogen compound transport
GO:0033036	5.34035641865235e-13	142	macromolecule localization
GO:0042221	1.03280732595627e-12	178	response to chemical
GO:0070887	1.23730107983119e-12	142	cellular response to chemical stimulus
GO:0006807	1.24494484825218e-12	352	nitrogen compound metabolic process
GO:0071345	1.87921422958185e-12	70	cellular response to cytokine stimulus
GO:0051246	9.40365538391233e-12	127	regulation of protein metabolic process
GO:0044237	1.05547664746654e-11	364	cellular metabolic process
GO:0034097	1.37006313345464e-11	71	response to cytokine
GO:0071310	1.73459634404644e-11	118	cellular response to organic substance
GO:1901701	1.85662459167653e-11	63	cellular response to oxygen-containing compound
GO:0071702	5.03079273594984e-11	127	organic substance transport
GO:0032268	5.06964450450862e-11	119	regulation of cellular protein metabolic process
GO:0044238	5.08189542406038e-11	355	primary metabolic process
GO:0060548	7.66209611093361e-11	63	negative regulation of cell death
GO:0042254	9.67388711326776e-11	39	ribosome biogenesis
GO:0071840	1.25497010017253e-10	234	cellular component organization or biogenesis
GO:0043069	1.27074903766454e-10	59	negative regulation of programmed cell death
GO:0043066	1.75256765169182e-10	58	negative regulation of apoptotic process
GO:0022613	1.84954444965317e-10	48	ribonucleoprotein complex biogenesis
GO:0006139	3.41036646232124e-10	233	nucleobase-containing compound metabolic process
GO:0006725	3.83427557586217e-10	238	cellular aromatic compound metabolic process
GO:0002181	7.84606452009325e-10	23	cytoplasmic translation
GO:0042273	8.26383273179986e-10	20	ribosomal large subunit biogenesis
GO:0051247	9.67676652673656e-10	82	positive regulation of protein metabolic process
GO:0046483	1.05043910412608e-09	235	heterocycle metabolic process

GO:0008219	1.28416512772112e-09	104	cell death
GO:1901700	1.343515163510791e-09	77	response to oxygen-containing compound
GO:1901360	1.80187060624 31e-09	241	organic cyclic compound metabolic process
GO:0012501	1.90376169956377e-09	99	programmed cell death
GO:0043933	2.19666284395489e-09	118	protein-containing complex subunit organization
GO:0051173	2.307312160876 08e-09	122	positive regulation of nitrogen compound metabolic process
GO:0050789	2.819852764377 44e-09	336	regulation of biological process
GO:0032270	4.1467519941813e-09	77	positive regulation of cellular protein metabolic process
GO:0043067	4.19511689531071e-09	79	regulation of programmed cell death
GO:0008152	4.50274239646485e-09	377	metabolic process
GO:0010941	5.243815039759 97e-09	83	regulation of cell death
GO:0016070	5.57492278854018e-09	192	RNA metabolic process
GO:0042981	6.201993458447 58e-09	78	regulation of apoptotic process
GO:0010467	6.57383506181973e-09	229	gene expression
GO:0019221	7.948530522133 98e-09	51	cytokine-mediated signaling pathway
GO:0070498	8.327509352642 62e-09	12	interleukin-1-mediated signaling pathway
GO:0042255	8.428709050737 44e-09	18	ribosome assembly
GO:0009893	8.435761624445 35e-09	133	positive regulation of metabolic process
GO:0048522	8.9889303714641e-09	179	positive regulation of cellular process
GO:0090304	1.0906062142129e-08	205	nucleic acid metabolic process
GO:0031325	1.104980444023 51e-08	123	positive regulation of cellular metabolic process
GO:0010604	1.1942720941715e-08	124	positive regulation of macromolecule metabolic process
GO:0033554	1.598799181566 75e-08	89	cellular response to stress
GO:0043170	1.668587361949 02e-08	322	macromolecule metabolic process
GO:0044085	1.701735884584 32e-08	139	cellular component biogenesis
GO:0051171	2.114796375344 47e-08	193	regulation of nitrogen compound metabolic process
GO:0016043	2.259134057927 33e-08	217	cellular component organization
GO:0080134	2.503630791851 27e-08	68	regulation of response to stress
GO:0048518	2.807399812724 23e-08	195	positive regulation of biological process
GO:0009636	3.1873125403042e-08	41	response to toxic substance
GO:0002376	3.493857320869 24e-08	119	immune system process
GO:0080090	3.534159603424 66e-08	196	regulation of primary metabolic process
GO:0006955	3.9992057974083e-08	89	immune response
GO:0033993	4.565867347184 02e-08	49	response to lipid
GO:0009987	4.654267803444 87e-08	454	cellular process
GO:0002684	5.175077997528 76e-08	53	positive regulation of immune system process
GO:0071704	5.838636458172 11e-08	359	organic substance metabolic process
GO:0065009	5.868723755664 08e-08	127	regulation of molecular function
GO:0009628	5.8862946501243e-08	57	response to abiotic stimulus
GO:0045321	6.111330567439 55e-08	62	leukocyte activation
GO:0048523	7.193921971294 09e-08	166	negative regulation of cellular process
GO:0001775	7.230465151518 93e-08	66	cell activation
GO:0006915	7.354830916261 66e-08	88	apoptotic process
GO:0060429	7.8198483362138e-08	58	epithelium development
GO:0034975	7.8222307259675e-08	6	protein folding in endoplasmic reticulum
GO:0050790	9.065441028168 79e-08	97	regulation of catalytic activity
GO:0009605	9.271812268203 33e-08	97	response to external stimulus
GO:0031323	9.274716408707 89e-08	198	regulation of cellular metabolic process
GO:0071222	9.317868432363 75e-08	21	cellular response to lipopolysaccharide
GO:0071347	9.513959382237 16e-08	17	cellular response to interleukin-1
GO:0042775	1.654817720448 76e-07	20	mitochondrial ATP synthesis coupled electron transport
GO:0031399	1.658471191069 84e-07	77	regulation of protein modification process
GO:0071219	1.704142219077 39e-07	21	cellular response to molecule of bacterial origin
GO:0071216	1.724025263744 43e-07	22	cellular response to biotic stimulus
GO:0042773	1.791842798177 71e-07	20	ATP synthesis coupled electron transport
GO:0071396	2.060512881420 82e-07	35	cellular response to lipid
GO:0065007	2.164940667857 31e-07	342	biological regulation
GO:0022618	2.282813370868 75e-07	28	ribonucleoprotein complex assembly
GO:0098609	2.396052224648 26e-07	40	cell-cell adhesion
GO:0016310	2.681304099848 19e-07	92	phosphorylation
GO:0048585	2.8959070229688e-07	69	negative regulation of response to stimulus
GO:0002237	3.231234609183 91e-07	27	response to molecule of bacterial origin
GO:0070555	3.283152903060 36e-07	18	response to interleukin-1
GO:0022407	3.467421063878 27e-07	27	regulation of cell-cell adhesion
GO:0031324	4.056689144703 76e-07	103	negative regulation of cellular metabolic process
GO:0071826	4.591447699328 88e-07	28	ribonucleoprotein complex subunit organization
GO:0065003	4.966322142256 49e-07	96	protein-containing complex assembly
GO:0042592	5.059199680037 06e-07	82	homeostatic process
GO:0031098	5.521321979439 71e-07	23	stress-activated protein kinase signaling cascade
GO:0097193	5.6083407744915e-07	27	intrinsic apoptotic signaling pathway
GO:0051403	6.031506436852 39e-07	22	stress-activated MAPK cascade
GO:0032496	6.514117175933 22e-07	26	response to lipopolysaccharide
GO:0019725	6.856571409579 97e-07	50	cellular homeostasis
GO:0051240	7.391227313106 79e-07	73	positive regulation of multicellular organismal process
GO:1902531	9.127785430217 65e-07	78	regulation of intracellular signal transduction
GO:0097190	1.016985647916 14e-06	41	apoptotic signaling pathway
GO:0022904	1.042481964216 73e-06	20	respiratory electron transport chain
GO:0002252	1.067831669917 25e-06	57	immune effector process
GO:0080135	1.1109352533454e-06	39	regulation of cellular response to stress
GO:0022900	1.248298600506 47e-06	27	electron transport chain
GO:0009607	1.468572523916 48e-06	51	response to biotic stimulus
GO:0001817	1.493996635954 88e-06	37	regulation of cytokine production
GO:0019058	1.587034737971 79e-06	24	viral life cycle
GO:0043207	1.694708566589 08e-06	50	response to external biotic stimulus
GO:0051707	1.694708566589 08e-06	50	response to other organism
GO:2001233	1.905264291060 27e-06	31	regulation of apoptotic signaling pathway
GO:0097237	2.247609893291 39e-06	23	cellular response to toxic substance
GO:0051338	2.294642496898 86e-06	47	regulation of transferase activity
GO:0006935	2.432776949746 92e-06	37	chemotaxis
GO:0014070	2.439639595897 34e-06	43	response to organic cyclic compound
GO:0006119	2.481093491220 53e-06	20	oxidative phosphorylation
GO:0006996	2.538419838560 73e-06	142	organelle organization
GO:0010243	2.594053221815 08e-06	45	response to organonitrogen compound
GO:0006950	2.649737059751 18e-06	140	response to stress
GO:0030155	2.653453049865 12e-06	35	regulation of cell adhesion
GO:0042330	2.692052330559 05e-06	37	taxis
GO:0001816	2.768052229839 26e-06	39	cytokine production
GO:0051172	3.312895594867 84e-06	96	negative regulation of nitrogen compound metabolic process
GO:1901698	3.419643031873 33e-06	47	response to nitrogen compound
GO:0010257	3.578159100380 93e-06	16	NADH dehydrogenase complex assembly
GO:0032981	3.578159100380 93e-06	16	mitochondrial respiratory chain complex I assembly
GO:0048870	3.579406037654 37e-06	68	cell motility
GO:0051674	3.579406037654 37e-06	68	localization of cell
GO:0016477	3.962830288581 11e-06	63	cell migration
GO:0040011	4.205087593007 05e-06	74	locomotion
GO:0051094	4.670661015389 77e-06	59	positive regulation of developmental process
GO:0002682	4.736932614499 96e-06	66	regulation of immune system process
GO:1903039	4.810897984532 99e-06	18	positive regulation of leukocyte cell-cell adhesion
GO:0007159	4.890030099869 11e-06	23	leukocyte cell-cell adhesion
GO:0050778	4.9193817444268e-06	37	positive regulation of immune response
GO:0048584	5.106940380695 65e-06	89	positive regulation of response to stimulus
GO:0006986	5.3576479762338e-06	16	response to unfolded protein
GO:0070482	5.405532327782 04e-06	24	response to oxygen levels
GO:0065008	5.742822303227 67e-06	133	regulation of biological quality
GO:0002764	5.785184082455 17e-06	27	immune response-regulating signaling pathway
GO:0036293	5.843821684839 09e-06	23	response to decreased oxygen levels
GO:0002274	5.947882319746 69e-06	39	myeloid leukocyte activation
GO:0035966	6.116505153543 02e-06	17	response to topologically incorrect protein
GO:0045859	6.783144757548 08e-06	39	regulation of protein kinase activity
GO:0009617	6.874305920811 87e-06	37	response to bacterium
GO:0022409	6.890156079241 65e-06	19	positive regulation of cell-cell adhesion
GO:0009888	6.979779024222 16e-06	75	tissue development
GO:0022607	6.999222995160 83e-06	119	cellular component assembly
GO:0006928	7.256820947287 54e-06	80	movement of cell or subcellular component
GO:0001932	7.298500268446 62e-06	60	regulation of protein phosphorylation
GO:0043405	7.365078444779e-06	22	regulation of MAP kinase activity
GO:0043588	8.117512504119 21e-06	26	skin development
GO:1903037	8.586841169616 51e-06	21	regulation of leukocyte cell-cell adhesion
GO:0048732	8.615600846092 67e-06	25	gland development

GO:0006457	8.63307926510805e-06	21	protein folding
GO:0071900	8.89697992088414e-06	29	regulation of protein serine/threonine kinase activity
GO:0006979	9.38747066302294e-06	30	response to oxidative stress
GO:0060326	1.01267477560543e-05	24	cell chemotaxis
GO:0070423	1.02652241913964e-05	7	nucleotide-binding oligomerization domain containing signaling pathway
GO:0030595	1.06580276405043e-05	20	leukocyte chemotaxis
GO:1902532	1.09983664988558e-05	30	negative regulation of intracellular signal transduction
GO:0050776	1.11168155924991e-05	43	regulation of immune response
GO:2000027	1.16275920587536e-05	16	regulation of animal organ morphogenesis
GO:0044419	1.17388070690816e-05	44	interspecies interaction between organisms
GO:0044092	1.17705159405932e-05	54	negative regulation of molecular function
GO:0002366	1.18224720926134e-05	39	leukocyte activation involved in immune response
GO:0043085	1.19889228034944e-05	59	positive regulation of catalytic activity
GO:0034622	1.22446725324987e-05	68	cellular protein-containing complex assembly
GO:0002263	1.23890156639719e-05	39	cell activation involved in immune response
GO:0001666	1.26282202938733e-05	22	response to hypoxia
GO:0035872	1.28144309566476e-05	7	nucleotide-binding domain, leucine rich repeat containing receptor signaling pathway
GO:0045333	1.29855832645103e-05	22	cellular respiration
GO:0019220	1.40821120800256e-05	68	regulation of phosphate metabolic process
GO:0009966	1.44705099911253e-05	113	regulation of signal transduction
GO:0044093	1.45131357217039e-05	69	positive regulation of molecular function
GO:0051174	1.45159536041322e-05	68	regulation of phosphorus metabolic process
GO:0016072	1.55421004104e-05	25	rRNA metabolic process
GO:0002253	1.56052120362344e-05	28	activation of immune response
GO:0071417	1.62277334254334e-05	28	cellular response to organonitrogen compound
GO:0009968	1.6229127968015e-05	53	negative regulation of signal transduction
GO:0002757	1.64735119653711e-05	25	immune response-activating signal transduction
GO:0042325	1.66850595012948e-05	62	regulation of phosphorylation
GO:0030855	1.72189753254252e-05	38	epithelial cell differentiation
GO:0051252	1.80243298304323e-05	120	regulation of RNA metabolic process
GO:0007050	1.8338776333568e-05	19	cell cycle arrest
GO:0050863	2.21169652336147e-05	20	regulation of T cell activation
GO:0007155	2.29454854133474e-05	52	cell adhesion
GO:0001819	2.34433220620024e-05	25	positive regulation of cytokine production
GO:0044257	2.3510036939732e-05	39	cellular protein catabolic process
GO:0071496	2.37944146512879e-05	21	cellular response to external stimulus
GO:0042119	2.4852270139924 9e-05	32	neutrophil activation
GO:2000112	2.50122232413905e-05	127	regulation of cellular macromolecule biosynthetic process
GO:0051347	2.58629141869186e-05	32	positive regulation of transferase activity
GO:0022610	2.59407383567038e-05	52	biological adhesion
GO:0006120	2.61616336538096e-05	13	mitochondrial electron transport, NADH to ubiquinone
GO:0098754	2.81347436884798e-05	18	detoxification
GO:0007005	2.84647110286127e-05	37	mitochondrion organization
GO:0015980	2.94171392921825e-05	24	energy derivation by oxidation of organic compounds
GO:0051704	3.16751137035838e-05	94	multi-organism process
GO:0048513	3.19435223270558e-05	115	animal organ development
GO:0031401	3.25543828315302e-05	51	positive regulation of protein modification process
GO:0006364	3.32104395312045e-05	23	rRNA processing
GO:0043435	3.51321216584311e-05	3	response to corticotropin-releasing hormone
GO:0071376	3.51321216584311e-05	3	cellular response to corticotropin-releasing hormone stimulus
GO:0036230	3.51750746260772e-05	32	granulocyte activation
GO:0022612	3.60381225183501e-05	11	gland morphogenesis
GO:0010648	3.6518075798489e-05	55	negative regulation of cell communication
GO:0016032	3.72778063699925e-05	38	viral process
GO:1901699	3.74932830064831e-05	29	cellular response to nitrogen compound
GO:0051249	3.79582585776 44e-05	24	regulation of lymphocyte activation
GO:0023057	3.79867936709386e-05	55	negative regulation of signaling
GO:0048583	3.92669415110469e-05	136	regulation of response to stimulus
GO:0044403	4.01594479357686e-05	40	symbiont process
GO:2001234	4.05933891020916e-05	19	negative regulation of apoptotic signaling pathway
GO:0019219	4.15582862498421e-05	126	regulation of nucleobase-containing compound metabolic process
GO:0043549	4.29864932923758e-05	39	regulation of kinase activity
GO:0002694	4.34537059138404e-05	27	regulation of leukocyte activation
GO:0006351	4.3682951340503e-05	116	transcription, DNA-templated
GO:0040012	4.39521436678939e-05	47	regulation of locomotion
GO:0000027	4.39680498196918e-05	9	ribosomal large subunit assembly
GO:0050870	4.40818673604653e-05	16	positive regulation of T cell activation
GO:0034599	4.42089197893735e-05	21	cellular response to oxidative stress
GO:0051248	4.4423009767946e-05	54	negative regulation of protein metabolic process
GO:2000145	4.61067691343167e-05	45	regulation of cell motility
GO:0030163	4.78033797553198e-05	43	protein catabolic process
GO:0051017	4.80774257475021e-05	12	actin filament bundle assembly
GO:0051253	4.98934548001332e-05	55	negative regulation of RNA metabolic process
GO:0023014	4.99654042899455e-05	42	signal transduction by protein phosphorylation
GO:0019438	5.41820101175634e-05	135	aromatic compound biosynthetic process
GO:0023051	5.4305500718883e-05	119	regulation of signaling
GO:0009889	5.49923208087065e-05	136	regulation of biosynthetic process
GO:0010556	5.53243138703686e-05	129	regulation of macromolecule biosynthetic process
GO:0051270	5.5696938913404e-05	47	regulation of cellular component movement
GO:1903311	5.62843007517924e-05	17	regulation of mRNA metabolic process
GO:0061572	5.63031002125055e-05	12	actin filament bundle organization
GO:0051603	5.65202804297342e-05	36	proteolysis involved in cellular protein catabolic process
GO:0010646	5.92692934868505e-05	118	regulation of cell communication
GO:0030216	6.12809768479959e-05	20	keratinocyte differentiation
GO:0097529	6.21000119340359e-05	18	myeloid leukocyte migration
GO:0006366	6.40809838299651e-05	89	transcription by RNA polymerase II
GO:0010628	6.41810625208107e-05	71	positive regulation of gene expression
GO:0045860	6.46974902091753e-05	27	positive regulation of protein kinase activity
GO:0007166	6.76377467099118e-05	100	cell surface receptor signaling pathway
GO:0000302	6.8437351043723e-05	19	response to reactive oxygen species
GO:0071453	6.86641539793059e-05	15	cellular response to oxygen levels
GO:0023056	6.882778700538 99e-05	70	positive regulation of signaling
GO:0071450	7.10062760775207e-05	7	cellular response to oxygen radical
GO:0071451	7.10062760775207e-05	7	cellular response to superoxide
GO:1901362	7.11165594581895e-05	139	organic cyclic compound biosynthetic process
GO:0032649	7.16165312456497e-05	10	regulation of interferon-gamma production
GO:0043299	7.19367045011333e-05	32	leukocyte degranulation
GO:0000165	7.43630690411943e-05	41	MAPK cascade
GO:0018130	7.56094144768685e-05	134	heterocycle biosynthetic process
GO:0051272	7.61354746230227e-05	31	positive regulation of cellular component movement
GO:0097659	7.64440587684817e-05	116	nucleic acid-templated transcription
GO:0035556	7.65950883804396e-05	96	intracellular signal transduction
GO:0042542	7.86556962651284e-05	14	response to hydrogen peroxide
GO:0030593	7.92589875460802e-05	13	neutrophil chemotaxis
GO:0042326	7.94653438831888e-05	25	negative regulation of phosphorylation
GO:0006355	8.09192828862045e-05	109	regulation of transcription, DNA-templated
GO:0006793	8.11972982135549e-05	111	phosphorus metabolic process
GO:0034654	8.17846226935194e-05	132	nucleobase-containing compound biosynthetic process
GO:0045934	8.30948018558161e-05	58	negative regulation of nucleobase-containing compound metabolic process
GO:0046916	8.38249352580048e-05	15	cellular transition metal ion homeostasis
GO:0045785	8.46117357933099e-05	23	positive regulation of cell adhesion
GO:0071621	8.64343953827602e-05	14	granulocyte chemotaxis
GO:0010035	8.71201675334173e-05	32	response to inorganic substance
GO:0007275	8.7439460123543e-05	160	multicellular organism development
GO:0051492	8.76740672069184e-05	9	regulation of stress fiber assembly
GO:0008406	8.87243557788226e-05	15	gonad development
GO:0002275	8.97230392553069e-05	32	myeloid cell activation involved in immune response
GO:0055082	9.03643746355764e-05	38	cellular chemical homeostasis
GO:0009205	9.06703510650753e-05	24	purine ribonucleoside triphosphate metabolic process
GO:0006796	9.08388023760027e-05	110	phosphate-containing compound metabolic process
GO:0030334	9.43577692506386e-05	42	regulation of cell migration
GO:0043312	9.64748907164831e-05	30	neutrophil degranulation
GO:0050900	9.98203363780623e-05	25	leukocyte migration
GO:0046677	0.000101019363400765	22	response to antibiotic
GO:0032774	0.000104092359224571	116	RNA biosynthetic process
GO:0008544	0.000104636130140185	26	epidermis development
GO:0002283	0.000104915927529131	30	neutrophil activation involved in immune response
GO:0030968	0.000105276239808933	11	endoplasmic reticulum unfolded protein response
GO:0010647	0.000105304106820299	69	positive regulation of cell communication

GO:0051402	0.000105775692425002	17	neuron apoptotic process
GO:0036294	0.000107483987185419	14	cellular response to decreased oxygen levels
GO:0033108	0.000109282229000503	16	mitochondrial respiratory chain complex assembly
GO:0045137	0.000111522853338761	15	development of primary sexual characteristics
GO:0032502	0.000113075109727771	183	developmental process
GO:0000303	0.000116650386785993	7	response to superoxide
GO:0055114	0.000117300645999116	52	oxidation-reduction process
GO:0009199	0.000117417165450696	24	ribonucleoside triphosphate metabolic process
GO:0050865	0.000117610799641312	27	regulation of cell activation
GO:0002444	0.000118995088765043	32	myeloid leukocyte mediated immunity
GO:0042274	0.000121427638998226	12	ribosomal small subunit biogenesis
GO:0040017	0.000121728652887065	31	positive regulation of locomotion
GO:0008283	0.000125053078635381	78	cell proliferation
GO:2000147	0.000125493507389183	30	positive regulation of cell motility
GO:0030335	0.000126638155987988	29	positive regulation of cell migration
GO:0032609	0.000129662463943336	10	interferon-gamma production
GO:0071407	0.000129825756888597	25	cellular response to organic cyclic compound
GO:0048731	0.000133121766312413	144	system development
GO:0001933	0.000134937564512146	23	negative regulation of protein phosphorylation
GO:0000305	0.000137954918855158	7	response to oxygen radical
GO:0009913	0.000141576981732712	21	epidermal cell differentiation
GO:0009141	0.000144492172601902	25	nucleoside triphosphate metabolic process
GO:1990266	0.00014609254781 12	13	neutrophil migration
GO:0009144	0.000149149018123362	24	purine nucleoside triphosphate metabolic process
GO:0006414	0.000151585188608199	19	translational elongation
GO:0031329	0.000152658595282159	36	regulation of cellular catabolic process
GO:0002446	0.000153643768354873	30	neutrophil mediated immunity
GO:0098869	0.000155308375147904	13	cellular oxidant detoxification
GO:0097530	0.000155806013230967	14	granulocyte migration
GO:1903506	0.000158932568435065	109	regulation of nucleic acid-templated transcription
GO:0002443	0.000159983114894594	39	leukocyte mediated immunity
GO:0006357	0.00016020660225341	82	regulation of transcription by RNA polymerase II
GO:0110020	0.000160378236034021	9	regulation of actomyosin structure organization
GO:0032269	0.000164457410335438	50	negative regulation of cellular protein metabolic process
GO:0000122	0.000166275878499736	35	negative regulation of transcription by RNA polymerase II
GO:0032101	0.000171160297584187	38	regulation of response to external stimulus
GO:0010562	0.000172183711938084	45	positive regulation of phosphorus metabolic process
GO:0045937	0.000172183711938084	45	positive regulation of phosphate metabolic process
GO:0042110	0.000173369205946468	23	T cell activation
GO:1902105	0.000174241536467526	16	regulation of leukocyte differentiation
GO:0010557	0.00017677486084794	66	positive regulation of macromolecule biosynthetic process
GO:0071902	0.000178982489708562	19	positive regulation of protein serine/threonine kinase activity
GO:0001934	0.000181965496069697	42	positive regulation of protein phosphorylation
GO:0033674	0.000181979175589903	27	positive regulation of kinase activity
GO:2001141	0.000193027333724534	109	regulation of RNA biosynthetic process
GO:2000630	0.000199514699494626	3	positive regulation of miRNA metabolic process
GO:0031424	0.000202527393135096	16	keratinization
GO:0009967	0.000204727600117306	63	positive regulation of signal transduction
GO:0006508	0.000205020781712923	70	proteolysis
GO:0030038	0.000206957756543233	9	contractile actin filament bundle assembly
GO:0043149	0.000206957756543233	9	stress fiber assembly
GO:0002753	0.000207621401020347	7	cytoplasmic pattern recognition receptor signaling pathway
GO:0009894	0.000210213457866093	39	regulation of catabolic process
GO:0034976	0.000214049046759709	17	response to endoplasmic reticulum stress
GO:0031326	0.000221230144866389	130	regulation of cellular biosynthetic process
GO:0031328	0.000222489447468796	68	positive regulation of cellular biosynthetic process
GO:0032231	0.000223682592561399	9	regulation of actin filament bundle assembly
GO:0045055	0.000227261395356027	38	regulated exocytosis
GO:0032872	0.000234960728472945	15	regulation of stress-activated MAPK cascade
GO:1990748	0.00024556903167064	13	cellular detoxification
GO:0043406	0.000247106346689194	16	positive regulation of MAP kinase activity
GO:0045936	0.000249744160798346	28	negative regulation of phosphate metabolic process
GO:0070302	0.000250085745471074	15	regulation of stress-activated protein kinase signaling cascade
GO:0002224	0.000252755964557853	11	toll-like receptor signaling pathway
GO:0035967	0.000255526258879799	12	cellular response to topologically incorrect protein
GO:0010563	0.00025644133718873	28	negative regulation of phosphorus metabolic process
GO:0071456	0.000257334796205588	13	cellular response to hypoxia
GO:0046034	0.000259919589519933	21	ATP metabolic process
GO:0006468	0.000263152579517143	66	protein phosphorylation
GO:0034620	0.000266977816523088	11	cellular response to unfolded protein
GO:0002262	0.000270111353239896	13	myeloid cell homeostasis
GO:0006123	0.000270712381097744	5	mitochondrial electron transport, cytochrome c to oxygen
GO:0019646	0.000270712381097744	5	aerobic electron transport chain
GO:0070997	0.000276752191614986	20	neuron death
GO:0009719	0.000276948145437026	59	response to endogenous stimulus
GO:0019430	0.00027884883140864	6	removal of superoxide radicals
GO:0006954	0.000283382867472514	35	inflammatory response
GO:0030260	0.000284043424587979	11	entry into host cell
GO:0044409	0.000284043424587979	11	entry into host
GO:0051806	0.000284043424587979	11	entry into cell of other organism involved in symbiotic interaction
GO:0051828	0.000284043424587979	11	entry into other organism involved in symbiotic interaction
GO:0031668	0.000294047783060328	16	cellular response to extracellular stimulus
GO:0045935	0.000294736029343331	64	positive regulation of nucleobase-containing compound metabolic process
GO:0009123	0.000295081578410366	24	nucleoside monophosphate metabolic process
GO:0009891	0.000303257816133274	69	positive regulation of biosynthetic process
GO:0034614	0.000305518218914604	14	cellular response to reactive oxygen species
GO:0045597	0.000307479677149443	39	positive regulation of cell differentiation
GO:2001242	0.000314215874804666	16	regulation of intrinsic apoptotic signaling pathway
GO:0035690	0.000320430067936885	20	cellular response to drug
GO:0002218	0.000320622606182595	15	activation of innate immune response
GO:0045944	0.000324425097636488	43	positive regulation of transcription by RNA polymerase II
GO:0006091	0.000338784159168084	31	generation of precursor metabolites and energy
GO:0030901	0.000342534008342881	9	midbrain development
GO:1903573	0.000342767341211803	6	negative regulation of response to endoplasmic reticulum stress
GO:0045444	0.000344197083222524	14	fat cell differentiation
GO:0031400	0.000344374659018455	29	negative regulation of protein modification process
GO:0000028	0.000348788667584805	7	ribosomal small subunit assembly
GO:0043065	0.000352598785204427	34	positive regulation of apoptotic process
GO:0042327	0.000364199018258015	42	positive regulation of phosphorylation
GO:0043068	0.00037334618044733	34	positive regulation of programmed cell death
GO:0030003	0.000376393834950288	31	cellular cation homeostasis
GO:0043408	0.00038070102418 04	34	regulation of MAPK cascade
GO:0002520	0.000381935980498879	41	immune system development
GO:0008150	0.000384899136621362	471	biological_process
GO:0002758	0.000384907279967727	14	innate immune response-activating signal transduction
GO:0042493	0.000391318594555951	42	response to drug
GO:0009167	0.000415385252552898	22	purine ribonucleoside monophosphate metabolic process
GO:0045730	0.000426696080893623	6	respiratory burst
GO:0055076	0.000431578557385727	15	transition metal ion homeostasis
GO:0002521	0.000432893595179884	24	leukocyte differentiation
GO:0030162	0.00043701012783337	39	regulation of proteolysis
GO:0031349	0.000442285346936016	23	positive regulation of defense response
GO:0002696	0.000442379173759104	19	positive regulation of leukocyte activation
GO:0061469	0.00044285165008916	3	regulation of type B pancreatic cell proliferation
GO:0002221	0.000451639685448029	12	pattern recognition receptor signaling pathway
GO:0006873	0.000452580202050972	31	cellular ion homeostasis
GO:0009126	0.000462995415027794	22	purine nucleoside monophosphate metabolic process
GO:0015949	0.000463278526099513	6	nucleobase-containing small molecule interconversion
GO:0043086	0.000466404316075454	39	negative regulation of catalytic activity
GO:0046683	0.000468928070022426	10	response to organophosphorus
GO:1902533	0.000476594035769113	47	positive regulation of intracellular signal transduction
GO:0032233	0.000479269243471649	7	positive regulation of actin filament bundle assembly
GO:0006875	0.000483151234546458	29	cellular metal ion homeostasis
GO:1903507	0.000491372890299454	49	negative regulation of nucleic acid-templated transcription
GO:0051251	0.000498305077871743	17	positive regulation of lymphocyte activation
GO:1902679	0.000502012431184629	49	negative regulation of RNA biosynthetic process
GO:0071901	0.000509987202377363	11	negative regulation of protein serine/threonine kinase activity
GO:0036498	0.000530827214100669	7	IRE1-mediated unfolded protein response
GO:0034101	0.000576911031015525	11	erythrocyte homeostasis

GO:0050867	0.0005841639982555527	19	positive regulation of cell activation
GO:0042127	0.0005913377838582227	63	regulation of cell proliferation
GO:0046649	0.0006174316193205370	29	lymphocyte activation
GO:0050801	0.0006271825752840070	35	ion homeostasis
GO:0032147	0.0006358400911685550	18	activation of protein kinase activity
GO:0048878	0.0006397133932864500	47	chemical homeostasis
GO:0031396	0.0006434476668909420	14	regulation of protein ubiquitination
GO:0010558	0.0006458586335401090	59	negative regulation of macromolecule biosynthetic process
GO:1903320	0.0006601204762475700	15	regulation of protein modification by small protein conjugation or removal
GO:0048534	0.0006640261658142200	39	hematopoietic or lymphoid organ development
GO:0007254	0.0006822014887673840	13	JNK cascade
GO:0038061	0.0006870184511937350	10	NIK/NF-kappaB signaling
GO:0006879	0.0006895544336356480	8	cellular iron ion homeostasis
GO:0051130	0.0006927824788850930	46	positive regulation of cellular component organization
GO:0009161	0.0006973058614462510	22	ribonucleoside monophosphate metabolic process
GO:0014074	0.0007007797241051640	10	response to purine-containing compound
GO:0046718	0.0007037567084473000	10	viral entry into host cell
GO:0010942	0.0007126598560986410	35	positive regulation of cell death
GO:0045089	0.0007173705823033010	17	positive regulation of innate immune response
GO:0032873	0.0007299499427567650	6	negative regulation of stress-activated MAPK cascade
GO:0070303	0.0007299499427567650	6	negative regulation of stress-activated protein kinase signaling cascade
GO:0030154	0.0007405721122321380	123	cell differentiation
GO:0070925	0.0007506736521919420	36	organelle assembly
GO:0051239	0.0007512196915990690	99	regulation of multicellular organismal process
GO:2000628	0.0007533044521647430	3	regulation of miRNA metabolic process
GO:1903895	0.0007550787797770240	2	negative regulation of IRE1-mediated unfolded protein response
GO:0051496	0.0007577548285724430	6	positive regulation of stress fiber assembly
GO:0002064	0.0007617522214577810	12	epithelial cell development
GO:0051254	0.0007669877831567060	57	positive regulation of RNA metabolic process
GO:0032729	0.0007711242141565460	7	positive regulation of interferon-gamma production
GO:0042089	0.0007713777845104920	9	cytokine biosynthetic process
GO:0071495	0.0007719991768523280	49	cellular response to endogenous stimulus
GO:0045892	0.0007793716695672350	47	negative regulation of transcription, DNA-templated
GO:0045454	0.0007822080003736781	9	cell redox homeostasis
GO:1905897	0.0007882048848319680	8	regulation of response to endoplasmic reticulum stress
GO:0051726	0.0007969781862768110	47	regulation of cell cycle
GO:0034405	0.0007997248509968740	5	response to fluid shear stress
GO:0071236	0.0008195610640551070	11	cellular response to antibiotic
GO:0006984	0.0008252830553123040	6	ER-nucleus signaling pathway
GO:0042107	0.0008351051058956240	9	cytokine metabolic process
GO:0000381	0.0008365131573785610	6	regulation of alternative mRNA splicing, via spliceosome
GO:0008284	0.0008401740136713240	41	positive regulation of cell proliferation
GO:0048869	0.0008493340936111120	128	cellular developmental process
GO:2001243	0.0008553386592612720	10	negative regulation of intrinsic apoptotic signaling pathway
GO:0051235	0.0008634687184491000	19	maintenance of location
GO:0048872	0.0008723313082389860	16	homeostasis of number of cells
GO:0031347	0.0008737572728560030	32	regulation of defense response
GO:0042035	0.0008865892829094230	8	regulation of cytokine biosynthetic process
GO:0043523	0.0009010168853861350	14	regulation of neuron apoptotic process
GO:0002762	0.0009081737656303410	6	negative regulation of myeloid leukocyte differentiation
GO:0050673	0.0009195369569856750	23	epithelial cell proliferation
GO:0007548	0.0009218856322066720	15	sex differentiation
GO:0007049	0.0009242235756002270	65	cell cycle
GO:0051169	0.0009438527548224240	21	nuclear transport
GO:0030097	0.0009468430749790270	37	hemopoiesis
GO:0032635	0.0009675182822991670	10	interleukin-6 production
GO:0055080	0.0009712200094808310	32	cation homeostasis
GO:0050896	0.0009776621183173640	245	response to stimulus
GO:0071214	0.0009915218595135135	18	cellular response to abiotic stimulus
GO:0104004	0.0009915218595135135	18	cellular response to environmental stimulus
GO:0120034	0.0010150084120035400	8	positive regulation of plasma membrane bounded cell projection assembly
GO:0022402	0.0010302153859727300	50	cell cycle process
GO:0002679	0.0010507938837043600	3	respiratory burst involved in defense response
GO:0006464	0.0010513208295054200	126	cellular protein modification process
GO:0036211	0.0010513208295054200	126	protein modification process
GO:2000113	0.0010582160468377100	56	negative regulation of cellular macromolecule biosynthetic process
GO:0052548	0.0010681783539640300	26	regulation of endopeptidase activity
GO:0009887	0.0010693652809237300	35	animal organ morphogenesis
GO:0008585	0.0010822916998878600	8	female gonad development
GO:0045786	0.0010978821787337380	29	negative regulation of cell cycle
GO:1902106	0.0011095862646838600	8	negative regulation of leukocyte differentiation
GO:0002755	0.0011110306086494700	5	MyD88-dependent toll-like receptor signaling pathway
GO:0097191	0.0011201938312608900	16	extrinsic apoptotic signaling pathway
GO:1990823	0.0011320136996628470	8	response to leukemia inhibitory factor
GO:1990830	0.0011320136996628470	8	cellular response to leukemia inhibitory factor
GO:0043000	0.0011391497810514600	2	Golgi to plasma membrane CFTR protein transport
GO:0016192	0.0011438756315968100	68	vesicle-mediated transport
GO:0050727	0.0011490518665626800	21	regulation of inflammatory response
GO:0098771	0.0011553221424055500	32	inorganic ion homeostasis
GO:0000377	0.0011649679986070300	22	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile
GO:0000398	0.0011649679986070300	22	mRNA splicing, via spliceosome
GO:2000052	0.0011653632650664400	3	positive regulation of non-canonical Wnt signaling pathway
GO:0051443	0.0011812157440950700	5	positive regulation of ubiquitin-protein transferase activity
GO:0002683	0.0011826795693092700	24	negative regulation of immune system process
GO:1903508	0.0011857264689228800	54	positive regulation of nucleic acid-templated transcription
GO:1902680	0.0011978358455337230	54	positive regulation of RNA biosynthetic process
GO:0051348	0.0012009262424428300	17	negative regulation of transferase activity
GO:0055065	0.0012173005594992950	30	metal ion homeostasis
GO:0045893	0.0012310585971427200	51	positive regulation of transcription, DNA-templated
GO:0071229	0.0012519448548478400	12	cellular response to acid chemical
GO:0009890	0.0012688880271021700	61	negative regulation of biosynthetic process
GO:0010742	0.0012757808096868500	5	macrophage derived foam cell differentiation
GO:0090077	0.0012757808096868500	5	foam cell differentiation
GO:0009991	0.0012827094566437200	25	response to extracellular stimulus
GO:0031663	0.0012829175459707600	7	lipopolysaccharide-mediated signaling pathway
GO:0031100	0.0013048539045245600	8	animal organ regeneration
GO:0006469	0.0013101746928983600	14	negative regulation of protein kinase activity
GO:0022411	0.0013379009449749300	30	cellular component disassembly
GO:0000375	0.0013594871702331400	22	RNA splicing, via transesterification reactions
GO:0007249	0.0013629073385377000	16	I-kappaB kinase/NF-kappaB signaling
GO:0046545	0.0013895824728868000	8	development of primary female sexual characteristics
GO:0043524	0.0013898963262740500	11	negative regulation of neuron apoptotic process
GO:0006952	0.0014051413637855300	59	defense response
GO:0050777	0.0014395102187458200	9	negative regulation of immune response
GO:0043951	0.0014750429831624900	4	negative regulation of cAMP-mediated signaling
GO:0002768	0.0014949772501581000	16	immune response-regulating cell surface receptor signaling pathway
GO:0043407	0.0015323650353316310	7	negative regulation of MAP kinase activity
GO:0001889	0.0015544241636103400	10	liver development
GO:0051438	0.0015629235314372790	7	regulation of ubiquitin-protein transferase activity
GO:0007165	0.0015719772223664860	165	signal transduction
GO:0031669	0.0015944977495241300	13	cellular response to nutrient levels
GO:0046903	0.0016318153410635600	58	secretion
GO:0045088	0.0016391115151327100	18	regulation of innate immune response
GO:0051336	0.0016454094228813550	50	regulation of hydrolase activity
GO:0021762	0.0016517236088658000	6	substantia nigra development
GO:0019941	0.0016846879063590100	28	modification-dependent protein catabolic process
GO:0006887	0.0016916012912290600	38	exocytosis
GO:0048856	0.0017105723820874900	165	anatomical structure development
GO:0061013	0.0017242842802928400	10	regulation of mRNA catabolic process
GO:0061008	0.0017433512709560800	10	hepaticobiliary system development
GO:0043488	0.0017506475384361900	9	regulation of mRNA stability
GO:2000095	0.0017564038174191500	3	regulation of Wnt signaling pathway, planar cell polarity pathway
GO:0033043	0.0017645513202805100	47	regulation of organelle organization
GO:0071230	0.0017685598008277800	6	cellular response to amino acid stimulus
GO:0035722	0.0017734002491010300	7	interleukin-12-mediated signaling pathway
GO:0007154	0.0017801499886610400	175	cell communication
GO:0048729	0.0017848494193933000	24	tissue morphogenesis
GO:0007568	0.0017889772582481000	18	aging
GO:2001235	0.0018256396943409600	14	positive regulation of apoptotic signaling pathway

GO:1903900	0.00187092676257607	12	regulation of viral life cycle
GO:0034660	0.00187583695477146	31	ncRNA metabolic process
GO:0060071	0.00188888675585567	6	Wnt signaling pathway, planar cell polarity pathway
GO:0048147	0.00189892255299485	5	negative regulation of fibroblast proliferation
GO:0006913	0.0019072900373477	20	nucleocytoplasmic transport
GO:0043497	0.00192992096495358	3	regulation of protein heterodimerization activity
GO:0032680	0.00196236717868749	10	regulation of tumor necrosis factor production
GO:0071349	0.00196388112002811	7	cellular response to interleukin-12
GO:0032501	0.00197276710470065	200	multicellular organismal process

(Significantly upregulated biological pathways in 6 min oscillatory condition).

Category	Overrepresented p-value	numDEInCat	Term - biological processes downregulated
GO:0048519	6.53730708762544e-36	210	negative regulation of biological process
GO:0006950	9.49794937120751e-36	173	response to stress
GO:0042221	4.79166053105996e-34	180	response to chemical
GO:0008219	4.48957909873772e-32	126	cell death
GO:0050896	5.63452858612644e-32	260	response to stimulus
GO:0012501	3.28726381764437e-30	119	programmed cell death
GO:0070887	1.24831271097848e-29	146	cellular response to chemical stimulus
GO:0010033	3.19390416487838e-29	146	response to organic substance
GO:0010941	1.88139360082511e-28	103	regulation of cell death
GO:0009888	8.03796009890965e-28	108	tissue development
GO:0048523	2.23385178147705e-27	181	negative regulation of cellular process
GO:0006915	2.31717172372853e-27	110	apoptotic process
GO:0043067	3.73438964138458e-27	97	regulation of programmed cell death
GO:0032502	5.83693359563238e-27	206	developmental process
GO:0042981	7.48832699449348e-27	96	regulation of apoptotic process
GO:0051716	9.59308097023453e-27	224	cellular response to stimulus
GO:0048856	2.04429823960331e-26	197	anatomical structure development
GO:0048583	1.02719966770318e-24	160	regulation of response to stimulus
GO:0007275	1.70031803996631e-24	183	multicellular organism development
GO:0097190	6.64243708750349e-24	58	apoptotic signaling pathway
GO:0071310	2.87477320481274e-23	120	cellular response to organic substance
GO:0007154	8.85197335808426e-23	197	cell communication
GO:0032501	1.00636436119289e-22	212	multicellular organismal process
GO:0048513	1.22602355484243e-22	138	animal organ development
GO:0008283	1.71208377577303e-22	103	cell proliferation
GO:0050789	2.01114572762762e-22	285	regulation of biological process
GO:0048869	2.42158351210269e-22	156	cellular developmental process
GO:0030154	1.31722739986207e-21	150	cell differentiation
GO:0048731	2.7325712850314e-21	165	system development
GO:0007165	4.47057303284572e-21	183	signal transduction
GO:0060548	4.87817178955677e-21	69	negative regulation of cell death
GO:0065007	6.07549563236562e-21	292	biological regulation
GO:0048518	7.76894439952941e-21	192	positive regulation of biological process
GO:0065009	9.25521264601393e-21	130	regulation of molecular function
GO:0009628	1.72503375344224e-20	73	response to abiotic stimulus
GO:0023052	1.82151339244257e-20	191	signaling
GO:0014070	2.35126553019964e-20	63	response to organic cyclic compound
GO:0051246	3.88487845612818e-20	120	regulation of protein metabolic process
GO:0042127	4.39107863890767e-20	86	regulation of cell proliferation
GO:0001775	5.25332781248837e-20	78	cell activation
GO:0010604	5.5236408847791e-20	133	positive regulation of macromolecule metabolic process
GO:0048585	5.81173768223313e-20	86	negative regulation of response to stimulus
GO:0048522	7.30948764038783e-20	176	positive regulation of cellular process
GO:0019222	1.02895256595909e-19	207	regulation of metabolic process
GO:0033554	1.22675528312579e-19	99	cellular response to stress
GO:0060429	1.32293828587028e-19	72	epithelium development
GO:0002376	1.7654099552937e-19	118	immune system process
GO:0080090	2.66799042516422e-19	192	regulation of primary metabolic process
GO:0009966	3.1318790564185e-19	127	regulation of signal transduction
GO:0097193	4.59941886701693e-19	37	intrinsic apoptotic signaling pathway
GO:0050793	7.53282316328623e-19	109	regulation of developmental process
GO:0007166	8.161694964044453e-19	118	cell surface receptor signaling pathway
GO:0009605	1.17521144307474e-18	100	response to external stimulus
GO:0010646	1.30079129892284e-18	134	regulation of cell communication
GO:0051173	1.58054157482762e-18	126	positive regulation of nitrogen compound metabolic process
GO:0060255	1.59749830383624e-18	194	regulation of macromolecule metabolic process
GO:0043069	1.60693596108775e-18	62	negative regulation of programmed cell death
GO:0009892	2.68318811918375e-18	122	negative regulation of metabolic process
GO:0043066	2.95291123174117e-18	61	negative regulation of apoptotic process
GO:0023051	3.13119411614215e-18	134	regulation of signaling
GO:0010605	3.22443930554476e-18	116	negative regulation of macromolecule metabolic process
GO:0010942	3.86035876789944e-18	53	positive regulation of cell death
GO:0032268	3.88535335675307e-18	111	regulation of cellular protein metabolic process
GO:0080134	4.1363287917301e-18	76	regulation of response to stress
GO:0031325	4.43441192384431e-18	128	positive regulation of cellular metabolic process
GO:0030855	5.65311047723418e-18	52	epithelial cell differentiation
GO:0050794	1.191524126207l2e-17	264	regulation of cellular process
GO:1901700	1.31692580948179e-17	80	response to oxygen-containing compound
GO:0009893	1.37184972614194e-17	134	positive regulation of metabolic process
GO:0051171	2.24284807725696e-17	184	regulation of nitrogen compound metabolic process
GO:0010648	2.41791321155405e-17	74	negative regulation of cell communication
GO:0023057	2.78375389984895e-17	74	negative regulation of signaling
GO:0035556	3.19533505372852e-17	114	intracellular signal transduction
GO:2001233	4.40376933587251e-17	40	regulation of apoptotic signaling pathway
GO:0031323	5.55961084585731e-17	189	regulation of cellular metabolic process
GO:1902531	6.32409248858281e-17	88	regulation of intracellular signal transduction
GO:0043065	8.39468619402128e-17	49	positive regulation of apoptotic process
GO:0048584	8.87934662947454e-17	97	positive regulation of response to stimulus
GO:0043068	1.01758539019593e-16	49	positive regulation of programmed cell death
GO:0065008	1.0220191065853e-16	137	regulation of biological quality
GO:2000026	1.15123445404771e-16	90	regulation of multicellular organismal development
GO:0034097	1.20999025001619e-16	65	response to cytokine
GO:0051239	2.35362123423046e-16	115	regulation of multicellular organismal process
GO:0051172	2.76962861583303e-16	102	negative regulation of nitrogen compound metabolic process
GO:0009968	3.31231707016365e-16	69	negative regulation of signal transduction
GO:0051248	6.29738510377931e-16	64	negative regulation of protein metabolic process
GO:0031324	8.23964020147814e-16	105	negative regulation of cellular metabolic process
GO:0009611	1.77470722571688e-15	46	response to wounding
GO:0045321	3.18303488590929e-15	65	leukocyte activation
GO:0009719	3.79643086948096e-15	77	response to endogenous stimulus
GO:0008544	4.30175608684671e-15	36	epidermis development
GO:0051247	6.82561350824534e-15	79	positive regulation of protein metabolic process
GO:2001234	1.23657047431265e-14	28	negative regulation of apoptotic signaling pathway
GO:0051094	1.41787921845428e-14	68	positive regulation of developmental process
GO:0050790	1.47710944761898e-14	95	regulation of catalytic activity
GO:0042325	2.00414777159828e-14	73	regulation of phosphorylation
GO:0045595	2.00623148919168e-14	79	regulation of cell differentiation
GO:0071345	2.37845555202183e-14	58	cellular response to cytokine stimulus
GO:0032270	2.39474575441494e-14	75	positive regulation of cellular protein metabolic process
GO:0042493	4.23678136611419e-14	56	response to drug
GO:0033993	4.28265819967168e-14	53	response to lipid
GO:0009725	4.3264521841442e-14	55	response to hormone
GO:0032879	4.96669277713487e-14	102	regulation of localization
GO:0031399	5.29820818582142e-14	81	regulation of protein modification process
GO:0001944	7.50456349718199e-14	47	vasculature development
GO:0032269	1.00256285588565e-13	58	negative regulation of cellular protein metabolic process
GO:0019220	1.15260873938266e-13	77	regulation of phosphate metabolic process
GO:0072358	1.18736527031422e-13	47	cardiovascular system development
GO:0051174	1.23912723717838e-13	77	regulation of phosphorus metabolic process
GO:0001932	1.36859766469109e-13	68	regulation of protein phosphorylation
GO:0044092	1.87053117272079e-13	58	negative regulation of molecular function
GO:0009636	1.91317235313017e-13	38	response to toxic substance

GO:0007155	2.22119812062468e-13	66	cell adhesion
GO:1901698	2.2367208834439e-13	56	response to nitrogen compound
GO:0022610	2.93351082350681e-13	66	biological adhesion
GO:0010035	3.03544388591288e-13	40	response to inorganic substance
GO:0006955	3.10487778862507e-13	80	immune response
GO:0040011	3.41245557355134e-13	77	locomotion
GO:0051240	4.0054391980754e-13	74	positive regulation of multicellular organismal process
GO:0048870	4.23316556890803e-13	71	cell motility
GO:0051674	4.23316556890803e-13	71	localization of cell
GO:0009408	4.56955462419946e-13	21	response to heat
GO:0010243	4.70436103475308e-13	53	response to organonitrogen compound
GO:0043588	4.88257480029101e-13	31	skin development
GO:0030162	6.27418507103693e-13	46	regulation of proteolysis
GO:0019221	7.67192568151455e-13	45	cytokine-mediated signaling pathway
GO:0098609	1.012581677540 26e-12	47	cell-cell adhesion
GO:0001568	1.02710594592241e-12	44	blood vessel development
GO:0051704	1.37800863362238e-12	90	multi-organism process
GO:0016477	1.40694937545394e-12	66	cell migration
GO:0043086	1.47195891558588e-12	46	negative regulation of catalytic activity
GO:0009967	1.71158964925255e-12	71	positive regulation of signal transduction
GO:0002684	1.85268101989961e-12	52	positive regulation of immune system process
GO:0009653	1.91598474513763e-12	96	anatomical structure morphogenesis
GO:0009266	2.14676645988357e-12	24	response to temperature stimulus
GO:0010647	2.29498106272713e-12	75	positive regulation of cell communication
GO:0042592	2.43466536761438e-12	77	homeostatic process
GO:0042060	2.54841434027591e-12	37	wound healing
GO:0023056	2.8944692443709e-12	75	positive regulation of signaling
GO:0008285	4.34254515615146e-12	43	negative regulation of cell proliferation
GO:0009913	4.35476781386006e-12	27	epidermal cell differentiation
GO:0009987	5.67297181420363e-12	327	cellular process
GO:0035295	6.60845651172842e-12	54	tube development
GO:0010468	8.58016119475984e-12	141	regulation of gene expression
GO:0070059	8.7781401066338e-12	14	intrinsic apoptotic signaling pathway in response to endoplasmic reticulum stress
GO:0006979	9.97716260875681e-12	34	response to oxidative stress
GO:0071248	1.14934536132956e-11	22	cellular response to metal ion
GO:0080135	1.20903046503237e-11	43	regulation of cellular response to stress
GO:0010038	1.22045763843102e-11	30	response to metal ion
GO:0048514	1.90425000796553e-11	39	blood vessel morphogenesis
GO:1902533	2.24137635038107e-11	53	positive regulation of intracellular signal transduction
GO:0009889	2.36836133224506e-11	134	regulation of biosynthetic process
GO:0006468	2.47712312133117e-11	77	protein phosphorylation
GO:0010629	3.54569221994169e-11	78	negative regulation of gene expression
GO:0046686	3.76342047250781e-11	14	response to cadmium ion
GO:0071496	4.24927292863902e-11	28	cellular response to external stimulus
GO:0006986	4.62386671324624e-11	21	response to unfolded protein
GO:0010628	4.98099773380043e-11	78	positive regulation of gene expression
GO:2001236	5.28201152576608e-11	20	regulation of extrinsic apoptotic signaling pathway
GO:0035966	5.55408392187682e-11	22	response to topologically incorrect protein
GO:0031667	5.80417150086083e-11	33	response to nutrient levels
GO:0031326	5.97388738074788e-11	131	regulation of cellular biosynthetic process
GO:0002682	6.39669656656048e-11	62	regulation of immune system process
GO:2000145	6.79323393138488e-11	48	regulation of cell motility
GO:1902532	6.9081897516401e-11	35	negative regulation of intracellular signal transduction
GO:0006952	7.191187655886 44e-11	62	defense response
GO:1901652	7.38865200264802e-11	33	response to peptide
GO:0030216	7.8611525141494e-11	23	keratinocyte differentiation
GO:0009991	8.04447927061346e-11	34	response to extracellular stimulus
GO:0043618	8.58286607620974e-11	14	regulation of transcription from RNA polymerase II promoter in response to stress
GO:0045862	9.1574159181989e-11	29	positive regulation of proteolysis
GO:0045597	9.65486813664373e-11	49	positive regulation of cell differentiation
GO:0040012	9.659642379796 46e-11	50	regulation of locomotion
GO:0030334	9.78107961092959e-11	46	regulation of cell migration
GO:0006928	1.011529124837 16e-10	78	movement of cell or subcellular component
GO:0051270	1.32433513260794e-10	50	regulation of cellular component movement
GO:0071241	1.48146298352387e-10	22	cellular response to inorganic substance
GO:0034605	1.57481652737053e-10	16	cellular response to heat
GO:0044267	1.63459654315874e-10	153	cellular protein metabolic process
GO:0051179	1.82356008977566e-10	175	localization
GO:0002064	1.856446836095 66e-10	21	epithelial cell development
GO:1901701	1.87536998218919e-10	52	cellular response to oxygen-containing compound
GO:0001817	1.94090231718521e-10	38	regulation of cytokine production
GO:0042326	1.9427937571924e-10	32	negative regulation of phosphorylation
GO:0030097	1.95812324543217e-10	44	hemopoiesis
GO:0097191	2.10454614895735e-10	23	extrinsic apoptotic signaling pathway
GO:0001525	2.44735681524543e-10	34	angiogenesis
GO:0043620	2.54517843552462e-10	14	regulation of DNA-templated transcription in response to stress
GO:0001816	2.71272180993746e-10	40	cytokine production
GO:0048534	3.17004537240251e-10	45	hematopoietic or lymphoid organ development
GO:0048468	3.43313993114642e-10	78	cell development
GO:0019538	3.49229749483065e-10	163	protein metabolic process
GO:0002521	4.38820560469302e-10	32	leukocyte differentiation
GO:0072359	4.72928166709798e-10	51	circulatory system development
GO:0009612	5.75905474154235e-10	21	response to mechanical stimulus
GO:0044260	6.41697871765269e-10	211	cellular macromolecule metabolic process
GO:0051241	7.92960133474009e-10	53	negative regulation of multicellular organismal process
GO:0048646	8.36391944471597e-10	51	anatomical structure formation involved in morphogenesis
GO:0045859	8.41303235393059e-10	42	regulation of protein kinase activity
GO:0035239	9.08296237845168e-10	44	tube morphogenesis
GO:0061687	9.85989526923492e-10	8	detoxification of inorganic compound
GO:0016310	1.11529078931077e-09	83	phosphorylation
GO:0043549	1.17210106378004e-09	44	regulation of kinase activity
GO:0010556	1.2157889395116e-09	124	regulation of macromolecule biosynthetic process
GO:0001934	1.25906976627006e-09	47	positive regulation of protein phosphorylation
GO:0071495	1.27963664874389e-09	58	cellular response to endogenous stimulus
GO:0046649	1.50301423063679e-09	36	lymphocyte activation
GO:0045766	1.53685239066326e-09	19	positive regulation of angiogenesis
GO:1904018	1.57721063491423e-09	20	positive regulation of vasculature development
GO:0044093	1.64898108087082e-09	69	positive regulation of molecular function
GO:0002520	1.71099790458423e-09	45	immune system development
GO:0097501	1.74262105451467e-09	8	stress response to metal ion
GO:0023014	1.92078834179932e-09	45	signal transduction by protein phosphorylation
GO:0008625	2.07638929510555e-09	14	extrinsic apoptotic signaling pathway via death domain receptors
GO:0071407	2.09678926236367e-09	33	cellular response to organic cyclic compound
GO:0050865	2.10291154703441e-09	32	regulation of cell activation
GO:0051338	2.11963031142964e-09	47	regulation of transferase activity
GO:0031401	2.61670730603234e-09	53	positive regulation of protein modification process
GO:0070482	2.73038527612068e-09	26	response to oxygen levels
GO:2001237	2.85841124293841e-09	15	negative regulation of extrinsic apoptotic signaling pathway
GO:2000112	2.89861405390471e-09	120	regulation of cellular macromolecule biosynthetic process
GO:0045936	3.10839442978313e-09	34	negative regulation of phosphate metabolic process
GO:0000165	3.17039471058716e-09	44	MAPK cascade
GO:2001235	3.19483061058759e-09	19	positive regulation of apoptotic signaling pathway
GO:0010563	3.27430266509544e-09	34	negative regulation of phosphorus metabolic process
GO:0008284	3.41579987237921e-09	44	positive regulation of cell proliferation
GO:0051726	3.4349934568624e-09	53	regulation of cell cycle
GO:0022603	3.50048004811588e-09	48	regulation of anatomical structure morphogenesis
GO:0071280	3.61786799583933e-09	9	cellular response to copper ion
GO:0010558	3.68728281703429e-09	62	negative regulation of macromolecule biosynthetic process
GO:0031400	3.93099829921255e-09	35	negative regulation of protein modification process
GO:0045765	4.19209145006371e-09	24	regulation of angiogenesis
GO:0009891	4.22631821288479e-09	74	positive regulation of biosynthetic process
GO:0051128	4.74596484785745e-09	87	regulation of cellular component organization
GO:0048545	4.99014602288376e-09	27	response to steroid hormone
GO:0042327	5.41026160802753e-09	47	positive regulation of phosphorylation
GO:0031327	6.35449318436982e-09	63	negative regulation of cellular biosynthetic process
GO:0034976	6.45143025852922e-09	23	response to endoplasmic reticulum stress
GO:0046688	6.58728404531762e-09	10	response to copper ion
GO:2001242	7.22921087379732e-09	18	regulation of intrinsic apoptotic signaling pathway
GO:0030856	8.24755123771878e-09	16	regulation of epithelial cell differentiation

GO:0001933	8.32979426603345e-09	28	negative regulation of protein phosphorylation
GO:0002274	8.60746454224867e-09	36	myeloid leukocyte activation
GO:0044271	9.36982739503557e-09	141	cellular nitrogen compound biosynthetic process
GO:0030155	9.66860408577485e-09	36	regulation of cell adhesion
GO:0031328	1.120201466111841e-08	72	positive regulation of cellular biosynthetic process
GO:0046685	1.145935142254 7e-08	9	response to arsenic-containing substance
GO:0009890	1.16488489818256e-08	63	negative regulation of biosynthetic process
GO:0048608	1.269832674767 61e-08	28	reproductive structure development
GO:0022008	1.2829627553831e-08	61	neurogenesis
GO:0010562	1.290037711015923e-08	48	positive regulation of phosphorus metabolic process
GO:0045937	1.290037711015923e-08	48	positive regulation of phosphate metabolic process
GO:0043434	1.31619765399382e-08	27	response to peptide hormone
GO:0036293	1.3726180743345e-08	24	response to decreased oxygen levels
GO:0006810	1.416534263536 61e-08	139	transport
GO:0061458	1.516843440691 83e-08	28	reproductive system development
GO:0019219	1.646086593322 02e-08	120	regulation of nucleobase-containing compound metabolic process
GO:1903506	1.690260045434 63e-08	108	regulation of nucleic acid-templated transcription
GO:1901564	1.734265098207 46e-08	178	organonitrogen compound metabolic process
GO:2001141	1.890224648999 3e-08	108	regulation of RNA biosynthetic process
GO:1903708	1.922504592483 04e-08	18	positive regulation of hemopoiesis
GO:0031669	1.939152633499 896e-08	20	cellular response to nutrient levels
GO:0002252	1.948757465847 99e-08	49	immune effector process
GO:0044419	1.974124986845 12e-08	41	interspecies interaction between organisms
GO:0043085	2.0961108575489e-08	57	positive regulation of catalytic activity
GO:1903706	2.097807597174 18e-08	27	regulation of hemopoiesis
GO:0010273	2.162491891233 92e-08	7	detoxification of copper ion
GO:1990169	2.162491891233 92e-08	7	stress response to copper ion
GO:0040007	2.168732659454 96e-08	45	growth
GO:0042594	2.195526463385 43e-08	18	response to starvation
GO:0006954	2.463375122076 06e-08	35	inflammatory response
GO:0009058	2.487911521385 17e-08	166	biosynthetic process
GO:1902041	2.584877206650 83e-08	11	regulation of extrinsic apoptotic signaling pathway via death domain receptors
GO:0002694	2.682530923340 37e-08	29	regulation of leukocyte activation
GO:0006355	2.773306943050 37e-08	106	regulation of transcription, DNA-templated
GO:0030260	2.924661764440 54e-08	15	entry into host cell
GO:0044409	2.924661764440 54e-08	15	entry into host
GO:0051806	2.924661764440 54e-08	15	entry into cell of other organism involved in symbiotic interaction
GO:0051828	2.924661764440 54e-08	15	entry into other organism involved in symbiotic interaction
GO:1901342	3.041641406388 19e-08	24	regulation of vasculature development
GO:0031668	3.076231082105 35e-08	21	cellular response to extracellular stimulus
GO:0044403	3.092401991015 89e-08	40	symbiont process
GO:0045935	3.243635943102 51e-08	69	positive regulation of nucleobase-containing compound metabolic process
GO:1900034	3.278470167736 47e-08	10	regulation of cellular response to heat
GO:0031331	3.330754357103 77e-08	25	positive regulation of cellular catabolic process
GO:0030335	3.498607250119 93e-08	30	positive regulation of cell migration
GO:0051234	3.528962529906 04e-08	140	establishment of localization
GO:0042089	3.604196575180 14e-08	13	cytokine biosynthetic process
GO:0030330	3.7246501675302e-08	14	DNA damage response, signal transduction by p53 class mediator
GO:0052547	3.786479949852 28e-08	27	regulation of peptidase activity
GO:0050673	3.789912441710 75e-08	26	epithelial cell proliferation
GO:0052548	3.990255051468 92e-08	26	regulation of endopeptidase activity
GO:0042107	4.193274484535 97e-08	13	cytokine metabolic process
GO:0010557	4.647999084012 53e-08	68	positive regulation of macromolecule biosynthetic process
GO:0098754	4.982275532400 3e-08	14	detoxification
GO:0031960	5.045257858374 13e-08	16	response to corticosteroid
GO:0051252	5.088497006397 57e-08	112	regulation of RNA metabolic process
GO:0061077	5.166435790025 05e-08	11	chaperone-mediated protein folding
GO:0051093	5.256231748274 04e-08	42	negative regulation of developmental process
GO:2000113	5.381168310137 83e-08	57	negative regulation of cellular macromolecule biosynthetic process
GO:0002237	5.558591166030 05e-08	23	response to molecule of bacterial origin
GO:0043408	5.985788185307 11e-08	37	regulation of MAPK cascade
GO:0002443	6.046833140720 74e-08	38	leukocyte mediated immunity
GO:2000147	6.184089857880 1e-08	30	positive regulation of cell motility
GO:1901576	6.294777526439 76e-08	163	organic substance biosynthetic process
GO:1901214	6.392357340987 52e-08	22	regulation of neuron death
GO:0044249	6.682901852696e-08	161	cellular biosynthetic process
GO:0040017	7.180463877270 79e-08	31	positive regulation of locomotion
GO:2000116	7.217410425564 57e-08	20	regulation of cysteine-type endopeptidase activity
GO:0051049	7.248048675541 79e-08	63	regulation of transport
GO:0043281	7.696348790435 24e-08	19	regulation of cysteine-type endopeptidase activity involved in apoptotic process
GO:0051254	8.001855664222 58e-08	63	positive regulation of RNA metabolic process
GO:2001243	8.131292711477 17e-08	13	negative regulation of intrinsic apoptotic signaling pathway
GO:0006796	8.167186961044 99e-08	99	phosphate-containing compound metabolic process
GO:0070848	8.749554065434 39e-08	36	response to growth factor
GO:0071363	8.892857824757 53e-08	35	cellular response to growth factor stimulus
GO:0097659	9.063046950398 86e-08	109	nucleic acid-templated transcription
GO:0042035	9.445864000851 17e-08	12	regulation of cytokine biosynthetic process
GO:0007568	9.796319429113 15e-08	22	aging
GO:0009607	1.018733928152 18e-07	40	response to biotic stimulus
GO:0032436	1.038223161023 64e-07	12	positive regulation of proteasomal ubiquitin-dependent protein catabolic process
GO:0051272	1.082905811077 14e-07	30	positive regulation of cellular component movement
GO:0051348	1.114164720075 31e-07	21	negative regulation of transferase activity
GO:0044706	1.125498209660 21e-07	18	multi-multicellular organism process
GO:0071276	1.139111904571 67e-07	9	cellular response to cadmium ion
GO:0043207	1.151182226137 41e-07	39	response to external biotic stimulus
GO:0051707	1.151182226137 41e-07	39	response to other organism
GO:0032774	1.163205220348 97e-07	109	RNA biosynthetic process
GO:0032940	1.2398757179365e-07	56	secretion by cell
GO:0006793	1.250007641005 98e-07	99	phosphorus metabolic process
GO:0070997	1.290094425468 17e-07	23	neuron death
GO:0009057	1.293194629002 88e-07	55	macromolecule catabolic process
GO:0001666	1.346397182162 89e-07	22	response to hypoxia
GO:0007399	1.355297701663 14e-07	76	nervous system development
GO:0051249	1.360333357052 35e-07	25	regulation of lymphocyte activation
GO:0007167	1.369108076921 23e-07	44	enzyme linked receptor protein signaling pathway
GO:0045596	1.382902894607 92e-07	34	negative regulation of cell differentiation
GO:0009059	1.392742846563 88e-07	139	macromolecule biosynthetic process
GO:0048871	1.444591332086 55e-07	27	multicellular organismal homeostasis
GO:0002366	1.4654941406446e-07	35	leukocyte activation involved in immune response
GO:1903507	1.483402083371 62e-07	51	negative regulation of nucleic acid-templated transcription
GO:0043535	1.501830553776 78e-07	13	regulation of blood vessel endothelial cell migration
GO:0050878	1.570319066117 04e-07	27	regulation of body fluid levels
GO:1902679	1.572211761263 38e-07	51	negative regulation of RNA biosynthetic process
GO:0002263	1.620558738838 22e-07	35	cell activation involved in immune response
GO:0001819	1.6336965120437e-07	25	positive regulation of cytokine production
GO:0034109	1.664711652617 13e-07	11	homotypic cell-cell adhesion
GO:0006351	1.710148477791 98e-07	107	transcription, DNA-templated
GO:0008637	1.757069852312 41e-07	14	apoptotic mitochondrial changes
GO:0010469	1.801207016597 49e-07	27	regulation of signaling receptor activity
GO:0045598	1.805783037114 92e-07	14	regulation of fat cell differentiation
GO:0009896	1.813409458901 93e-07	26	positive regulation of catabolic process
GO:0009267	1.973560033702 86e-07	15	cellular response to starvation
GO:0045926	2.205627056090 79e-07	20	negative regulation of growth
GO:0036499	2.308780088590 08e-07	7	PERK-mediated unfolded protein response
GO:0006464	2.402152859218 88e-07	118	cellular protein modification process
GO:0036211	2.402152859218 88e-07	118	protein modification process
GO:0008150	2.629808008167 09e-07	335	biological_process
GO:0033673	3.0904245159394e-07	19	negative regulation of kinase activity
GO:0035690	3.341855850518 84e-07	23	cellular response to drug
GO:0040008	3.443966299773 06e-07	34	regulation of growth
GO:0001667	3.548744798123 95e-07	25	ameboidal-type cell migration
GO:0009894	3.577996196924 32e-07	41	regulation of catabolic process
GO:0016032	3.743658389222 22e-07	36	viral process
GO:0071260	3.795870458661 07e-07	11	cellular response to mechanical stimulus
GO:0051384	3.825152961689 33e-07	14	response to glucocorticoid
GO:0045892	3.854226741393 07e-07	49	negative regulation of transcription, DNA-templated
GO:0046718	3.896893221640 16e-07	13	viral entry into host cell
GO:0034645	4.22151662140 13e-07	134	cellular macromolecule biosynthetic process
GO:0000122	4.405288971764 31e-07	39	negative regulation of transcription by RNA polymerase II

GO:0019058	4.40881050619736e-07	21	viral life cycle
GO:0042770	4.41238700540793e-07	14	signal transduction in response to DNA damage
GO:0009617	4.42662461629816e-07	29	response to bacterium
GO:0007565	4.55769248916237e-07	16	female pregnancy
GO:0045682	4.7272570496622e-07	11	regulation of epidermis development
GO:0002526	4.75619830756159e-07	13	acute inflammatory response
GO:0043170	5.07237882561761e-07	223	macromolecule metabolic process
GO:0003158	5.18065947522326e-07	13	endothelium development
GO:0032870	5.3008307475445e-07	33	cellular response to hormone stimulus
GO:0045944	5.51082947488646e-07	47	positive regulation of transcription by RNA polymerase II
GO:0032496	5.61908229774707e-07	21	response to lipopolysaccharide
GO:0061041	5.7503615836281e-07	13	regulation of wound healing
GO:2000060	5.76634212434618e-07	12	positive regulation of ubiquitin-dependent protein catabolic process
GO:0090559	5.812579517320 56e-07	11	regulation of membrane permeability
GO:0071294	5.86358018045141e-07	7	cellular response to zinc ion
GO:0061061	6.21646496295806e-07	31	muscle structure development
GO:0050817	6.80110780576677e-07	21	coagulation
GO:0010467	6.94257896387641e-07	148	gene expression
GO:0031329	6.95449172898813e-07	37	regulation of cellular catabolic process
GO:0072657	7.00832593396634e-07	32	protein localization to membrane
GO:0042176	7.05132500193625e-07	24	regulation of protein catabolic process
GO:0010632	7.17807904006201e-07	18	regulation of epithelial cell migration
GO:0042119	7.31123489187153e-07	28	neutrophil activation
GO:0070527	7.35132038617559e-07	9	platelet aggregation
GO:0048878	7.41694289852097e-07	44	chemical homeostasis
GO:0050730	7.43690230809186e-07	18	regulation of peptidyl-tyrosine phosphorylation
GO:0072331	7.74404997394911e-07	18	signal transduction by p53 class mediator
GO:0034620	7.87827835355468e-07	14	cellular response to unfolded protein
GO:0022407	7.90679483994789e-07	23	regulation of cell-cell adhesion
GO:0045446	8.17941145527981e-07	12	endothelial cell differentiation
GO:0036003	8.20227666884295e-07	7	positive regulation of transcription from RNA polymerase II promoter in response to stress
GO:0045934	8.4124032722102e-07	55	negative regulation of nucleobase-containing compound metabolic process
GO:0006882	9.01943516939196e-07	8	cellular zinc ion homeostasis
GO:0036230	9.152101159227787e-07	28	granulocyte activation
GO:0055076	9.361048102396 72e-07	14	transition metal ion homeostasis
GO:0046903	9.76223810980349e-07	57	secretion
GO:1903364	9.84560563131474e-07	14	positive regulation of cellular protein catabolic process
GO:0061028	1.05737885386945e-06	8	establishment of endothelial barrier
GO:0006508	1.11673232675457e-06	61	proteolysis
GO:0055069	1.11868893801531e-06	8	zinc ion homeostasis
GO:0045861	1.13071281280447e-06	21	negative regulation of proteolysis
GO:0030183	1.28762548985562e-06	12	B cell differentiation
GO:0032101	1.31152914019433e-06	34	regulation of response to external stimulus
GO:1901800	1.34982449147654e-06	12	positive regulation of proteasomal protein catabolic process
GO:1903037	1.36835327815215e-06	19	regulation of leukocyte cell-cell adhesion
GO:0043523	1.44070291807989e-06	16	regulation of neuron apoptotic process
GO:0034599	1.44569200531554e-06	20	cellular response to oxidative stress
GO:0003006	1.47964448585578e-06	31	developmental process involved in reproduction
GO:0032434	1.516529852801e-06	13	regulation of proteasomal ubiquitin-dependent protein catabolic process
GO:0019725	1.52316675163275e-06	38	cellular homeostasis
GO:0045732	1.52818065160323e-06	17	positive regulation of protein catabolic process
GO:0042149	1.57299892674865e-06	8	cellular response to glucose starvation
GO:1902105	1.61774190555943e-06	18	regulation of leukocyte differentiation
GO:0043534	1.61911848382211e-06	13	blood vessel endothelial cell migration
GO:0019438	1.64852057635379e-06	118	aromatic compound biosynthetic process
GO:0045893	1.72332572910073e-06	55	positive regulation of transcription, DNA-templated
GO:0051253	1.77652543933449e-06	51	negative regulation of RNA metabolic process
GO:0001885	1.78541003571678e-06	9	endothelial cell development
GO:0070661	1.78979877056444e-06	18	leukocyte proliferation
GO:0050867	1.79838664647105e-06	20	positive regulation of cell activation
GO:0051402	1.80816996414621e-06	17	neuron apoptotic process
GO:0071243	1.84239758188194e-06	6	cellular response to arsenic-containing substance
GO:0042110	1.84370377852312e-06	24	T cell activation
GO:0048699	1.86199587923671e-06	53	generation of neurons
GO:0071900	1.87005494396338e-06	27	regulation of protein serine/threonine kinase activity
GO:0007159	1.96219857582149e-06	20	leukocyte cell-cell adhesion
GO:0051051	1.96853569448496e-06	25	negative regulation of transport
GO:0022414	2.00958398392031e-06	50	reproductive process
GO:0008630	2.03238251039784e-06	12	intrinsic apoptotic signaling pathway in response to DNA damage
GO:0006469	2.09098124817724e-06	17	negative regulation of protein kinase activity
GO:0000003	2.16184360814478e-06	50	reproduction
GO:0051050	2.23436150905115e-06	38	positive regulation of transport
GO:0032880	2.24995044617698e-06	40	regulation of protein localization
GO:0007596	2.26176659548233e-06	20	blood coagulation
GO:0045860	2.38381397664937e-06	27	positive regulation of protein kinase activity
GO:0071396	2.39657986295559e-06	29	cellular response to lipid
GO:0048771	2.52222174810313e-06	14	tissue remodeling
GO:0042542	2.69836366790119e-06	13	response to hydrogen peroxide
GO:0071453	2.74089512736267e-06	15	cellular response to oxygen levels
GO:0034654	2.75081635363009e-06	116	nucleobase-containing compound biosynthetic process
GO:1905475	2.94220380127418e-06	15	regulation of protein localization to membrane
GO:0048732	3.00328588254353e-06	24	gland development
GO:0007599	3.01780546536438e-06	20	hemostasis
GO:0046916	3.0426026134124e-06	12	cellular transition metal ion homeostasis
GO:0051701	3.09704104303122e-06	16	interaction with host
GO:0044265	3.13657528201482e-06	46	cellular macromolecule catabolic process
GO:0050670	3.19966919458301e-06	15	regulation of lymphocyte proliferation
GO:0030098	3.38921692276578e-06	20	lymphocyte differentiation
GO:0035967	3.44347668601101e-06	14	cellular response to topologically incorrect protein
GO:0051085	3.45091566150896e-06	7	chaperone cofactor-dependent protein refolding
GO:0032944	3.45907695354462e-06	15	regulation of mononuclear cell proliferation
GO:0043412	3.51193863271978e-06	119	macromolecule modification
GO:0002275	3.54762435479423e-06	28	myeloid cell activation involved in immune response
GO:0050801	3.61660471042734e-06	33	ion homeostasis
GO:1902107	3.64202467629572e-06	13	positive regulation of leukocyte differentiation
GO:0006820	3.79612408172379e-06	28	anion transport
GO:0072332	3.81847017248867e-06	10	intrinsic apoptotic signaling pathway by p53 class mediator
GO:0007169	3.89614986295495e-06	32	transmembrane receptor protein tyrosine kinase signaling pathway
GO:0050778	4.02429755147451e-06	31	positive regulation of immune response
GO:0001836	4.12813192524621e-06	9	release of cytochrome c from mitochondria
GO:0006807	4.13228232332239e-06	232	nitrogen compound metabolic process
GO:0002696	4.18771450157007e-06	19	positive regulation of leukocyte activation
GO:0036294	4.20624258942165e-06	14	cellular response to decreased oxygen levels
GO:1903034	4.39942737143838e-06	13	regulation of response to wounding
GO:0002444	4.6389417080 87e-06	28	myeloid leukocyte mediated immunity
GO:0032103	4.69126727990077e-06	18	positive regulation of response to external stimulus
GO:0030099	4.77707571088585e-06	23	myeloid cell differentiation
GO:0043536	5.17075829645042e-06	9	positive regulation of blood vessel endothelial cell migration
GO:1903508	5.28473179789443e-06	56	positive regulation of nucleic acid-templated transcription
GO:0045444	5.33073157406328e-06	16	fat cell differentiation
GO:0051090	5.35500465248491e-06	23	regulation of DNA-binding transcription factor activity
GO:1902680	5.4008520194484e-06	56	positive regulation of RNA biosynthetic process
GO:0030182	5.44808744404602e-06	48	neuron differentiation
GO:1903052	5.4963402653518e-06	12	positive regulation of proteolysis involved in cellular protein catabolic process
GO:0071704	5.55118464547855e-06	247	organic substance metabolic process
GO:0050731	5.55354410299739e-06	14	positive regulation of peptidyl-tyrosine phosphorylation
GO:0071214	5.67874377576878e-06	20	cellular response to abiotic stimulus
GO:0104004	5.67874377576878e-06	20	cellular response to environmental stimulus
GO:0045055	5.77268632727206e-06	35	regulated exocytosis
GO:0043154	5.84236395099717e-06	10	negative regulation of cysteine-type endopeptidase activity involved in apoptotic process
GO:1901216	5.87681639393343e-06	10	positive regulation of neuron death
GO:1905898	6.08875227328425e-06	7	positive regulation of response to endoplasmic reticulum stress
GO:0055082	6.14899625546515e-06	32	cellular chemical homeostasis
GO:0006984	6.25108331690176e-06	8	ER-nucleus signaling pathway
GO:0018130	6.26085564402463e-06	116	heterocycle biosynthetic process
GO:0070663	6.27274025105852e-06	15	regulation of leukocyte proliferation
GO:0051129	6.31189227145387e-06	32	negative regulation of cellular component organization
GO:0071417	6.37257807132914e-06	27	cellular response to organonitrogen compound
GO:0010594	6.45506611201121e-06	14	regulation of endothelial cell migration

GO:0010631	6.52087601663682e-06	19	epithelial cell migration
GO:1901362	6.64092247669751e-06	119	organic cyclic compound biosynthetic process
GO:0032354	6.69020623811982e-06	5	response to follicle-stimulating hormone
GO:1903531	6.77025815888958e-06	14	negative regulation of secretion by cell
GO:0006357	6.92424569357789e-06	80	regulation of transcription by RNA polymerase II
GO:0043299	7.06558677919495e-06	27	leukocyte degranulation
GO:0050900	7.09892574492577e-06	22	leukocyte migration
GO:0031571	7.23382777725878e-06	9	mitotic G1 DNA damage checkpoint
GO:0044819	7.23382777725878e-06	9	mitotic G1/S transition checkpoint
GO:0002699	7.23491280462927e-06	15	positive regulation of immune effector process
GO:0006518	7.26088587959078e-06	37	peptide metabolic process
GO:0090132	7.26796469489195e-06	19	epithelium migration
GO:0050678	7.6707126723999e-06	20	regulation of epithelial cell proliferation
GO:0044237	7.67704521285199e-06	242	cellular metabolic process
GO:0006935	7.72341235994152e-06	28	chemotaxis
GO:0010043	7.84187927894699e-06	8	response to zinc ion
GO:0097237	7.88621019641672e-06	16	cellular response to toxic substance
GO:0002446	7.99314902072778e-06	26	neutrophil mediated immunity
GO:0002262	8.16614822252323e-06	13	myeloid cell homeostasis
GO:0042330	8.24636341778918e-06	28	taxis
GO:0044783	8.27903557433631e-06	9	G1 DNA damage checkpoint
GO:1903039	8.42530029693302e-06	15	positive regulation of leukocyte cell-cell adhesion
GO:0051251	8.44649803236958e-06	17	positive regulation of lymphocyte activation
GO:0043616	8.92497808984437e-06	7	keratinocyte proliferation
GO:0034698	8.95519085692455e-06	6	response to gonadotropin
GO:0006402	9.18110677423205e-06	20	mRNA catabolic process
GO:0006366	9.36256492766583e-06	83	transcription by RNA polymerase II
GO:0090130	9.57154841996298e-06	19	tissue migration
GO:0098656	9.65645407575602e-06	17	anion transmembrane transport
GO:0090049	9.78096542246325e-06	8	regulation of cell migration involved in sprouting angiogenesis
GO:0033674	9.83198661060492e-06	27	positive regulation of kinase activity
GO:0000302	9.98569115222509e-06	16	response to reactive oxygen species
GO:0051084	1.0019312015381e-05	7	'de novo' posttranslational protein folding
GO:0071456	1.01455649714103e-05	13	cellular response to hypoxia
GO:0045639	1.05683093066574e-05	10	positive regulation of myeloid cell differentiation
GO:0046651	1.06997961992372e-05	16	lymphocyte proliferation
GO:1902042	1.0766324666146e-05	7	negative regulation of extrinsic apoptotic signaling pathway via death domain receptors
GO:0090083	1.10790543118834e-05	5	regulation of inclusion body assembly
GO:0043410	1.13202077261507e-05	26	positive regulation of MAPK cascade
GO:1903362	1.13961039788338e-05	17	regulation of cellular protein catabolic process
GO:2000117	1.17904687244513e-05	10	negative regulation of cysteine-type endopeptidase activity
GO:0050863	1.18481446869798e-05	18	regulation of T cell activation
GO:0032943	1.21213452276028e-05	16	mononuclear cell proliferation
GO:0051336	1.25259570944721e-05	46	regulation of hydrolase activity
GO:0045604	1.28222125910285e-05	8	regulation of epidermal cell differentiation
GO:2000058	1.29739682145098e-05	13	regulation of ubiquitin-dependent protein catabolic process
GO:0050776	1.30970510601714e-05	35	regulation of immune response
GO:0008585	1.31825227295248e-05	10	female gonad development
GO:0038034	1.32208710018685e-05	9	signal transduction in absence of ligand
GO:0097192	1.32208710018685e-05	9	extrinsic apoptotic signaling pathway in absence of ligand
GO:0042129	1.33454677113152e-05	12	regulation of T cell proliferation
GO:0043312	1.4036915376881e-05	25	neutrophil degranulation
GO:0042063	1.40370343220692e-05	17	gliogenesis
GO:0051961	1.41328859459379e-05	18	negative regulation of nervous system development
GO:0006887	1.41937962374278e-05	37	exocytosis
GO:1903827	1.42643343782847e-05	26	regulation of cellular protein localization
GO:0030003	1.44491045682571e-05	27	cellular cation homeostasis
GO:0018108	1.48720426733669e-05	21	peptidyl-tyrosine phosphorylation
GO:0046902	1.49551342542431e-05	9	regulation of mitochondrial membrane permeability
GO:0050671	1.56062938320938e-05	11	positive regulation of lymphocyte proliferation
GO:0002283	1.58241706826731e-05	25	neutrophil activation involved in immune response
GO:0045786	1.59505601650933e-05	28	negative regulation of cell cycle
GO:0045087	1.62443514417517e-05	32	innate immune response
GO:0042098	1.63861051045982e-05	13	T cell proliferation
GO:0034330	1.65833281104128e-05	18	cell junction organization
GO:0018212	1.7033127259544e-05	21	peptidyl-tyrosine modification
GO:0043603	1.70751893785881e-05	43	cellular amide metabolic process
GO:0032946	1.71641442985893e-05	11	positive regulation of mononuclear cell proliferation
GO:0006457	1.73310476148558e-05	16	protein folding
GO:0002456	1.74545953836229e-05	10	T cell mediated immunity
GO:0010951	1.75674616857547e-05	15	negative regulation of endopeptidase activity
GO:0042113	1.78249131717422e-05	15	B cell activation
GO:0006970	1.87124962220312e-05	9	response to osmotic stress
GO:0044344	1.93252888292976e-05	12	cellular response to fibroblast growth factor stimulus
GO:0044703	1.94676420343913e-05	36	multi-organism reproductive process
GO:0045445	1.97047873350459e-05	9	myoblast differentiation
GO:0006873	1.97547335048754e-05	27	cellular ion homeostasis
GO:0007249	1.98236213456456e-05	17	I-kappaB kinase/NF-kappaB signaling
GO:0046545	1.99881173367065e-05	10	development of primary female sexual characteristics
GO:0050818	2.00543929660519e-05	9	regulation of coagulation
GO:0032147	2.01448841701943e-05	19	activation of protein kinase activity
GO:0030163	2.03093572030315e-05	37	protein catabolic process
GO:0034329	2.06298734834792e-05	16	cell junction assembly
GO:0055080	2.07061079096772e-05	29	cation homeostasis
GO:1901215	2.09551836601328e-05	14	negative regulation of neuron death
GO:0050768	2.13758389533787e-05	17	negative regulation of neurogenesis
GO:0045637	2.15262984208589e-05	16	regulation of myeloid cell differentiation
GO:1902686	2.15809377123974e-05	8	mitochondrial outer membrane permeabilization involved in programmed cell death
GO:0006458	2.18275515347632e-05	7	'de novo' protein folding
GO:1901028	2.21773866357017e-05	7	regulation of mitochondrial outer membrane permeabilization involved in apoptotic signaling pathway
GO:0061136	2.23864341680083e-05	14	regulation of proteasomal protein catabolic process
GO:0051048	2.24688608883461e-05	14	negative regulation of secretion
GO:1902235	2.27128271445965e-05	6	regulation of endoplasmic reticulum stress-induced intrinsic apoptotic signaling pathway
GO:0061024	2.28012721628127e-05	33	membrane organization
GO:0001844	2.33318946237513e-05	6	protein insertion into mitochondrial membrane involved in apoptotic signaling pathway
GO:0045785	2.35297537209425e-05	21	positive regulation of cell adhesion
GO:0070201	2.37959137365375e-05	30	regulation of establishment of protein localization
GO:0006977	2.43754288930542e-05	8	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest
GO:1903829	2.43802880473792e-05	19	positive regulation of cellular protein localization
GO:0043542	2.44364100261105e-05	15	endothelial cell migration
GO:0090050	2.44547951321747e-05	6	positive regulation of cell migration involved in sprouting angiogenesis
GO:0070665	2.47157913251066e-05	11	positive regulation of leukocyte proliferation
GO:0071774	2.62323641644866e-05	12	response to fibroblast growth factor
GO:0010466	2.64439429699503e-05	15	negative regulation of peptidase activity
GO:0098771	2.66717716456215e-05	29	inorganic ion homeostasis
GO:0072431	2.67751069878431e-05	8	signal transduction involved in mitotic G1 DNA damage checkpoint
GO:1902400	2.67751069878431e-05	8	intracellular signal transduction involved in G1 DNA damage checkpoint
GO:0044238	2.68404281227802e-05	237	primary metabolic process
GO:1905897	2.69928428906026e-05	9	regulation of response to endoplasmic reticulum stress
GO:0002573	2.76002366287389e-05	14	myeloid leukocyte differentiation
GO:0035794	2.84410471605377e-05	8	positive regulation of mitochondrial membrane permeability
GO:1903050	3.00290080711483e-05	15	regulation of proteolysis involved in cellular protein catabolic process
GO:0043405	3.0106829578804e-05	19	regulation of MAP kinase activity
GO:0001893	3.04266468023275e-05	6	maternal placenta development
GO:0072413	3.06161595371855e-05	8	signal transduction involved in mitotic cell cycle checkpoint
GO:1902402	3.06161595371855e-05	8	signal transduction involved in mitotic DNA damage checkpoint
GO:1902403	3.06161595371855e-05	8	signal transduction involved in mitotic DNA integrity checkpoint
GO:0046697	3.18195072852025e-05	5	decidualization
GO:0002009	3.21267066571324e-05	24	morphogenesis of an epithelium
GO:0035914	3.21563444567968e-05	8	skeletal muscle cell differentiation
GO:0006401	3.25837499140099e-05	20	RNA catabolic process
GO:1905710	3.28625777216138e-05	8	positive regulation of membrane permeability
GO:0046700	3.31096626738273e-05	28	heterocycle catabolic process
GO:2001239	3.35705548579809e-05	7	regulation of extrinsic apoptotic signaling pathway in absence of ligand
GO:0007050	3.40671813519759e-05	16	cell cycle arrest
GO:0007049	3.435536913291 9e-05	60	cell cycle
GO:1901699	3.61933310607315e-05	27	cellular response to nitrogen compound
GO:0090084	3.64902741048248e-05	4	negative regulation of inclusion body assembly
GO:1901575	3.65096864737847e-05	66	organic substance catabolic process

GO:0007566	3.69800403683437e-05	7	embryo implantation
GO:0009790	3.73807297694101e-05	37	embryo development
GO:0071372	3.75893506080484e-05	4	cellular response to follicle-stimulating hormone stimulus
GO:0043491	3.88372252167003e-05	15	protein kinase B signaling
GO:0070841	3.9031396069466e-05	5	inclusion body assembly
GO:0046677	4.03165434422044e-05	18	response to antibiotic
GO:0010721	4.04156048827385e-05	18	negative regulation of cell development
GO:0051347	4.15319472982141e-05	28	positive regulation of transferase activity
GO:0007584	4.22182793241864e-05	14	response to nutrient
GO:0034248	4.29193728606373e-05	22	regulation of cellular amide metabolic process
GO:0051409	4.31824873598626e-05	4	response to nitrosative stress
GO:0098657	4.35162598235987e-05	32	import into cell
GO:0038066	4.39828165152079e-05	7	p38MAPK cascade
GO:0051204	4.41623155980836e-05	6	protein insertion into mitochondrial membrane
GO:1901030	4.4168663714952e-05	6	positive regulation of mitochondrial outer membrane permeabilization involved in apoptotic signaling pathway
GO:0042108	4.5054667782e-05	7	positive regulation of cytokine biosynthetic process
GO:1901361	4.51148766315201e-05	29	organic cyclic compound catabolic process
GO:1990440	4.74056326823847e-05	4	positive regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress
GO:0001890	4.76497740921396e-05	12	placenta development
GO:0043525	4.8216425681114e-05	7	positive regulation of neuron apoptotic process
GO:0045646	4.89271838484825e-05	7	regulation of erythrocyte differentiation
GO:0031345	4.95987679481843e-05	13	negative regulation of cell projection organization
GO:0010634	4.99697330738232e-05	12	positive regulation of epithelial cell migration
GO:0019439	5.06297073142714e-05	28	aromatic compound catabolic process
GO:0001101	5.07499681810378e-05	18	response to acid chemical
GO:0046824	5.10537848633017e-05	8	positive regulation of nucleocytoplasmic transport
GO:0072593	5.23928240754745e-05	16	reactive oxygen species metabolic process
GO:0051346	5.31662839820595e-05	21	negative regulation of hydrolase activity
GO:1901099	5.32779567678732e-05	6	negative regulation of signal transduction in absence of ligand
GO:2001240	5.32779567678732e-05	6	negative regulation of extrinsic apoptotic signaling pathway in absence of ligand
GO:0002460	5.37709781288963e-05	15	adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superf
GO:0070613	5.79450527923364e-05	9	regulation of protein processing
GO:0090199	5.98350645140115e-05	7	regulation of release of cytochrome c from mitochondria
GO:0045619	6.01432608119062e-05	12	regulation of lymphocyte differentiation
GO:0022409	6.04995837077663e-05	15	positive regulation of cell-cell adhesion
GO:0001655	6.06958557423007e-05	18	urogenital system development
GO:0048666	6.32894089569375e-05	39	neuron development
GO:1901522	6.34284776908121e-05	5	positive regulation of transcription from RNA polymerase II promoter involved in cellular response to chemical stim
GO:0046660	6.34371747699323e-05	10	female sex differentiation
GO:0010595	6.63031857948136e-05	10	positive regulation of endothelial cell migration
GO:0006953	6.69050623096549e-05	6	acute-phase response
GO:0048729	6.73418462192803e-05	27	tissue morphogenesis
GO:0001974	6.87143884733321e-05	6	blood vessel remodeling
GO:0002042	6.87374171143535e-05	8	cell migration involved in sprouting angiogenesis
GO:1904951	6.9401923320795e-05	21	positive regulation of establishment of protein localization
GO:1903317	7.03032894756427e-05	9	regulation of protein maturation
GO:0016192	7.18147142693371e-05	62	vesicle-mediated transport
GO:0016070	7.20006953801461e-05	123	RNA metabolic process
GO:0043524	7.29192271573166e-05	11	negative regulation of neuron apoptotic process
GO:0008152	7.30347816187173e-05	251	metabolic process
GO:0050729	7.539727530471 52e-05	10	positive regulation of inflammatory response
GO:0061097	7.6397900940348e-05	9	regulation of protein tyrosine kinase activity
GO:0089718	7.69417353157236e-05	5	amino acid import across plasma membrane
GO:0060284	7.93528976772696e-05	34	regulation of cell development
GO:0045665	7.9834180636795e-05	14	negative regulation of neuron differentiation
GO:0034612	8.20032548521749e-05	15	response to tumor necrosis factor
GO:0060326	8.34453824939099e-05	16	cell chemotaxis
GO:0010821	8.42869771966853e-05	13	regulation of mitochondrion organization
GO:0050870	8.74084146932922e-05	13	positive regulation of T cell activation
GO:0097345	8.78358610838555e-05	7	mitochondrial outer membrane permeabilization
GO:0072594	8.93877527274497e-05	26	establishment of protein localization to organelle
GO:0060537	9.16766657233868e-05	19	muscle tissue development
GO:1902339	9.26041672941015e-05	3	positive regulation of apoptotic process involved in morphogenesis
GO:1904747	9.26041672941015e-05	3	positive regulation of apoptotic process involved in development
GO:0044270	9.32242404218801e-05	27	cellular nitrogen compound catabolic process
GO:0030193	9.94362673011585e-05	8	regulation of blood coagulation
GO:1900046	9.94362673011585e-05	8	regulation of hemostasis
GO:0001818	0.000100018866223711	15	negative regulation of cytokine production
GO:0097327	0.000101949596748741	9	response to antineoplastic agent
GO:0007162	0.000102174953062761	15	negative regulation of cell adhesion
GO:0097201	0.000102219813211504	4	negative regulation of transcription from RNA polymerase II promoter in response to stress
GO:0001541	0.000104305623457367	7	ovarian follicle development
GO:0006974	0.000105268863893278	34	cellular response to DNA damage stimulus
GO:0031589	0.000108845037098439	18	cell-substrate adhesion
GO:1903076	0.000114467455011372	9	regulation of protein localization to plasma membrane
GO:0032623	0.000115516387956411	7	interleukin-2 production
GO:0031175	0.000116152732304627	35	neuron projection development
GO:0090068	0.000116535861646255	16	positive regulation of cell cycle process
GO:0072401	0.000121532882658548	8	signal transduction involved in DNA integrity checkpoint
GO:0072422	0.000121532882658548	8	signal transduction involved in DNA damage checkpoint
GO:0045685	0.000121746171408755	7	regulation of glial cell differentiation
GO:0030198	0.000124489288362078	18	extracellular matrix organization
GO:0150076	0.000125392924400998	6	neuroinflammatory response
GO:0070555	0.000129649063524075	11	response to interleukin-1
GO:1900739	0.000130213527701988	5	regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway
GO:1900740	0.000130213527701988	5	positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway
GO:1902110	0.000132297048073279	7	positive regulation of mitochondrial membrane permeability involved in apoptotic process
GO:0072395	0.000132327797500492	8	signal transduction involved in cell cycle checkpoint
GO:0010952	0.000135576912240324	13	positive regulation of peptidase activity
GO:0016485	0.000135799198307909	14	protein processing
GO:0006875	0.000136146159377594	23	cellular metal ion homeostasis
GO:0051091	0.000142581176287321	15	positive regulation of DNA-binding transcription factor activity
GO:0048872	0.000143106558575545	15	homeostasis of number of cells
GO:0045577	0.000144740099696723	5	regulation of B cell differentiation
GO:0031347	0.000146432401734082	27	regulation of defense response
GO:0050727	0.000148410543063989	17	regulation of inflammatory response
GO:1903825	0.000148968068966643	10	organic acid transmembrane transport
GO:1905039	0.000148968068966643	10	carboxylic acid transmembrane transport
GO:0043090	0.000151356572395613	5	amino acid import
GO:0009887	0.000155556535012912	35	animal organ morphogenesis
GO:0034205	0.000159010974627377	5	amyloid-beta formation
GO:0034101	0.000159120651931843	10	erythrocyte homeostasis
GO:0000956	0.000159454865003352	14	nuclear-transcribed mRNA catabolic process
GO:0055065	0.000159496848318601	25	metal ion homeostasis
GO:0034641	0.000159837270031777	160	cellular nitrogen compound metabolic process
GO:0030968	0.000165825761741863	10	endoplasmic reticulum unfolded protein response
GO:0002705	0.000166925890847827	10	positive regulation of leukocyte mediated immunity
GO:0043009	0.00016979470788264	25	chordate embryonic development
GO:0090150	0.000171295010530329	18	establishment of protein localization to membrane
GO:0007346	0.000171774580096129	26	regulation of mitotic cell cycle
GO:0034655	0.000173315799081663	25	nucleobase-containing compound catabolic process
GO:0010977	0.000179223451508033	11	negative regulation of neuron projection development
GO:0032989	0.000180218615319318	38	cellular component morphogenesis
GO:0010837	0.000183473339527071	5	regulation of keratinocyte proliferation
GO:0010950	0.000184897752948282	12	positive regulation of endopeptidase activity
GO:0072503	0.000186524531838328	20	cellular divalent inorganic cation homeostasis
GO:2001244	0.000187113852492662	7	positive regulation of intrinsic apoptotic signaling pathway
GO:0007519	0.000188483165812409	11	skeletal muscle tissue development
GO:1990000	0.000189281071944111	4	amyloid fibril formation
GO:0051271	0.000189916817421884	17	negative regulation of cellular component movement
GO:0006521	0.000195807049362464	4	regulation of cellular amino acid metabolic process
GO:0010564	0.000196246712528099	29	regulation of cell cycle process
GO:0001701	0.000197458483693916	17	in utero embryonic development
GO:0010575	0.000198330126745241	5	positive regulation of vascular endothelial growth factor production
GO:0110110	0.000198862727403714	8	positive regulation of animal organ morphogenesis
GO:0090087	0.000198870734156319	27	regulation of peptide transport
GO:0042102	0.000201372325667504	8	positive regulation of T cell proliferation
GO:0043122	0.000202057544460192	14	regulation of I-kappaB kinase/NF-kappaB signaling
GO:2000045	0.000202064031065167	11	regulation of G1/S transition of mitotic cell cycle

GO:1901565	0.000203451399932454	43	organonitrogen compound catabolic process
GO:0043062	0.000208443048446183	19	extracellular structure organization
GO:0090303	0.000209533756622515	6	positive regulation of wound healing
GO:0044773	0.000209737905458028	9	mitotic DNA damage checkpoint
GO:0044070	0.000210896389116449	8	regulation of anion transport
GO:0007176	0.000214146225948637	5	regulation of epidermal growth factor-activated receptor activity
GO:0000077	0.00022918630622865	11	DNA damage checkpoint
GO:0071371	0.000235010927966808	4	cellular response to gonadotropin stimulus
GO:0045600	0.000237557075257384	7	positive regulation of fat cell differentiation
GO:0042026	0.000239111999078636	5	protein refolding
GO:1902108	0.000239464907998004	7	regulation of mitochondrial membrane permeability involved in apoptotic process
GO:0045787	0.000240376878309394	19	positive regulation of cell cycle
GO:0002702	0.000245311075490163	8	positive regulation of production of molecular mediator of immune response
GO:0031349	0.000246602054507446	19	positive regulation of defense response
GO:0030336	0.000249461170085297	15	negative regulation of cell migration
GO:0048145	0.000262098389404326	8	regulation of fibroblast proliferation
GO:0009792	0.000262729892344398	25	embryo development ending in birth or egg hatching
GO:0051223	0.000271751096782969	26	regulation of protein transport
GO:2000134	0.000271756246063474	9	negative regulation of G1/S transition of mitotic cell cycle
GO:0032663	0.000277642392778644	6	regulation of interleukin-2 production
GO:0071158	0.000281569286515546	8	positive regulation of cell cycle arrest
GO:0015711	0.000285944634144769	20	organic anion transport
GO:0048144	0.000286188772188956	8	fibroblast proliferation
GO:0060538	0.000294872423515117	11	skeletal muscle organ development
GO:0050864	0.000296193705787296	9	regulation of B cell activation
GO:1902043	0.000298813285511596	4	positive regulation of extrinsic apoptotic signaling pathway via death domain receptors
GO:1903670	0.000300003001991409	8	regulation of sprouting angiogenesis
GO:0043200	0.00030986176814132	9	response to amino acid
GO:1903672	0.000312166080215815	6	positive regulation of sprouting angiogenesis
GO:0120036	0.000313454068359935	47	plasma membrane bounded cell projection organization
GO:0010001	0.000314490250554019	12	glial cell differentiation
GO:0030850	0.000317407102099869	6	prostate gland development
GO:0072507	0.000321083869904608	20	divalent inorganic cation homeostasis
GO:0090647	0.000321368815914665	3	modulation of age-related behavioral decline
GO:0051345	0.000323958602945292	29	positive regulation of hydrolase activity
GO:0002720	0.000330530711798531	6	positive regulation of cytokine production involved in immune response
GO:0006413	0.000331729645467299	13	translational initiation
GO:0045599	0.000344121692014715	6	negative regulation of fat cell differentiation
GO:0009056	0.000345653942814542	72	catabolic process
GO:0043123	0.000349196866476599	12	positive regulation of I-kappaB kinase/NF-kappaB signaling
GO:0070371	0.000350536564978373	16	ERK1 and ERK2 cascade
GO:0006750	0.00035311785290568	4	glutathione biosynthetic process
GO:0022604	0.000356467316883944	21	regulation of cell morphogenesis
GO:0015698	0.000359559864944393	11	inorganic anion transport
GO:1900151	0.00036315393650342	4	regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay
GO:1900153	0.00036315393650342	4	positive regulation of nuclear-transcribed mRNA catabolic process, deadenylation-dependent decay
GO:0051205	0.000363780215755995	6	protein insertion into membrane
GO:0003008	0.000364152679361525	48	system process
GO:0010955	0.000369947543723554	5	negative regulation of protein processing
GO:1903318	0.000369947543723554	5	negative regulation of protein maturation
GO:0002683	0.000370476853074327	19	negative regulation of immune system process
GO:0002250	0.000372443104782146	17	adaptive immune response
GO:0002367	0.000373716204626466	8	cytokine production involved in immune response
GO:0002246	0.000374924310798658	3	wound healing involved in inflammatory response
GO:0090594	0.000374924310798658	3	inflammatory response to wounding
GO:0071230	0.000380606476797791	7	cellular response to amino acid stimulus
GO:0003169	0.000381436706357644	2	coronary vein morphogenesis
GO:0034105	0.000386027611204608	5	positive regulation of tissue remodeling
GO:1901653	0.000392221607201667	17	cellular response to peptide
GO:0048661	0.000397663198224492	8	positive regulation of smooth muscle cell proliferation
GO:0070301	0.000397837946893691	8	cellular response to hydrogen peroxide
GO:0001763	0.000398302854191495	12	morphogenesis of a branching structure
GO:2000379	0.000398458758923835	8	positive regulation of reactive oxygen species metabolic process
GO:0033002	0.000401415316514544	12	muscle cell proliferation
GO:0062012	0.000403167551806538	17	regulation of small molecule metabolic process
GO:0050767	0.000403415848354111	29	regulation of neurogenesis
GO:0044774	0.000415651249683168	9	mitotic DNA integrity checkpoint
GO:0071356	0.000416258663616267	13	cellular response to tumor necrosis factor
GO:0010574	0.00042309304934891	5	regulation of vascular endothelial growth factor production
GO:0008593	0.000429748598760964	8	regulation of Notch signaling pathway
GO:0048660	0.000431368245977215	10	regulation of smooth muscle cell proliferation
GO:0001570	0.000431720413979539	7	vasculogenesis
GO:0034198	0.000435472785713874	6	cellular response to amino acid starvation
GO:1904375	0.000437978954848069	9	regulation of protein localization to cell periphery
GO:0016049	0.000438023498231673	21	cell growth
GO:1902807	0.000438896608326665	9	negative regulation of cell cycle G1/S phase transition
GO:0010565	0.000442650689217681	9	regulation of cellular ketone metabolic process
GO:0090200	0.000443908783036505	5	positive regulation of release of cytochrome c from mitochondria
GO:0071236	0.000448027718307133	10	cellular response to antibiotic
GO:0043604	0.000450510487690502	32	amide biosynthetic process
GO:0042094	0.000456768173179295	4	interleukin-2 biosynthetic process
GO:0002043	0.000458041436349094	5	blood vessel endothelial cell proliferation involved in sprouting angiogenesis
GO:0016043	0.00046163606240376	151	cellular component organization
GO:2000146	0.000465675222281467	15	negative regulation of cell motility
GO:0031570	0.000466449040528625	11	DNA integrity checkpoint
GO:0002543	0.000467546139539353	2	activation of blood coagulation via clotting cascade
GO:0045621	0.000469189759108864	8	positive regulation of lymphocyte differentiation
GO:0014706	0.00047233587138513	17	striated muscle tissue development
GO:0097069	0.000472347460704433	2	cellular response to thyroxine stimulus
GO:1904387	0.000472347460704433	2	cellular response to L-phenylalanine derivative
GO:0002697	0.000474203563879993	17	regulation of immune effector process
GO:0061436	0.000483532712241939	4	establishment of skin barrier
GO:0043406	0.000483816394621861	14	positive regulation of MAP kinase activity
GO:0001912	0.000485119838941485	6	positive regulation of leukocyte mediated cytotoxicity
GO:0032868	0.000487609577816936	14	response to insulin
GO:0031394	0.000489935011994154	2	positive regulation of prostaglandin biosynthetic process
GO:0022612	0.00049028799598726	9	gland morphogenesis
GO:0048659	0.000490619253565921	10	smooth muscle cell proliferation
GO:0014028	0.000496887157243484	2	notochord formation
GO:0090304	0.000499834096751O1	130	nucleic acid metabolic process
GO:0030168	0.000503124591608523	10	platelet activation
GO:0061741	0.000507408632270075	2	chaperone-mediated protein transport involved in chaperone-mediated autophagy
GO:0044257	0.000513764321008641	29	cellular protein catabolic process
GO:0060341	0.000518143468026052	32	regulation of cellular localization
GO:0072659	0.000518287539690955	14	protein localization to plasma membrane
GO:1903036	0.000522822388020648	6	positive regulation of response to wounding
GO:0044248	0.000525618045681266	65	cellular catabolic process
GO:0061394	0.000528774389312199	2	regulation of transcription from RNA polymerase II promoter in response to arsenic-containing substance
GO:1902806	0.000532549491277392	11	regulation of cell cycle G1/S phase transition
GO:1903747	0.000533673741289093	7	regulation of establishment of protein localization to mitochondrion
GO:0051960	0.000535377186526075	31	regulation of nervous system development
GO:0097084	0.000538170811617319	3	vascular smooth muscle cell development
GO:0071634	0.000542329062152834	5	regulation of transforming growth factor beta production
GO:0030030	0.000542482230798808	47	cell projection organization
GO:1990928	0.000543751827645022	6	response to amino acid starvation
GO:0002718	0.000544653595251974	7	regulation of cytokine production involved in immune response
GO:0000902	0.000546838694575941	34	cell morphogenesis
GO:0001660	0.000549264459262759	3	fever generation
GO:0031098	0.000549822276149523	16	stress-activated protein kinase signaling cascade
GO:0033043	0.000551463931502741	42	regulation of organelle organization
GO:1905906	0.000556923964801295	3	regulation of amyloid fibril formation
GO:0045601	0.000563231614406033	5	regulation of endothelial cell differentiation
GO:0044341	0.000566917925040697	3	sodium-dependent phosphate transport
GO:0051130	0.000568580933684681	40	positive regulation of cellular component organization
GO:0019184	0.000569608506281243	4	nonribosomal peptide biosynthetic process
GO:0010573	0.000572784294536098	5	vascular endothelial growth factor production
GO:0061635	0.000575973410179079	3	regulation of protein complex stability
GO:0051403	0.000577737567810797	15	stress-activated MAPK cascade
GO:0070423	0.00058281943597414	5	nucleotide-binding oligomerization domain containing signaling pathway

GO:0043161	0.000583084606133981	19	proteasome-mediated ubiquitin-dependent protein catabolic process
GO:0002700	0.000587232300910443	9	regulation of production of molecular mediator of immune response
GO:0010498	0.000590378179736795	21	proteasomal protein catabolic process
GO:1902003	0.000592328959431884	4	regulation of amyloid-beta formation
GO:0003170	0.000598420323526041	6	heart valve development
GO:2001238	0.000603585197356350	6	positive regulation of extrinsic apoptotic signaling pathway
GO:0006919	0.000605817052385725	8	activation of cysteine-type endopeptidase activity involved in apoptotic process
GO:0043043	0.000615067113067297	28	peptide biosynthetic process
GO:0098739	0.000615723761818688	8	import across plasma membrane
GO:0007006	0.000618121091592915	9	mitochondrial membrane organization
GO:0031424	0.000628559298186431	10	keratinization
GO:0042987	0.000640454230884850	5	amyloid precursor protein catabolic process
GO:1905477	0.000646948350927675	9	positive regulation of protein localization to membrane
GO:1900221	0.000652749187422118	3	regulation of amyloid-beta clearance
GO:0002708	0.000663372361278995	8	positive regulation of lymphocyte mediated immunity
GO:0001894	0.000671476640295095	12	tissue homeostasis
GO:0035872	0.000679804777357029	5	nucleotide-binding domain, leucine rich repeat containing receptor signaling pathway
GO:0120035	0.000699601539831140	25	regulation of plasma membrane bounded cell projection organization
GO:0050435	0.000701119760989830	5	amyloid-beta metabolic process
GO:1903203	0.000720897723578911	4	regulation of oxidative stress-induced neuron death
GO:0071385	0.000723485249542475	6	cellular response to glucocorticoid stimulus
GO:0071604	0.000725402535103896	5	transforming growth factor beta production
GO:0051603	0.000735181493170460	27	proteolysis involved in cellular protein catabolic process
GO:0010810	0.000738712113268669	12	regulation of cell-substrate adhesion
GO:0033561	0.000747768483936792	4	regulation of water loss via skin
GO:0031343	0.000775125463737310	6	positive regulation of cell killing
GO:0070278	0.000777432823407742	3	extracellular matrix constituent secretion
GO:2001026	0.000778252519694209	4	regulation of endothelial cell chemotaxis
GO:0031663	0.000778984791382212	6	lipopolysaccharide-mediated signaling pathway
GO:0031396	0.000783668265666737	12	regulation of protein ubiquitination
GO:0071702	0.000788822443831597	75	organic substance transport
GO:0040013	0.000793964106670316	16	negative regulation of locomotion
GO:0008360	0.000796607796154551	10	regulation of cell shape
GO:0051092	0.000802735917528393	10	positive regulation of NF-kappaB transcription factor activity
GO:1901988	0.000802898982693372	12	negative regulation of cell cycle phase transition
GO:0002576	0.000810914831113597	9	platelet degranulation
GO:0001935	0.000812617322442584	10	endothelial cell proliferation
GO:0033365	0.000819497311180051	33	protein localization to organelle
GO:0045216	0.000823689739392256	10	cell-cell junction organization
GO:0060135	0.000837515926991732	6	maternal process involved in female pregnancy
GO:0045616	0.000849555676030277	5	regulation of keratinocyte differentiation
GO:0031344	0.000852434545630398	25	regulation of cell projection organization
GO:0007219	0.000860468721177360	11	Notch signaling pathway
GO:1902237	0.000862434779760484	3	positive regulation of endoplasmic reticulum stress-induced intrinsic apoptotic signaling pathway
GO:0043903	0.000863486696515698	12	regulation of symbiosis, encompassing mutualism through parasitism
GO:0046683	0.000868491896237411	9	response to organophosphorus
GO:0071470	0.000870922211139424	5	cellular response to osmotic stress
GO:0036475	0.000894880490831263	4	neuron death in response to oxidative stress
GO:1901360	0.000898755464658850	149	organic cyclic compound metabolic process
GO:0006725	0.000905358713801673	145	cellular aromatic compound metabolic process
GO:0090557	0.000911810013566 1	3	establishment of endothelial intestinal barrier
GO:0046827	0.000917707048642530	4	positive regulation of protein export from nucleus
GO:0071222	0.000926064603674881	11	cellular response to lipopolysaccharide
GO:0034762	0.000932068659084985	20	regulation of transmembrane transport
GO:0071216	0.000963620543298485	12	cellular response to biotic stimulus
GO:0003333	0.000966880741565135	7	amino acid transmembrane transport
GO:0032677	0.000968584498793108	6	regulation of interleukin-8 production
GO:1900182	0.000978449403316267	7	positive regulation of protein localization to nucleus
GO:2001056	0.000986013124039126	10	positive regulation of cysteine-type endopeptidase activity
GO:0045582	0.001001488710308520	7	positive regulation of T cell differentiation
GO:0097435	0.001010397796842470	25	supramolecular fiber organization
GO:0002703	0.001046302930758460	11	regulation of leukocyte mediated immunity
GO:0021544	0.001049509541733	4	subpallium development
GO:0014013	0.001053269373028 1	8	regulation of gliogenesis
GO:0045746	0.001063491099465650	5	negative regulation of Notch signaling pathway
GO:1902004	0.001065163289171810	3	positive regulation of amyloid-beta formation
GO:0007160	0.001074431208398490	12	cell-matrix adhesion
GO:0002449	0.001085058273163560	12	lymphocyte mediated immunity
GO:0070498	0.001112426149702470	6	interleukin-1-mediated signaling pathway
GO:0071384	0.001118520262427	6	cellular response to corticosteroid stimulus
GO:0009299	0.001119584959553660	4	mRNA transcription
GO:0042307	0.001122934588691190	5	positive regulation of protein import into nucleus
GO:0007267	0.001125670904786690	45	cell-cell signaling
GO:0032757	0.001128608836993280	5	positive regulation of interleukin-8 production
GO:0003176	0.001132146920304430	4	aortic valve development
GO:0002761	0.001139353664922931	8	regulation of myeloid leukocyte differentiation
GO:0006897	0.001179611686065430	25	endocytosis
GO:0051222	0.001205062649629730	17	positive regulation of protein transport
GO:0050820	0.001215945874552840	4	positive regulation of coagulation
GO:0050927	0.001229961805985160	4	positive regulation of positive chemotaxis
GO:0015807	0.001234700983772310	6	L-amino acid transport
GO:0071901	0.001234982312511530	9	negative regulation of protein serine/threonine kinase activity
GO:0007548	0.001235486707207050	13	sex differentiation
GO:0042033	0.001238115401604700	3	chemokine biosynthetic process
GO:0050755	0.001238115401604700	3	chemokine metabolic process
GO:0032388	0.001239152193338240	12	positive regulation of intracellular transport
GO:0060948	0.001239358663161900	2	cardiac vascular smooth muscle cell development
GO:0071219	0.001243863894435420	11	cellular response to molecule of bacterial origin
GO:0019752	0.001246949834359180	33	carboxylic acid metabolic process
GO:1901991	0.001249906358229070	11	negative regulation of mitotic cell cycle phase transition
GO:0001558	0.001250027020602070	18	regulation of cell growth
GO:1902263	0.001259349566440940	2	apoptotic process involved in embryonic digit morphogenesis
GO:0036473	0.001266323427634100	7	cell death in response to oxidative stress
GO:0050918	0.001269409193026720	6	positive chemotaxis
GO:0090316	0.001278314999892740	10	positive regulation of intracellular protein transport
GO:0010812	0.001278454141324810	6	negative regulation of cell-substrate adhesion
GO:0051098	0.001280055865755350	17	regulation of binding
GO:0070727	0.001301820198477400	56	cellular macromolecule localization
GO:0042730	0.001320926816464640	4	fibrinolysis
GO:0043010	0.001325140266786650	14	camera-type eye development
GO:0003334	0.001344743722025900	3	keratinocyte development
GO:0002040	0.001348640854285180	9	sprouting angiogenesis
GO:1900744	0.001352720939068440	5	regulation of p38MAPK cascade
GO:0045930	0.001356969811116670	14	negative regulation of mitotic cell cycle
GO:0071156	0.001363010630205830	8	regulation of cell cycle arrest
GO:0010638	0.001370983416509140	24	positive regulation of organelle organization
GO:0071383	0.001377036910735630	13	cellular response to steroid hormone stimulus
GO:0001889	0.001381218526258540	9	liver development
GO:0070426	0.001388223346294910	2	positive regulation of nucleotide-binding oligomerization domain containing signaling pathway
GO:0070434	0.001388223346294910	2	positive regulation of nucleotide-binding oligomerization domain containing 2 signaling pathway
GO:1902337	0.001397393781852940	3	regulation of apoptotic process involved in morphogenesis
GO:1904748	0.001397393781852940	3	regulation of apoptotic process involved in development
GO:0070837	0.001405242853103320	2	dehydroascorbic acid transport
GO:0007611	0.001405850521059310	12	learning or memory
GO:0071840	0.001405863242773490	152	cellular component organization or biogenesis
GO:0031670	0.001411147576016180	6	cellular response to nutrient
GO:0043619	0.001428184100276860	3	regulation of transcription from RNA polymerase II promoter in response to oxidative stress
GO:0044752	0.001434488709163640	2	response to human chorionic gonadotropin
GO:0034614	0.001434929092275540	10	cellular response to reactive oxygen species
GO:0033387	0.001436880225197870	2	putrescine biosynthetic process from ornithine
GO:1904591	0.001440127813055110	5	positive regulation of protein import
GO:0061740	0.001441389156081100	2	protein targeting to lysosome involved in chaperone-mediated autophagy
GO:0050926	0.001445570491483240	4	regulation of positive chemotaxis
GO:0046483	0.001449900878771050	143	heterocycle metabolic process
GO:1990834	0.001450466165957442	2	response to odorant
GO:0050866	0.001454554185195850	10	negative regulation of cell activation
GO:1904580	0.001462033859861480	2	regulation of intracellular mRNA localization
GO:1904582	0.001462033859861480	2	positive regulation of intracellular mRNA localization
GO:0006139	0.001472930397320330	140	nucleobase-containing compound metabolic process

GO:0006811	0.00147841321147566	45	ion transport
GO:0035850	0.00149713391867421	5	epithelial cell differentiation involved in kidney development
GO:1900408	0.00151139145469799	5	negative regulation of cellular response to oxidative stress
GO:1903202	0.00151139145469799	5	negative regulation of oxidative stress-induced cell death
GO:1902991	0.00152073114383354	4	regulation of amyloid precursor protein catabolic process
GO:0070431	0.00152376819622244	3	nucleotide-binding oligomerization domain containing 2 signaling pathway
GO:1903587	0.00153722198378485	4	regulation of blood vessel endothelial cell proliferation involved in sprouting angiogenesis
GO:0001659	0.00154615858160447	10	temperature homeostasis
GO:0071229	0.00155249325513535	11	cellular response to acid chemical
GO:1903573	0.00155574791014014	5	negative regulation of response to endoplasmic reticulum stress
GO:2000120	0.00155596694442018	2	positive regulation of sodium-dependent phosphate transport
GO:0032990	0.00155835704911397	24	cell part morphogenesis
GO:0048710	0.00157366569239245	4	regulation of astrocyte differentiation
GO:0032637	0.00157478616176722	6	interleukin-8 production
GO:0016480	0.00157828601781292	2	negative regulation of transcription by RNA polymerase III
GO:0055094	0.00159031532536958	4	response to lipoprotein particle
GO:0019852	0.00159743110636008	3	L-ascorbic acid metabolic process
GO:0014074	0.00160322587763648	9	response to purine-containing compound
GO:1902445	0.00162162492269049	2	regulation of mitochondrial membrane permeability involved in programmed necrotic cell death
GO:0061008	0.00162371399559181	9	hepaticobiliary system development
GO:0060576	0.00163546415477375	3	intestinal epithelial cell development
GO:0014009	0.00163861106525859	5	glial cell proliferation
GO:1990442	0.00165022173852591	2	intrinsic apoptotic signaling pathway in response to nitrosative stress
GO:0070372	0.00165307360221988	14	regulation of ERK1 and ERK2 cascade
GO:0036462	0.00166261816900573	3	TRAIL-activated apoptotic signaling pathway
GO:0015849	0.00168402248253803	14	organic acid transport
GO:0046942	0.00168402248253803	14	carboxylic acid transport
GO:0043280	0.00168714958774934	9	positive regulation of cysteine-type endopeptidase activity involved in apoptotic process
GO:0043900	0.00168922490309151	16	regulation of multi-organism process
GO:0071375	0.00170473343278959	14	cellular response to peptide hormone stimulus
GO:0050892	0.00170645965439554	4	intestinal absorption
GO:1904950	0.00171611619752385	10	negative regulation of establishment of protein localization
GO:0030218	0.00174079205241716	8	erythrocyte differentiation
GO:0072182	0.00175281885841558	3	regulation of nephron tubule epithelial cell differentiation
GO:0072080	0.00176449981126359	7	nephron tubule development
GO:1903959	0.00177937785800962	4	regulation of anion transmembrane transport
GO:0030101	0.0017902948166794	6	natural killer cell activation
GO:1902992	0.00179168990000342	3	negative regulation of amyloid precursor protein catabolic process
GO:1903201	0.0017938608050275	6	regulation of oxidative stress-induced cell death
GO:0042036	0.00180978731646611	4	negative regulation of cytokine biosynthetic process
GO:0002673	0.00181154327204422	6	regulation of acute inflammatory response
GO:0006511	0.00181611577003137	23	ubiquitin-dependent protein catabolic process
GO:1901566	0.00182148130285071	54	organonitrogen compound biosynthetic process
GO:0070885	0.00182214493028927	3	negative regulation of calcineurin-NFAT signaling cascade
GO:0106057	0.00182214493028927	3	negative regulation of calcineurin-mediated signaling
GO:0051896	0.00182390311515847	11	regulation of protein kinase B signaling
GO:0060742	0.00182412274627739	3	epithelial cell differentiation involved in prostate gland development
GO:0000184	0.00183192361713776	9	nuclear-transcribed mRNA catabolic process, nonsense-mediated decay
GO:0051604	0.00185434599783839	14	protein maturation
GO:0030595	0.00186962492240962	11	leukocyte chemotaxis
GO:1902882	0.00188456555361634	7	regulation of response to oxidative stress
GO:0002687	0.00188654196059893	8	positive regulation of leukocyte migration
GO:0045661	0.00189172231774509	5	regulation of myoblast differentiation
GO:1902883	0.00189983970339398	5	negative regulation of response to oxidative stress
GO:0061614	0.00190078951872019	5	pri-miRNA transcription by RNA polymerase II
GO:0061045	0.0019113430023659	6	negative regulation of wound healing
GO:0000075	0.00200379201836984	12	cell cycle checkpoint
GO:0006809	0.00201796748635799	6	nitric oxide biosynthetic process
GO:0061326	0.00202253033557215	7	renal tubule development
GO:0061684	0.00206355685292746	3	chaperone-mediated autophagy
GO:0045664	0.00206486636421195	23	regulation of neuron differentiation
GO:0008406	0.00208428592739341	11	gonad development
GO:0019941	0.00209400502043419	23	modification-dependent protein catabolic process
GO:0071560	0.00210397496125158	12	cellular response to transforming growth factor beta stimulus
GO:0070268	0.00210701053795675	8	cornification
GO:0002440	0.00210914316997989	10	production of molecular mediator of immune response
GO:0071364	0.00211990054927223	5	cellular response to epidermal growth factor stimulus
GO:0006898	0.00215010501182127	13	receptor-mediated endocytosis
GO:1904659	0.00215850300371106	7	glucose transmembrane transport
GO:0032102	0.00216098824545712	14	negative regulation of response to external stimulus
GO:0071402	0.0021730391608916	4	cellular response to lipoprotein particle stimulus
GO:0048713	0.002175279262156	4	regulation of oligodendrocyte differentiation
GO:0002285	0.00217925944763806	9	lymphocyte activation involved in immune response
GO:0051591	0.00218337220727983	7	response to cAMP
GO:0043409	0.00218555089109943	10	negative regulation of MAPK cascade
GO:0022617	0.00218898250713005	6	extracellular matrix disassembly
GO:0006614	0.00219166120037271	8	SRP-dependent cotranslational protein targeting to membrane
GO:0051881	0.00219269001321841	6	regulation of mitochondrial membrane potential
GO:0046822	0.00219270498365271	8	regulation of nucleocytoplasmic transport
GO:0001503	0.00219399991879172	16	ossification
GO:0001654	0.00219642333856372	15	eye development
GO:0042271	0.00221120300180843	3	susceptibility to natural killer cell mediated cytotoxicity
GO:0022402	0.00221337484843897	41	cell cycle process
GO:1904589	0.00222153750645151	6	regulation of protein import
GO:1903320	0.00222178819234906	12	regulation of protein modification by small protein conjugation or removal
GO:0001892	0.00223195701659843	7	embryonic placenta development
GO:0046427	0.00224159560133862	6	positive regulation of JAK-STAT cascade
GO:0150063	0.00226500127034023	15	visual system development
GO:0044087	0.00229814028950102	31	regulation of cellular component biogenesis
GO:0032869	0.00234066858260882	11	cellular response to insulin stimulus
GO:0060712	0.00234093377258585	3	spongiotrophoblast layer development
GO:0050920	0.00234132838623 9	11	regulation of chemotaxis
GO:0001822	0.00235253906636313	13	kidney development
GO:0090288	0.00236578990789571	9	negative regulation of cellular response to growth factor stimulus
GO:0010830	0.0023861691083817	5	regulation of myotube differentiation
GO:0061029	0.00238630881242681	3	eyelid development in camera-type eye
GO:1900745	0.00239300658907953	4	positive regulation of p38MAPK cascade
GO:0010746	0.00241650078328479	2	regulation of plasma membrane long-chain fatty acid transport
GO:0010748	0.00241650078328479	2	negative regulation of plasma membrane long-chain fatty acid transport
GO:0007043	0.00241783390214527	8	cell-cell junction assembly
GO:1903589	0.00241810455555313	3	positive regulation of blood vessel endothelial cell proliferation involved in sprouting angiogenesis
GO:0038061	0.00242439330847826	8	NIK/NF-kappaB signaling
GO:1902993	0.00243682219342956	3	positive regulation of amyloid precursor protein catabolic process
GO:0070373	0.00244570248528774	6	negative regulation of ERK1 and ERK2 cascade
GO:0033036	0.00245461711317458	80	macromolecule localization
GO:0010822	0.00249945073873467	8	positive regulation of mitochondrion organization
GO:0034250	0.00250847162053292	9	positive regulation of cellular amide metabolic process
GO:0007517	0.00250989898537299	16	muscle organ development
GO:0001913	0.00251021382178405	5	T cell mediated cytotoxicity
GO:0060841	0.0025287782697702	3	venous blood vessel development
GO:0002685	0.00252939332247951	10	regulation of leukocyte migration
GO:0048711	0.0025323462207798	3	positive regulation of astrocyte differentiation
GO:0043632	0.00253264660940245	23	modification-dependent macromolecule catabolic process
GO:0002824	0.00253442212530146	7	positive regulation of adaptive immune response based on somatic recombination of immune receptors built from i
GO:0030195	0.00253945922737448	5	negative regulation of blood coagulation
GO:1900047	0.00253945922737448	5	negative regulation of hemostasis
GO:0072655	0.0025443822259168	9	establishment of protein localization to mitochondrion
GO:0061013	0.00254663778298991	9	regulation of mRNA catabolic process
GO:0006931	0.00255968202241112	2	substrate-dependent cell migration, cell attachment to substrate
GO:0003332	0.00256840176575522	2	negative regulation of extracellular matrix constituent secretion
GO:0048880	0.00256985222699083	15	sensory system development
GO:0045137	0.0025796487999973	11	development of primary sexual characteristics
GO:0002070	0.00259899431735619	3	epithelial cell maturation
GO:0046661	0.00260632560491982	9	male sex differentiation
GO:0061564	0.00261167336706254	19	axon development
GO:0043436	0.00262161385126064	34	oxoacid metabolic process
GO:0036337	0.00263500975218232	2	Fas signaling pathway
GO:0001910	0.00268063854538039	6	regulation of leukocyte mediated cytotoxicity
GO:0090063	0.00268145067539826	2	positive regulation of microtubule nucleation

GO:0071559	0.00268276524425859	12	response to transforming growth factor beta
GO:0090066	0.00268666078274334	19	regulation of anatomical structure size
GO:1902475	0.00268861501548266	5	L-alpha-amino acid transmembrane transport
GO:2001280	0.00269581155325791	2	positive regulation of unsaturated fatty acid biosynthetic process
GO:0006865	0.00269989228230065	8	amino acid transport
GO:0009314	0.00270452174211057	18	response to radiation
GO:0071211	0.00270758953115474	2	protein targeting to vacuole involved in autophagy
GO:1990778	0.00271648940195358	14	protein localization to cell periphery
GO:0071603	0.00271895627350769	2	endothelial cell-cell adhesion
GO:2001027	0.00272064851876531	2	negative regulation of endothelial cell chemotaxis
GO:0071705	0.0027347348766329	64	nitrogen compound transport
GO:0006613	0.00273656430781144	8	cotranslational protein targeting to membrane
GO:0097068	0.00274832999372068	2	response to thyroxine
GO:1904386	0.00274832999372068	2	response to L-phenylalanine derivative
GO:0072160	0.00275926635170878	3	nephron tubule epithelial cell differentiation
GO:0007093	0.00276424314831561	10	mitotic cell cycle checkpoint
GO:1905908	0.00276565836130838	2	positive regulation of amyloid fibril formation
GO:0061138	0.00277749318268217	10	morphogenesis of a branching epithelium
GO:0046209	0.00279158476187938	6	nitric oxide metabolic process
GO:0033598	0.00280116484117557	4	mammary gland epithelial cell proliferation
GO:0001909	0.0028088864576424	7	leukocyte mediated cytotoxicity
GO:0090092	0.00281546699138972	11	regulation of transmembrane receptor protein serine/threonine kinase signaling pathway
GO:0006749	0.00281952884380389	5	glutathione metabolic process
GO:0071347	0.00282112517123918	8	cellular response to interleukin-1
GO:0010718	0.0028796822048739	5	positive regulation of epithelial to mesenchymal transition
GO:0022408	0.00289049941486902	9	negative regulation of cell-cell adhesion
GO:2000554	0.00289175027360453	2	regulation of T-helper 1 cell cytokine production
GO:2000556	0.00289175027360453	2	positive regulation of T-helper 1 cell cytokine production
GO:1904894	0.00289706737154728	6	positive regulation of STAT cascade
GO:1905907	0.00290920916600811	2	negative regulation of amyloid fibril formation
GO:0002763	0.00294378592079372	5	positive regulation of myeloid leukocyte differentiation
GO:2000118	0.00294711840669022	2	regulation of sodium-dependent phosphate transport
GO:0070585	0.00295279780185031	9	protein localization to mitochondrion
GO:0035767	0.00296357642029517	4	endothelial cell chemotaxis
GO:0019216	0.00297978535881657	16	regulation of lipid metabolic process
GO:0007173	0.00299409670444484	8	epidermal growth factor receptor signaling pathway
GO:0032355	0.0030000115096291	8	response to estradiol
GO:0001906	0.00300043704095893	8	cell killing
GO:0042180	0.00303778352034267	10	cellular ketone metabolic process
GO:0007175	0.00304141170419574	3	negative regulation of epidermal growth factor-activated receptor activity
GO:0031099	0.0030500077549636	10	regeneration
GO:0051101	0.00309093310993747	8	regulation of DNA binding
GO:0034613	0.00309814413175125	54	cellular protein localization
GO:0050819	0.00312523689427914	5	negative regulation of coagulation
GO:0070849	0.00313790747608676	5	response to epidermal growth factor
GO:0002317	0.00315091814864934	2	plasma cell differentiation
GO:0014805	0.00315203740622681	2	smooth muscle adaptation
GO:0009743	0.00315427794592121	11	response to carbohydrate
GO:0050921	0.00315906946761695	8	positive regulation of chemotaxis
GO:0007178	0.00320602807820396	14	transmembrane receptor protein serine/threonine kinase signaling pathway
GO:0097286	0.00320735749715669	3	iron ion import
GO:0006082	0.00321809402663155	34	organic acid metabolic process
GO:0099173	0.0032236318603263	9	postsynapse organization
GO:0008645	0.00324791261552252	7	hexose transmembrane transport
GO:0032092	0.0032566949202425	7	positive regulation of protein binding
GO:0045076	0.00328026575506201	3	regulation of interleukin-2 biosynthetic process
GO:0006839	0.00328718958058455	12	mitochondrial transport
GO:0043488	0.00330096198369 89	8	regulation of mRNA stability
GO:0002253	0.00333331284264708	19	activation of immune response
GO:0010039	0.00334761740950565	4	response to iron ion
GO:0061005	0.00338063152691272	5	cell differentiation involved in kidney development
GO:0034341	0.0033833382689402	10	response to interferon-gamma
GO:0051302	0.00338340434787054	9	regulation of cell division
GO:0045648	0.00342209889196727	4	positive regulation of erythrocyte differentiation
GO:0022607	0.00342665778323802	79	cellular component assembly
GO:0002483	0.00342708224376506	3	antigen processing and presentation of endogenous peptide antigen
GO:0061900	0.00346880523571913	4	glial cell activation
GO:1905314	0.00351368925075091	4	semi-lunar valve development
GO:0002821	0.00351536705614305	7	positive regulation of adaptive immune response
GO:0048568	0.00352104297833648	17	embryonic organ development
GO:0043269	0.00352442331611854	21	regulation of ion transport
GO:2001057	0.00353094142838422	6	reactive nitrogen species metabolic process
GO:0050679	0.00354208284231921	10	positive regulation of epithelial cell proliferation
GO:0050792	0.00354438549572682	10	regulation of viral process
GO:1903204	0.00354809332217988	3	negative regulation of oxidative stress-induced neuron death
GO:0055085	0.00359885787144142	41	transmembrane transport
GO:2000696	0.00360533099666359	3	regulation of epithelial cell differentiation involved in kidney development
GO:0007613	0.00360970244279343	7	memory
GO:0072001	0.00363398316 1447	13	renal system development
GO:0090136	0.00364897734863693	3	epithelial cell-cell adhesion
GO:0015749	0.00365933804544334	7	monosaccharide transmembrane transport
GO:0002369	0.00367004449879443	4	T cell cytokine production
GO:0061418	0.00368079636616366	4	regulation of transcription from RNA polymerase II promoter in response to hypoxia
GO:0060322	0.00370680202786144	25	head development
GO:0031100	0.00372286762777501	6	animal organ regeneration
GO:0048146	0.00372814436914329	5	positive regulation of fibroblast proliferation
GO:2000516	0.00373412708335764	4	positive regulation of CD4-positive, alpha-beta T cell activation
GO:0042982	0.00373790091280399	5	amyloid precursor protein metabolic process
GO:0045580	0.0037701234321081	8	regulation of T cell differentiation
GO:0070265	0.0038208853295248	5	necrotic cell death
GO:0009746	0.00383325418961609	10	response to hexose
GO:0015804	0.00385244688318159	4	neutral amino acid transport
GO:0043392	0.00385847357624094	5	negative regulation of DNA binding
GO:0007492	0.0038751560276374	6	endoderm development
GO:0042533	0.00394336255259611	3	tumor necrosis factor biosynthetic process
GO:0042534	0.00394336255259611	3	regulation of tumor necrosis factor biosynthetic process
GO:0031341	0.0039689995509158	6	regulation of cell killing
GO:0071277	0.00397232319251474	6	cellular response to calcium ion
GO:0031649	0.00397449353893368	3	heat generation

(Significantly upregulated biological pathways in 6 min oscillatory condition).

Category	Overrepresented p-value	numDEInCat	Term - biological processes upregulated
GO:0006613	3.43342879207477e-29	38	cotranslational protein targeting to membrane
GO:0006614	2.35164024999915e-28	37	SRP-dependent cotranslational protein targeting to membrane
GO:0045047	3.49367838249089e-28	38	protein targeting to ER
GO:0000184	4.99696484931668e-28	38	nuclear-transcribed mRNA catabolic process, nonsense-mediated decay
GO:0072599	6.93345643264106e-28	38	establishment of protein localization to endoplasmic reticulum
GO:0070972	2.18260772303435e-27	39	protein localization to endoplasmic reticulum
GO:0006401	5.79433731098037e-26	47	RNA catabolic process
GO:0016071	2.41823201892563e-25	63	mRNA metabolic process
GO:0006402	3.74585586911872e-25	45	mRNA catabolic process
GO:0006413	4.10279526361793e-25	40	translational initiation
GO:0006612	2.10472951258632e-23	38	protein targeting to membrane
GO:0000956	3.37002779081421e-23	39	nuclear-transcribed mRNA catabolic process
GO:0034655	1.27963158023851e-21	50	nucleobase-containing compound catabolic process
GO:0046700	2.1295636697517e-20	50	heterocycle catabolic process
GO:0044270	2.3299070289425e-20	50	cellular nitrogen compound catabolic process
GO:0006412	3.49564768453165e-20	56	translation
GO:0019439	4.83544211434862e-20	50	aromatic compound catabolic process
GO:0090150	5.31063744256766e-20	40	establishment of protein localization to membrane
GO:0043043	1.18467531503358e-19	56	peptide biosynthetic process
GO:1901361	2.09139626255435e-19	50	organic cyclic compound catabolic process
GO:0006518	1.36594722414354e-17	57	peptide metabolic process
GO:0043604	1.85402674140516e-17	56	amide biosynthetic process

GO:0072594	3.10806664570779e-17	45	establishment of protein localization to organelle
GO:0010629	4.03233852078122e-17	80	negative regulation of gene expression
GO:0033365	1.16949418383714e-16	53	protein localization to organelle
GO:0006605	2.50553501281638e-16	40	protein targeting
GO:0042254	2.601026114984 9e-16	33	ribosome biogenesis
GO:0072657	4.426059756734 57e-16	44	protein localization to membrane
GO:0022613	1.26001546271973e-15	39	ribonucleoprotein complex biogenesis
GO:0044265	2.727690695406 77e-15	57	cellular macromolecule catabolic process
GO:0010468	1.27091470812552e-14	118	regulation of gene expression
GO:0016070	1.600913119791 84e-14	124	RNA metabolic process
GO:0016072	1.847054911833 55e-14	28	rRNA metabolic process
GO:0090304	2.4311216266984e-14	132	nucleic acid metabolic process
GO:0009057	3.1670776847996e-14	60	macromolecule catabolic process
GO:0043603	4.689053479058 93e-14	57	cellular amide metabolic process
GO:0010605	4.757962304900 79e-14	90	negative regulation of macromolecule metabolic process
GO:0010467	5.037702471069 06e-14	140	gene expression
GO:0006364	7.715612699745 47e-14	26	rRNA processing
GO:0009892	2.786637997025 32e-13	92	negative regulation of metabolic process
GO:0034645	3.299073844183 24e-13	121	cellular macromolecule biosynthetic process
GO:0044271	3.522337769679 13e-13	122	cellular nitrogen compound biosynthetic process
GO:0002181	6.415440793985 13e-13	19	cytoplasmic translation
GO:0009059	2.703051317327 82e-12	121	macromolecule biosynthetic process
GO:0034641	6.493837562520 53e-12	149	cellular nitrogen compound metabolic process
GO:0006725	9.400195367242 55e-12	139	cellular aromatic compound metabolic process
GO:0006139	1.097229760357 99e-11	136	nucleobase-containing compound metabolic process
GO:1901360	4.907033776789 28e-11	140	organic cyclic compound metabolic process
GO:0046483	7.030154278376 63e-11	136	heterocycle metabolic process
GO:0060255	8.677333815917 23e-11	133	regulation of macromolecule metabolic process
GO:0019222	2.448064768685 1e-10	139	regulation of metabolic process
GO:0034470	2.953771269724 08e-10	27	ncRNA processing
GO:0048519	3.217420956042 07e-10	121	negative regulation of biological process
GO:0008104	3.600428886252 36e-10	78	protein localization
GO:0034613	4.171725675693 06e-10	62	cellular protein localization
GO:0006886	4.517199680852 45e-10	48	intracellular protein transport
GO:0070727	5.155671909685 95e-10	62	cellular macromolecule localization
GO:0051276	5.251058148148 65e-10	47	chromosome organization
GO:0033036	7.790999110469 95e-10	83	macromolecule localization
GO:0006396	1.360347665946 84e-09	48	RNA processing
GO:1901576	2.895360146069 8e-09	129	organic substance biosynthetic process
GO:0015031	3.958571355101 82e-09	63	protein transport
GO:0051641	5.487761918232 62e-09	77	cellular localization
GO:0009058	6.236152575875 79e-09	129	biosynthetic process
GO:0034660	6.587473029243 41e-09	30	ncRNA metabolic process
GO:0015833	6.721089242935 97e-09	63	peptide transport
GO:1901566	6.969942349706 51e-09	61	organonitrogen compound biosynthetic process
GO:0045184	9.429635970008 9e-09	64	establishment of protein localization
GO:0044249	9.736675303365 87e-09	126	cellular biosynthetic process
GO:0042886	1.080897094837 06e-08	63	amide transport
GO:0042273	1.348574338575 83e-08	13	ribosomal large subunit biogenesis
GO:0071840	1.482540616765 49e-08	133	cellular component organization or biogenesis
GO:0044085	2.061990813460 85e-08	84	cellular component biogenesis
GO:0006996	2.3781890276192e-08	92	organelle organization
GO:0043170	4.790329000311 39e-08	175	macromolecule metabolic process
GO:1901575	5.337306407390 46e-08	61	organic substance catabolic process
GO:0006325	5.532412926742 52e-08	34	chromatin organization
GO:0044260	6.084490184426 91e-08	154	cellular macromolecule metabolic process
GO:0034728	9.489715091992 52e-08	18	nucleosome organization
GO:0071705	1.070142534446 16e-07	65	nitrogen compound transport
GO:0044248	2.224027030314 79e-07	62	cellular catabolic process
GO:0051649	3.143900833845 02e-07	61	establishment of localization in cell
GO:0042255	3.828899895648 14e-07	11	ribosome assembly
GO:0051253	4.608787727020 14e-07	41	negative regulation of RNA metabolic process
GO:0050789	4.953548739817 93e-07	183	regulation of biological process
GO:0046907	6.653437690523 75e-07	55	intracellular transport
GO:0006807	7.085131047461 52e-07	179	nitrogen compound metabolic process
GO:0006333	7.836098709738 57e-07	17	chromatin assembly or disassembly
GO:0071702	9.507403308644 76e-07	69	organic substance transport
GO:0071824	1.242381879251 65e-06	20	protein-DNA complex subunit organization
GO:0044238	1.291145895545 95e-06	183	primary metabolic process
GO:0009056	1.356233872113 07e-06	65	catabolic process
GO:0065007	1.471292074635 17e-06	189	biological regulation
GO:0045934	1.756856843824 29e-06	42	negative regulation of nucleobase-containing compound metabolic process
GO:0044267	1.771307165654 07e-06	109	cellular protein metabolic process
GO:0097194	1.986097020178 71e-06	9	execution phase of apoptosis
GO:0042274	2.392232180329 38e-06	10	ribosomal small subunit biogenesis
GO:0044237	2.393622190107 17e-06	185	cellular metabolic process
GO:0000462	2.8181604084737e-06	7	maturation of SSU-rRNA from tricistronic rRNA transcript (SSU-rRNA, 5.8S rRNA, LSU-rRNA)
GO:0022618	3.516371442668 67e-06	17	ribonucleoprotein complex assembly
GO:0033044	3.591692447844 2e-06	17	regulation of chromosome organization
GO:1902275	4.509531515963 96e-06	12	regulation of chromatin organization
GO:0071103	5.687217150404 76e-06	18	DNA conformation change
GO:0071826	6.146688217516 24e-06	17	ribonucleoprotein complex subunit organization
GO:0008152	8.036301560197 37e-06	194	metabolic process
GO:0000027	9.545503895617 43e-06	7	ribosomal large subunit assembly
GO:1903311	1.056416679379 62e-05	14	regulation of mRNA metabolic process
GO:0034622	1.170185444347 57e-05	40	cellular protein-containing complex assembly
GO:0006337	1.226618808221 65e-05	5	nucleosome disassembly
GO:0016584	1.260525605598 58e-05	5	nucleosome positioning
GO:0071704	1.310987729861 58e-05	187	organic substance metabolic process
GO:0031498	1.827557864805e-05	5	chromatin disassembly
GO:0030490	1.902958108974 56e-05	7	maturation of SSU-rRNA
GO:0008380	2.245948427034 68e-05	20	RNA splicing
GO:1903507	2.728177615365 93e-05	35	negative regulation of nucleic acid-templated transcription
GO:1902679	2.900300116731 58e-05	35	negative regulation of RNA biosynthetic process
GO:0006323	2.912590237396 05e-05	15	DNA packaging
GO:0032986	3.063162306049 49e-05	5	protein-DNA complex disassembly
GO:0045892	3.116311143947 26e-05	34	negative regulation of transcription, DNA-templated
GO:0019538	3.526982467138 25e-05	112	protein metabolic process
GO:0050684	4.117331708282 12e-05	9	regulation of mRNA processing
GO:0000377	4.467173223350 54e-05	17	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile
GO:0000398	4.467173223350 54e-05	17	mRNA splicing, via spliceosome
GO:0000375	5.128661049328 03e-05	17	RNA splicing, via transesterification reactions
GO:0006259	5.260494057520 68e-05	31	DNA metabolic process
GO:0051252	5.321017675725 81e-05	74	regulation of RNA metabolic process
GO:0051179	5.658904982714 84e-05	116	localization
GO:2001251	6.579453328163 56e-05	10	negative regulation of chromosome organization
GO:0000122	7.850054172837 5e-05	25	negative regulation of transcription by RNA polymerase II
GO:0006397	8.136660876207 71e-05	20	mRNA processing
GO:0035722	8.270678602672 76e-05	6	interleukin-12-mediated signaling pathway
GO:0051172	8.793285344264 16e-05	55	negative regulation of nitrogen compound metabolic process
GO:2000113	8.866246253016 44e-05	38	negative regulation of cellular macromolecule biosynthetic process
GO:0030261	9.192937603175 68e-05	6	chromosome condensation
GO:0080090	9.479557271310 11e-05	107	regulation of primary metabolic process
GO:0071349	9.977994968185 3e-05	6	cellular response to interleukin-12
GO:0031497	0.000100911428738501	13	chromatin assembly
GO:0070671	0.000109310610250661	6	response to interleukin-12
GO:0010558	0.000117892740234675	39	negative regulation of macromolecule biosynthetic process
GO:0045870	0.000137811579435088	2	positive regulation of single stranded viral RNA replication via double stranded DNA intermediate
GO:2000112	0.000141122169992815	76	regulation of cellular macromolecule biosynthetic process
GO:1900118	0.000155597680650446	4	negative regulation of execution phase of apoptosis
GO:0030262	0.000162673006011346	5	apoptotic nuclear changes
GO:0031935	0.000163332007224945	5	regulation of chromatin silencing
GO:0016043	0.000176714745504061	115	cellular component organization
GO:0048024	0.000184890122375165	7	regulation of mRNA splicing, via spliceosome
GO:0080182	0.000189658268485643	4	histone H3-K4 trimethylation
GO:0031324	0.000197723888537645	56	negative regulation of cellular metabolic process
GO:0006334	0.000197730890169389	12	nucleosome assembly
GO:0033043	0.000208626188955896	33	regulation of organelle organization
GO:0006921	0.000211630302643849	5	cellular component disassembly involved in execution phase of apoptosis

GO:0001731	0.000212533063672687	3	formation of translation preinitiation complex
GO:0010557	0.000220362983652061	42	positive regulation of macromolecule biosynthetic process
GO:0065004	0.000228685633946492	15	protein-DNA complex assembly
GO:0051171	0.000244135547837946	103	regulation of nitrogen compound metabolic process
GO:0043933	0.000250922144910616	56	protein-containing complex subunit organization
GO:0031327	0.000258018190883583	39	negative regulation of cellular biosynthetic process
GO:0048524	0.000261205288849289	7	positive regulation of viral process
GO:0000380	0.000270055251621033	6	alternative mRNA splicing, via spliceosome
GO:1903902	0.000294975357328998	6	positive regulation of viral life cycle
GO:0031328	0.000296540777561049	43	positive regulation of cellular biosynthetic process
GO:1905268	0.000308400557826213	6	negative regulation of chromatin organization
GO:0043484	0.000325531561161198	8	regulation of RNA splicing
GO:0019219	0.000332080292468109	75	regulation of nucleobase-containing compound metabolic process
GO:1902369	0.000336632681499514	5	negative regulation of RNA catabolic process
GO:0032784	0.000339923774587 92	5	regulation of DNA-templated transcription, elongation
GO:0045935	0.00036392064922975	41	positive regulation of nucleobase-containing compound metabolic process
GO:0044419	0.000366906269871288	25	interspecies interaction between organisms
GO:0043902	0.000372715358505	9	positive regulation of multi-organism process
GO:0009890	0.000374446828961419	39	negative regulation of biosynthetic process
GO:0043487	0.000375807207047208	8	regulation of RNA stability
GO:0033979	0.000411220074066571	2	box H/ACA snoRNA metabolic process
GO:0097010	0.000412342237070883	2	eukaryotic translation initiation factor 4F complex assembly
GO:0010556	0.000415785583614753	76	regulation of macromolecule biosynthetic process
GO:0048523	0.00044518880788378	87	negative regulation of cellular process
GO:0006265	0.000459840339612042	3	DNA topological change
GO:0000447	0.000473467784146807	3	endonucleolytic cleavage in ITS1 to separate SSU-rRNA from 5.8S rRNA and LSU-rRNA from tricistronic rRNA transc
GO:0009891	0.000475113118999594	43	positive regulation of biosynthetic process
GO:0009889	0.000505051235064205	79	regulation of biosynthetic process
GO:0031936	0.000514302062798394	4	negative regulation of chromatin silencing
GO:0034243	0.000526496342499836	4	regulation of transcription elongation from RNA polymerase II promoter
GO:0098532	0.000532151299213109	3	histone H3-K27 trimethylation
GO:0051234	0.00054884156248844 2	93	establishment of localization
GO:1903508	0.000550266057761 86	36	positive regulation of nucleic acid-templated transcription
GO:1902680	0.000556174414280667	36	positive regulation of RNA biosynthetic process
GO:0032786	0.000569156488790539	4	positive regulation of DNA-templated transcription, elongation

(Significantly upregulated biological pathways in 6 min stochastic oscillatory condition).

Category	Overrepresented p-value	numDEInCat	Term
GO:0072599	8.75681197956462e-27	65	establishment of protein localization to endoplasmic reticulum
GO:0006613	2.24387162139419e-26	62	cotranslational protein targeting to membrane
GO:0070972	2.40253647420459e-26	68	protein localization to endoplasmic reticulum
GO:0045047	2.56630650978022e-26	64	protein targeting to ER
GO:0006614	3.40305274155061e-26	61	SRP-dependent cotranslational protein targeting to membrane
GO:0006518	1.867548144723 85e-25	144	peptide metabolic process
GO:0006413	1.11299733710946e-24	73	translational initiation
GO:0043603	1.66476389066995e-24	159	cellular amide metabolic process
GO:0000184	7.603971164059 13e-24	61	nuclear-transcribed mRNA catabolic process, nonsense-mediated decay
GO:1901564	4.96287048206429e-23	461	organonitrogen compound metabolic process
GO:0043604	1.082467759005 75e-21	134	amide biosynthetic process
GO:0043043	8.06423267969977e-21	124	peptide biosynthetic process
GO:0000956	1.95601343029552e-20	68	nuclear-transcribed mRNA catabolic process
GO:0044265	2.06377986905486e-20	135	cellular macromolecule catabolic process
GO:0006412	7.72405655097889e-20	120	translation
GO:0090150	1.51512983154989e-19	78	establishment of protein localization to membrane
GO:0006612	3.44050438911697e-19	65	protein targeting to membrane
GO:0009057	9.43088288443446e-19	144	macromolecule catabolic process
GO:1901566	1.89081338206925e-18	189	organonitrogen compound biosynthetic process
GO:0006402	2.69282835907326e-18	72	mRNA catabolic process
GO:0072594	7.00331061911749e-18	95	establishment of protein localization to organelle
GO:0006401	1.64865986941044e-17	73	RNA catabolic process
GO:0072657	3.40380889186971e-17	93	protein localization to membrane
GO:0044267	4.20119386802705e-17	357	cellular protein metabolic process
GO:0044248	1.13848381521416e-16	193	cellular catabolic process
GO:0006810	1.87821883867087e-16	316	transport
GO:0033365	3.38983670640183e-16	110	protein localization to organelle
GO:0019538	5.90740508265411e-16	377	protein metabolic process
GO:0006605	8.04734877148736e-16	83	protein targeting
GO:0051234	1.25954055980076e-15	318	establishment of localization
GO:0046907	1.81110275385867e-15	165	intracellular transport
GO:0015833	3.12489859071357e-15	177	peptide transport
GO:0042886	4.42253290368258e-15	178	amide transport
GO:0045184	5.93472794923627e-15	180	establishment of protein localization
GO:0015031	7.98323663569 59e-15	174	protein transport
GO:0034613	8.38430887900333e-15	161	cellular protein localization
GO:0070727	1.38554715941512e-14	161	cellular macromolecule localization
GO:0034655	2.52316877869924e-14	84	nucleobase-containing compound catabolic process
GO:0006886	2.64339940794 43e-14	124	intracellular protein transport
GO:0008104	2.89266609773924e-14	204	protein localization
GO:0009056	2.98077809491877e-14	201	catabolic process
GO:0046700	6.07745398435504e-14	87	heterocycle catabolic process
GO:0019439	7.43786677567361e-14	88	aromatic compound catabolic process
GO:0044270	8.3893524165654e-14	87	cellular nitrogen compound catabolic process
GO:0051649	1.92694106834982e-13	175	establishment of localization in cell
GO:1901361	3.16158195363644e-13	89	organic cyclic compound catabolic process
GO:0048519	3.58684635153462e-13	329	negative regulation of biological process
GO:0071705	4.76609602289056e-13	185	nitrogen compound transport
GO:0051641	7.39099304556673e-13	203	cellular localization
GO:0033036	1.15854895733404e-12	215	macromolecule localization
GO:0010033	1.44693156100954e-12	211	response to organic substance
GO:0051179	1.66334295540246e-12	362	localization
GO:1901575	2.9659779753909e-12	171	organic substance catabolic process
GO:0009987	4.89164427184744e-12	755	cellular process
GO:0046034	7.7662382422178e-12	46	ATP metabolic process
GO:0006119	8.79050205616587e-12	36	oxidative phosphorylation
GO:0042221	1.30918387745043e-11	266	response to chemical
GO:0034976	1.76605730836133e-11	39	response to endoplasmic reticulum stress
GO:0071702	1.82071372655503e-11	197	organic substance transport
GO:0002181	2.05141626581062e-11	32	cytoplasmic translation
GO:0009123	2.06117702309532e-11	52	nucleoside monophosphate metabolic process
GO:0008219	2.11017608798963e-11	165	cell death
GO:0010243	2.48036514521538e-11	78	response to organonitrogen compound
GO:0009144	2.50115740046853e-11	50	purine nucleoside triphosphate metabolic process
GO:0016071	2.67812092108234e-11	95	mRNA metabolic process
GO:0043933	2.69856265580117e-11	187	protein-containing complex subunit organization
GO:0042773	2.72199200188004e-11	32	ATP synthesis coupled electron transport
GO:0071840	2.78044467271746e-11	369	cellular component organization or biogenesis
GO:0009141	2.81881422026062e-11	52	nucleoside triphosphate metabolic process
GO:0022900	3.38766509147521e-11	46	electron transport chain
GO:0017144	3.72790712200064e-11	85	drug metabolic process
GO:1901698	3.94934299832862e-11	82	response to nitrogen compound
GO:0012501	4.04248596411603e-11	157	programmed cell death
GO:0009161	4.48815248463432e-11	49	ribonucleoside monophosphate metabolic process
GO:0044237	4.68634643258666e-11	582	cellular metabolic process
GO:0009205	7.96887392898487e-11	48	purine ribonucleoside triphosphate metabolic process
GO:0065003	8.89657999246528e-11	162	protein-containing complex assembly
GO:0006915	1.01684444880464e-10	145	apoptotic process
GO:0044260	1.22757129376613e-10	447	cellular macromolecule metabolic process
GO:0044085	1.27041962413655e-10	223	cellular component biogenesis
GO:0009167	1.33876224447366e-10	47	purine ribonucleoside monophosphate metabolic process
GO:0042775	1.48288889752737e-10	31	mitochondrial ATP synthesis coupled electron transport
GO:0007005	1.54635763881844e-10	70	mitochondrion organization
GO:0009199	1.55790268565652e-10	48	ribonucleoside triphosphate metabolic process
GO:0009126	1.7879652795603e-10	47	purine nucleoside monophosphate metabolic process
GO:0009892	2.28313942441511e-10	210	negative regulation of metabolic process

GO:0006950	2.90408631562 75e-10	243	response to stress
GO:0010605	6.060396033576 73e-10	198	negative regulation of macromolecule metabolic process
GO:0022904	1.02660230619726e-09	32	respiratory electron transport chain
GO:0097193	1.21616640960545e-09	44	intrinsic apoptotic signaling pathway
GO:0051246	1.21871015056515e-09	186	regulation of protein metabolic process
GO:0070887	1.2403017679245e-09	202	cellular response to chemical stimulus
GO:0006508	1.273913233336 54e-09	132	proteolysis
GO:0009725	1.27760427037019e-09	75	response to hormone
GO:0044419	1.50626262422366e-09	79	interspecies interaction between organisms
GO:0006807	1.99568122199146e-09	547	nitrogen compound metabolic process
GO:0030162	2.08339141525109e-09	78	regulation of proteolysis
GO:0034622	2.37024577193646e-09	116	cellular protein-containing complex assembly
GO:0019725	2.43586672271186e-09	79	cellular homeostasis
GO:0044403	2.50125551458531e-09	74	symbiont process
GO:0008152	2.54630127161263e-09	608	metabolic process
GO:0009117	3.42257843382831e-09	73	nucleotide metabolic process
GO:0016043	3.62509408828785e-09	345	cellular component organization
GO:0016032	3.67415005696153e-09	69	viral process
GO:0009719	3.99199029950981e-09	106	response to endogenous stimulus
GO:0010941	4.04286587841019e-09	125	regulation of cell death
GO:0006753	5.83589468152625e-09	73	nucleoside phosphate metabolic process
GO:0060548	6.78020956221381e-09	85	negative regulation of cell death
GO:0016192	7.41357245280834e-09	131	vesicle-mediated transport
GO:0014070	7.70683874096601e-09	69	response to organic cyclic compound
GO:0043067	8.57450994663313e-09	117	regulation of programmed cell death
GO:0042981	9.9626566235809e-09	116	regulation of apoptotic process
GO:0022607	1.10710512518095e-08	196	cellular component assembly
GO:0050896	1.2859025627553e-08	431	response to stimulus
GO:0030163	1.39291909503623e-08	77	protein catabolic process
GO:0006091	1.58212693736058e-08	58	generation of precursor metabolites and energy
GO:0044257	1.78896253078855e-08	67	cellular protein catabolic process
GO:0032268	1.8845200554612 3e-08	171	regulation of cellular protein metabolic process
GO:0031329	2.02143358271717e-08	65	regulation of cellular catabolic process
GO:0019222	2.08709505435476e-08	358	regulation of metabolic process
GO:0009636	2.16112310950622e-08	58	response to toxic substance
GO:0033554	2.22718500801792e-08	136	cellular response to stress
GO:0051704	2.30829892212601e-08	160	multi-organism process
GO:0050789	2.3493621273356e-08	531	regulation of biological process
GO:0019693	2.37180631011141e-08	61	ribose phosphate metabolic process
GO:0055086	2.38725688524853e-08	77	nucleobase-containing small molecule metabolic process
GO:0045333	2.54993165576276e-08	37	cellular respiration
GO:0080134	2.62262952671378e-08	102	regulation of response to stress
GO:0009259	2.78957515737306e-08	59	ribonucleotide metabolic process
GO:0034641	2.88721971701727e-08	388	cellular nitrogen compound metabolic process
GO:0055114	2.94953458221965e-08	95	oxidation-reduction process
GO:0044271	3.01380561724458e-08	287	cellular nitrogen compound biosynthetic process
GO:1901700	4.28860896321181e-08	107	response to oxygen-containing compound
GO:0043069	4.3136881496914e-08	77	negative regulation of programmed cell death
GO:0006163	4.51809085909136e-08	60	purine nucleotide metabolic process
GO:0042119	5.19505038347951e-08	56	neutrophil activation
GO:2001242	5.80024920546177e-08	31	regulation of intrinsic apoptotic signaling pathway
GO:0009150	6.20548231185338e-08	57	purine ribonucleotide metabolic process
GO:0010035	7.05707959870674e-08	57	response to inorganic substance
GO:0042592	7.24655503809122e-08	127	homeostatic process
GO:0043066	8.68015719257071e-08	75	negative regulation of apoptotic process
GO:0036230	9.04642133428955e-08	56	granulocyte activation
GO:0072521	1.24367756456024e-07	61	purine-containing compound metabolic process
GO:0035966	1.28793815144476e-07	27	response to topologically incorrect protein
GO:0048522	1.31333982214033e-07	272	positive regulation of cellular process
GO:0051603	1.43243393185882e-07	61	proteolysis involved in cellular protein catabolic process
GO:0071704	1.49677511757897e-07	575	organic substance metabolic process
GO:0048518	1.52197008009257e-07	302	positive regulation of biological process
GO:0006511	1.65840458803292e-07	54	ubiquitin-dependent protein catabolic process
GO:0001775	1.74943839841143e-07	99	cell activation
GO:0097190	1.7965632082681e-07	63	apoptotic signaling pathway
GO:0009605	1.80425468912157e-07	145	response to external stimulus
GO:0035967	1.84212945843478e-07	23	cellular response to topologically incorrect protein
GO:0006986	1.85025423707501e-07	25	response to unfolded protein
GO:0048585	1.92268193300034e-07	103	negative regulation of response to stimulus
GO:0071310	1.93665958185173e-07	158	cellular response to organic substance
GO:0044238	1.98544241823838e-07	551	primary metabolic process
GO:0060255	2.12199526188764e-07	328	regulation of macromolecule metabolic process
GO:0043632	2.14176408401763e-07	55	modification-dependent macromolecule catabolic process
GO:0019941	2.38741001237285e-07	54	modification-dependent protein catabolic process
GO:0010629	2.43913905524855e-07	143	negative regulation of gene expression
GO:0008150	2.46673284947424e-07	788	biological_process
GO:0030855	2.83467068503159e-07	64	epithelial cell differentiation
GO:0043312	2.87844486546926e-07	53	neutrophil degranulation
GO:0009894	2.97034199151866e-07	68	regulation of catabolic process
GO:0002446	2.97941952394301e-07	54	neutrophil mediated immunity
GO:0034620	2.99074723918618e-07	21	cellular response to unfolded protein
GO:1905897	3.33238649595437e-07	16	regulation of response to endoplasmic reticulum stress
GO:0043161	3.33263526829539e-07	44	proteasome-mediated ubiquitin-dependent protein catabolic process
GO:0022613	3.46704898256151e-07	60	ribonucleoprotein complex biogenesis
GO:0006996	3.51994119059197e-07	226	organelle organization
GO:0045454	3.69796967843423e-07	17	cell redox homeostasis
GO:0051384	4.39820137363192e-07	22	response to glucocorticoid
GO:0010498	5.10557700553534e-07	48	proteasomal protein catabolic process
GO:0002274	5.27258741837253e-07	61	myeloid leukocyte activation
GO:0002283	5.31793297519102e-07	53	neutrophil activation involved in immune response
GO:0034097	5.48324752635071e-07	88	response to cytokine
GO:2001233	5.85715095867373e-07	47	regulation of apoptotic signaling pathway
GO:1901652	7.94411713217858e-07	41	response to peptide
GO:0055082	8.23787681566708e-07	62	cellular chemical homeostasis
GO:0015980	8.329016658356e-07	38	energy derivation by oxidation of organic compounds
GO:0061024	8.390618535082 38e-07	61	membrane organization
GO:0030968	9.68944326476138e-07	19	endoplasmic reticulum unfolded protein response
GO:0042254	1.0027602379862e-06	46	ribosome biogenesis
GO:0044249	1.00894882045216e-06	329	cellular biosynthetic process
GO:0043299	1.0613400402892e-06	55	leukocyte degranulation
GO:0080135	1.14398075842702e-06	57	regulation of cellular response to stress
GO:0002252	1.15633732286188e-06	88	immune effector process
GO:0032940	1.16614233122602e-06	101	secretion by cell
GO:0031960	1.2929101705006e-06	23	response to corticosteroid
GO:1903362	1.30134571151759e-06	29	regulation of cellular protein catabolic process
GO:0006120	1.30631839242542e-06	19	mitochondrial electron transport, NADH to ubiquinone
GO:0098754	1.36224809870918e-06	27	detoxification
GO:1901565	1.37941845051589e-06	93	organonitrogen compound catabolic process
GO:0045321	1.52565789560031e-06	90	leukocyte activation
GO:0006887	1.53190531081629e-06	72	exocytosis
GO:0033108	1.58757960614529e-06	26	mitochondrial respiratory chain complex assembly
GO:0071345	1.71811834703898e-06	83	cellular response to cytokine stimulus
GO:0002275	1.73546583763102e-06	55	myeloid cell activation involved in immune response
GO:0048545	1.80346834012162e-06	36	response to steroid hormone
GO:0002444	2.40121967924814e-06	55	myeloid leukocyte mediated immunity
GO:0072593	2.80095595639418e-06	34	reactive oxygen species metabolic process
GO:0002443	2.85505859258414e-06	67	leukocyte mediated immunity
GO:0002366	3.0682954154978e-06	62	leukocyte activation involved in immune response
GO:0009058	3.17838347765389e-06	335	biosynthetic process
GO:0002263	3.1926550911871e-06	62	cell activation involved in immune response
GO:0043065	3.19384543740573e-06	58	positive regulation of apoptotic process
GO:0051099	3.30054754574274e-06	24	positive regulation of binding
GO:0043068	3.44020857477611e-06	58	positive regulation of programmed cell death
GO:0046903	3.48443198342139e-06	105	secretion
GO:0044281	3.64306914837167e-06	137	small molecule metabolic process
GO:0045862	3.66890756701784e-06	38	positive regulation of proteolysis
GO:1902532	3.77982668801953e-06	44	negative regulation of intracellular signal transduction
GO:0002376	3.86518729121958e-06	177	immune system process
GO:0097237	4.06187572841837e-06	31	cellular response to toxic substance

GO:0010038	4.14426585365196e-06	39	response to metal ion
GO:0006979	4.47095970859393e-06	46	response to oxidative stress
GO:0009607	4.59661026054913e-06	75	response to biotic stimulus
GO:0001732	4.60384693952324e-06	8	formation of cytoplasmic translation initiation complex
GO:0033993	4.62870521370711e-06	66	response to lipid
GO:0009611	5.0250030063728e-06	51	response to wounding
GO:1903573	5.25902493067224e-06	10	negative regulation of response to endoplasmic reticulum stress
GO:0051716	5.35169892347519e-06	349	cellular response to stimulus
GO:0045055	5.51207390335574e-06	65	regulated exocytosis
GO:0065008	5.54681374608472e-06	205	regulation of biological quality
GO:1901576	5.8948707652398e-06	330	organic substance biosynthetic process
GO:0042176	6.19507249065813e-06	37	regulation of protein catabolic process
GO:0032270	6.39675622939003e-06	104	positive regulation of cellular protein metabolic process
GO:0098869	7.055687161346 74e-06	20	cellular oxidant detoxification
GO:0030003	8.22358298445453e-06	51	cellular cation homeostasis
GO:0070671	8.23375529264608e-06	12	response to interleukin-12
GO:0051247	8.2683037561373e-06	109	positive regulation of protein metabolic process
GO:0035150	8.41764709566829e-06	16	regulation of tube size
GO:0050880	8.41764709566829e-06	16	regulation of blood vessel size
GO:2000058	8.47656322656386e-06	20	regulation of ubiquitin-dependent protein catabolic process
GO:0031667	8.5290347853736e-06	41	response to nutrient levels
GO:0019058	8.66987918894868e-06	32	viral life cycle
GO:0065007	8.71403207617412e-06	543	biological regulation
GO:0044093	8.85605719941485e-06	107	positive regulation of molecular function
GO:0007568	9.25472767514428e-06	33	aging
GO:0070059	9.75245575951481e-06	12	intrinsic apoptotic signaling pathway in response to endoplasmic reticulum stress
GO:0006875	9.98352932600858e-06	48	cellular metal ion homeostasis
GO:0043434	1.00448818581763e-05	34	response to peptide hormone
GO:0048878	1.02957081524328e-05	79	chemical homeostasis
GO:0006955	1.03532909740464e-05	129	immune response
GO:0046916	1.08495151788087e-05	22	cellular transition metal ion homeostasis
GO:2001244	1.11959826847767e-05	16	positive regulation of intrinsic apoptotic signaling pathway
GO:0042255	1.12894439608491e-05	19	ribosome assembly
GO:0009991	1.16495936754278e-05	43	response to extracellular stimulus
GO:0042273	1.20289952591231e-05	20	ribosomal large subunit biogenesis
GO:0002183	1.21846019488232e-05	10	cytoplasmic translational initiation
GO:1903050	1.2404499864168e-05	25	regulation of proteolysis involved in cellular protein catabolic process
GO:0006873	1.25246668544713e-05	51	cellular ion homeostasis
GO:0032436	1.34222623518461e-05	13	positive regulation of proteasomal ubiquitin-dependent protein catabolic process
GO:0051173	1.34281493682769e-05	171	positive regulation of nitrogen compound metabolic process
GO:0051098	1.36446264558322e-05	37	regulation of binding
GO:0010942	1.52824423444188e-05	59	positive regulation of cell death
GO:1990748	1.537246014290 63e-05	20	cellular detoxification
GO:1902600	1.58569709346627e-05	23	proton transmembrane transport
GO:0022618	1.64782073201634e-05	35	ribonucleoprotein complex assembly
GO:0010604	1.65924071392866e-05	178	positive regulation of macromolecule metabolic process
GO:0010648	1.6811281295506e-05	84	negative regulation of cell communication
GO:0052548	1.70025546101149e-05	46	regulation of endopeptidase activity
GO:1901135	1.74828756147578e-05	91	carbohydrate derivative metabolic process
GO:0052547	1.776879174157e-05	48	regulation of peptidase activity
GO:0023057	1.78080823786362e-05	84	negative regulation of signaling
GO:0070498	1.785766729727 33e-05	11	interleukin-1-mediated signaling pathway
GO:2000116	1.83682281442361e-05	31	regulation of cysteine-type endopeptidase activity
GO:0006914	2.00606634168327e-05	40	autophagy
GO:0061919	2.00606634168327e-05	40	process utilizing autophagic mechanism
GO:0031325	2.006167395923 52e-05	175	positive regulation of cellular metabolic process
GO:0098609	2.01001198947873e-05	50	cell-cell adhesion
GO:0030260	2.01509474484657e-05	17	entry into host cell
GO:0044409	2.01509474484657e-05	17	entry into host
GO:0051806	2.01509474484657e-05	17	entry into cell of other organism involved in symbiotic interaction
GO:0051828	2.01509474484657e-05	17	entry into other organism involved in symbiotic interaction
GO:0010257	2.04053173012249e-05	20	NADH dehydrogenase complex assembly
GO:0032981	2.04053173012249e-05	20	mitochondrial respiratory chain complex I assembly
GO:2001243	2.06770103732073e-05	17	negative regulation of intrinsic apoptotic signaling pathway
GO:0032434	2.10902791270735e-05	17	regulation of proteasomal ubiquitin-dependent protein catabolic process
GO:0006984	2.13285542093436e-05	10	ER-nucleus signaling pathway
GO:0051248	2.17680613615613e-05	84	negative regulation of protein metabolic process
GO:0071417	2.20028667148013e-05	38	cellular response to organonitrogen compound
GO:0050790	2.4294941233 8095e-05	140	regulation of catalytic activity
GO:0034248	2.52490727648558e-05	42	regulation of cellular amide metabolic process
GO:0009968	2.53757376068647e-05	78	negative regulation of signal transduction
GO:0031396	2.58398123075628e-05	23	regulation of protein ubiquitination
GO:0050801	2.59108506850237e-05	58	ion homeostasis
GO:0034645	2.65087437411041e-05	265	cellular macromolecule biosynthetic process
GO:0043281	2.69635282799008e-05	29	regulation of cysteine-type endopeptidase activity involved in apoptotic process
GO:0009893	2.81205883334084e-05	190	positive regulation of metabolic process
GO:0048523	2.89457881195136e-05	246	negative regulation of cellular process
GO:0043207	3.14744305179032e-05	71	response to external biotic stimulus
GO:0051707	3.14744305179032e-05	71	response to other organism
GO:0055080	3.30354853394053e-05	53	cation homeostasis
GO:0071826	3.39080183463186e-05	35	ribonucleoprotein complex subunit organization
GO:0035722	3.59283125637289e-05	11	interleukin-12-mediated signaling pathway
GO:0055065	3.66910547432119e-05	50	metal ion homeostasis
GO:0009408	3.83226464136996e-05	17	response to heat
GO:2000060	3.87130716184728e-05	13	positive regulation of ubiquitin-dependent protein catabolic process
GO:0009617	3.88059060580036e-05	53	response to bacterium
GO:0009628	3.93749986998146e-05	74	response to abiotic stimulus
GO:0007566	4.01197661575417e-05	11	embryo implantation
GO:0071349	4.17842771923394e-05	11	cellular response to interleukin-12
GO:0046718	4.18419422703922e-05	16	viral entry into host cell
GO:0055076	4.29961501161106e-05	23	transition metal ion homeostasis
GO:1901653	4.38589478639912e-05	29	cellular response to peptide
GO:2001234	4.43948304962401e-05	27	negative regulation of apoptotic signaling pathway
GO:0098771	4.47502660808378e-05	53	inorganic ion homeostasis
GO:0044092	4.94858479017762e-05	81	negative regulation of molecular function
GO:0042274	4.95547559416024e-05	17	ribosomal small subunit biogenesis
GO:0021761	5.16388034721015e-05	13	limbic system development
GO:0009059	5.34832340546808e-05	270	macromolecule biosynthetic process
GO:0032092	5.50354682256687e-05	14	positive regulation of protein binding
GO:0043086	5.60959987634691e-05	64	negative regulation of catalytic activity
GO:0050818	5.94566565520029e-05	12	regulation of coagulation
GO:0060429	6.23084832851845e-05	78	epithelium development
GO:0035296	6.28847503998534e-05	14	regulation of tube diameter
GO:0097746	6.28847503998534e-05	14	regulation of blood vessel diameter
GO:0070647	6.53873110371754e-05	73	protein modification by small protein conjugation or removal
GO:0042060	6.97653189248421e-05	40	wound healing
GO:1903364	7.12998530305735e-05	16	positive regulation of cellular protein catabolic process
GO:0061136	7.35853178340861e-05	21	regulation of proteasomal protein catabolic process
GO:0034975	7.36307333699114e-05	5	protein folding in endoplasmic reticulum
GO:0051128	8.34170420556034e-05	130	regulation of cellular component organization
GO:0009888	8.59980781735316e-05	110	tissue development
GO:1901654	8.82421599465151e-05	21	response to ketone
GO:0019637	8.82760310884589e-05	84	organophosphate metabolic process
GO:0071248	9.0603401227263e-05	23	cellular response to metal ion
GO:0032602	9.10674219458155e-05	14	chemokine production
GO:0051186	9.22147636823264e-05	52	cofactor metabolic process
GO:0010506	9.35603288385927e-05	27	regulation of autophagy
GO:0033043	9.39319104285965e-05	78	regulation of organelle organization
GO:0032269	9.52941223612834e-05	78	negative regulation of cellular protein metabolic process
GO:1901701	9.58497762026857e-05	68	cellular response to oxygen-containing compound
GO:2000377	0.00010361962694065	22	regulation of reactive oxygen species metabolic process
GO:0035556	0.00010618386726257	149	intracellular signal transduction
GO:0006364	0.00010787015 1682348	32	rRNA processing
GO:0016072	0.00010834541382439	34	rRNA metabolic process
GO:0044794	0.00011380311730 4325	6	positive regulation by host of viral process
GO:0065009	0.00011425876411 1238	183	regulation of molecular function
GO:1902531	0.00011575119058 0714	108	regulation of intracellular signal transduction
GO:0097755	0.00011892039160 8215	10	positive regulation of blood vessel diameter
GO:0008283	0.00012242354150 2287	121	cell proliferation

GO:0007154	0.0001334435458585383	290	cell communication
GO:0045861	0.0001370742398290888	37	negative regulation of proteolysis
GO:0046794	0.0001391913767191290	7	transport of virus
GO:1901699	0.0001401950532861770	39	cellular response to nitrogen compound
GO:0003018	0.0001409078501823590	16	vascular process in circulatory system
GO:2001235	0.000145450415780360	24	positive regulation of apoptotic signaling pathway
GO:1903034	0.0001518875664027350	17	regulation of response to wounding
GO:1903320	0.0001523787585242230	23	regulation of protein modification by small protein conjugation or removal
GO:0061041	0.0001589300533701350	15	regulation of wound healing
GO:0010821	0.0001641305596308740	21	regulation of mitochondrion organization
GO:0050819	0.0001665086790745740	9	negative regulation of coagulation
GO:0030193	0.0001695380737150410	11	regulation of blood coagulation
GO:1900046	0.0001695380737150410	11	regulation of hemostasis
GO:1905898	0.0001745134028109120	8	positive regulation of response to endoplasmic reticulum stress
GO:0006457	0.0001791323937558960	27	protein folding
GO:0036499	0.0001800128871974840	7	PERK-mediated unfolded protein response
GO:0001765	0.0001846387081194550	5	membrane raft assembly
GO:0021766	0.0001893176280112260	10	hippocampus development
GO:1903409	0.0001946329259040350	15	reactive oxygen species biosynthetic process
GO:0006878	0.0002013810728437080	6	cellular copper ion homeostasis
GO:0010468	0.0002023626272245460	235	regulation of gene expression
GO:0031639	0.0002065595021384920	6	plasminogen activation
GO:0042311	0.0002084535425467180	7	vasodilation
GO:0009267	0.0002285076005753920	15	cellular response to starvation
GO:1903052	0.0002344516581929930	14	positive regulation of proteolysis involved in cellular protein catabolic process
GO:0045787	0.0002355678641642860	33	positive regulation of cell cycle
GO:0051701	0.0002438469396054110	21	interaction with host
GO:1900102	0.0002441382028454630	4	negative regulation of endoplasmic reticulum unfolded protein response
GO:0000422	0.0002460139683551190	12	autophagy of mitochondrion
GO:0061726	0.0002460139683551190	12	mitochondrion disassembly
GO:0023052	0.0002509280806256830	285	signaling
GO:0051130	0.0002569900069455830	70	positive regulation of cellular component organization
GO:0007165	0.0002616751155648550	270	signal transduction
GO:0046686	0.0002703619576393710	15	response to cadmium ion
GO:0031323	0.0002724302747214560	295	regulation of cellular metabolic process
GO:0071496	0.000272448363713416	27	cellular response to external stimulus
GO:0043085	0.0002794409716719410	83	positive regulation of catalytic activity
GO:0043170	0.0002834224345296870	482	macromolecule metabolic process
GO:0071284	0.0002886391815511480	3	cellular response to lead ion
GO:0097066	0.0002919711403209843	6	response to thyroid hormone
GO:0006749	0.000302007904366280	12	glutathione metabolic process
GO:0071709	0.0003101755992420760	6	membrane assembly
GO:0071241	0.0003312182685655140	23	cellular response to inorganic substance
GO:0050878	0.0003350507890656470	35	regulation of body fluid levels
GO:0051336	0.0003400729338237930	81	regulation of hydrolase activity
GO:1901800	0.0003441070683926680	13	positive regulation of proteasomal protein catabolic process
GO:0019221	0.0003592907760711710	60	cytokine-mediated signaling pathway
GO:0048584	0.0003648741462199050	129	positive regulation of response to stimulus
GO:0042594	0.0003758064208014370	17	response to starvation
GO:0031952	0.0003760947835194880	6	regulation of protein autophosphorylation
GO:0009266	0.0003770282957173520	20	response to temperature stimulus
GO:0032502	0.0003874790095475560	285	developmental process
GO:1902533	0.0003876358836107830	72	positive regulation of intracellular signal transduction
GO:2001056	0.0003931386908322960	20	positive regulation of cysteine-type endopeptidase activity
GO:0071407	0.000398170207537130	35	cellular response to organic cyclic compound
GO:0071495	0.0004047074400510760	73	cellular response to endogenous stimulus
GO:0046677	0.0004087617076841560	30	response to antibiotic
GO:0046688	0.0004174996164609750	12	response to copper ion
GO:0031330	0.000424900478343860	22	negative regulation of cellular catabolic process
GO:0042542	0.0004315681390792260	18	response to hydrogen peroxide
GO:0009060	0.0004328894307936630	15	aerobic respiration
GO:1902235	0.0004395059479589180	7	regulation of endoplasmic reticulum stress-induced intrinsic apoptotic signaling pathway
GO:0051881	0.0004840576977924110	12	regulation of mitochondrial membrane potential
GO:0032446	0.0004964674104647870	55	protein modification by small protein conjugation
GO:0061077	0.0005068412973807770	10	chaperone-mediated protein folding
GO:0016050	0.0005304894909683660	26	vesicle organization
GO:0042127	0.0005385075074206750	99	regulation of cell proliferation
GO:0030195	0.0005429288278229360	8	negative regulation of blood coagulation
GO:1900047	0.0005429288278229360	8	negative regulation of hemostasis
GO:0006122	0.0005612093068859810	6	mitochondrial electron transport, ubiquinol to cytochrome c
GO:0051412	0.0005619485492889490	5	response to corticosterone
GO:0002684	0.0005652460203029360	64	positive regulation of immune system process
GO:0016236	0.0005678798059271480	25	macroautophagy
GO:2000379	0.0005697037829595480	13	positive regulation of reactive oxygen species metabolic process
GO:1990823	0.0005829782546988730	11	response to leukemia inhibitory factor
GO:1990830	0.0005829782546988730	11	cellular response to leukemia inhibitory factor
GO:2000271	0.0006089949296864330	3	positive regulation of fibroblast apoptotic process
GO:0001919	0.0006118135044231750	5	regulation of receptor recycling
GO:0051726	0.0006182228959636250	73	regulation of cell cycle
GO:0032227	0.0006379541688034710	2	negative regulation of synaptic transmission, dopaminergic
GO:0016567	0.0006388549723132230	51	protein ubiquitination
GO:0006465	0.0006623849345095430	5	signal peptide processing
GO:0043900	0.0006785210608737240	34	regulation of multi-organism process
GO:0009895	0.000681767513048680	24	negative regulation of catabolic process
GO:0072332	0.0006929267245746720	13	intrinsic apoptotic signaling pathway by p53 class mediator
GO:0007596	0.0006968077749129730	26	blood coagulation
GO:0043154	0.000699425711574560	13	negative regulation of cysteine-type endopeptidase activity involved in apoptotic process
GO:0051084	0.0007156263416969740	7	'de novo' posttranslational protein folding
GO:0033059	0.0007176480581969790	9	cellular pigmentation
GO:0007155	0.0007464657895546480	70	cell adhesion
GO:0032870	0.0007705727309980390	41	cellular response to hormone stimulus
GO:0050817	0.0007875183816780630	26	coagulation
GO:0006809	0.0007939276770041980	10	nitric oxide biosynthetic process
GO:0036500	0.0008526689044846660	4	ATF6-mediated unfolded protein response
GO:0022610	0.0008568701587857630	70	biological adhesion
GO:0000027	0.0008695282035473760	10	ribosomal large subunit assembly
GO:0051172	0.0008739222612498320	134	negative regulation of nitrogen compound metabolic process
GO:0031099	0.0008863638540915270	19	regeneration
GO:0032642	0.0009115411776823980	11	regulation of chemokine production
GO:0031669	0.0009211239193381540	19	cellular response to nutrient levels
GO:1901798	0.0009357730874210980	7	positive regulation of signal transduction by p53 class mediator
GO:0007599	0.0009381828906601760	26	hemostasis
GO:0006900	0.0009421311630898130	13	vesicle budding from membrane
GO:0010950	0.0009483465814343580	21	positive regulation of endopeptidase activity
GO:0043112	0.0009550963372633090	16	receptor metabolic process
GO:0035633	0.0009572703608119590	2	maintenance of permeability of blood-brain barrier
GO:0002237	0.0009647717332217140	29	response to molecule of bacterial origin
GO:0001921	0.0009738996843142710	4	positive regulation of receptor recycling
GO:0031324	0.0009819306032694440	140	negative regulation of cellular metabolic process
GO:0097501	0.0010058681909092500	9	stress response to metal ion
GO:0032101	0.0010070326540078400	54	regulation of response to external stimulus
GO:0046209	0.0010241662116599580	10	nitric oxide metabolic process
GO:1903578	0.0010339783317864700	10	regulation of ATP metabolic process
GO:0021543	0.0010438372215917800	14	pallium development
GO:1903019	0.0010519580884835670	5	negative regulation of glycoprotein metabolic process
GO:0034660	0.0010594999841440400	50	ncRNA metabolic process
GO:0050794	0.0010658444122987500	458	regulation of cellular process
GO:0061097	0.0010685016209169600	10	regulation of protein tyrosine kinase activity
GO:0001881	0.0010798381061546400	6	receptor recycling
GO:0071375	0.0010831738875156900	22	cellular response to peptide hormone stimulus
GO:0010638	0.0010868269258083920	41	positive regulation of organelle organization
GO:0019065	0.0011713093120958800	2	receptor-mediated endocytosis of virus by host cell
GO:0075509	0.0011713093120958800	2	endocytosis involved in viral entry into host cell
GO:0045732	0.0011728168774121500	19	positive regulation of protein catabolic process
GO:0006417	0.0011756636634108800	34	regulation of translation
GO:0009913	0.0011784833085567170	31	epidermal cell differentiation
GO:0055070	0.0011824496009026500	6	copper ion homeostasis
GO:0035821	0.0011919254923798900	20	modification of morphology or physiology of other organism
GO:0034605	0.0012039047285918800	11	cellular response to heat

GO:1900101	0.00121160937656554	6	regulation of endoplasmic reticulum unfolded protein response
GO:1902253	0.00121324812925169	8	regulation of intrinsic apoptotic signaling pathway by p53 class mediator
GO:0043280	0.0012208784800476	18	positive regulation of cysteine-type endopeptidase activity involved in apoptotic process
GO:0022411	0.0012374631908227	45	cellular component disassembly
GO:0031668	0.00124352741205911	21	cellular response to extracellular stimulus
GO:0051129	0.00124841972521211	46	negative regulation of cellular component organization
GO:0044091	0.00129428995500812	6	membrane biogenesis
GO:0007565	0.00129497017572096	19	female pregnancy
GO:0032743	0.00129616984164439	5	positive regulation of interleukin-2 production
GO:0072507	0.00130320618553669	36	divalent inorganic cation homeostasis
GO:2001057	0.00131616952302978	10	reactive nitrogen species metabolic process
GO:0010466	0.00131838216215109	27	negative regulation of peptidase activity
GO:1903426	0.00132589503923492	12	regulation of reactive oxygen species biosynthetic process
GO:0055093	0.00136934317509507	5	response to hyperoxia
GO:0040015	0.00137523279035395	4	negative regulation of multicellular organism growth
GO:0051085	0.0013945091792625	6	chaperone cofactor-dependent protein refolding
GO:0031331	0.00139882722681074	25	positive regulation of cellular catabolic process
GO:0007346	0.00140627523629101	44	regulation of mitotic cell cycle
GO:0010952	0.00142803649242564	22	positive regulation of peptidase activity
GO:0061045	0.00143590834143273	9	negative regulation of wound healing
GO:0099188	0.00144422925443579	3	postsynaptic cytoskeleton organization
GO:0022407	0.00144861109846926	28	regulation of cell-cell adhesion
GO:0043618	0.00145242293365704	10	regulation of transcription from RNA polymerase II promoter in response to stress
GO:0098657	0.00145607685059626	45	import into cell
GO:0030330	0.00149340486078569	13	DNA damage response, signal transduction by p53 class mediator
GO:2000117	0.00151062124944814	13	negative regulation of cysteine-type endopeptidase activity
GO:0043473	0.00153345182302657	11	pigmentation
GO:0021762	0.0015422505634199	8	substantia nigra development
GO:1990440	0.00156381747690839	4	positive regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress
GO:0010951	0.00158030017625274	26	negative regulation of endopeptidase activity
GO:0072503	0.00160510939009832	35	cellular divalent inorganic cation homeostasis

(Significantly downregulated biological pathways in 6 min stochastic oscillatory condition).

Category	Over represented p-value	numDEInCat	Term
GO:0007049	2.90275351262785e-51	537	cell cycle
GO:0051276	1.01007362603586e-49	397	chromosome organization
GO:0006996	4.58247824220937e-45	924	organelle organization
GO:0022402	7.45537684909117e-44	412	cell cycle process
GO:0071840	4.33532870507767e-43	1366	cellular component organization or biogenesis
GO:0000278	2.337171941190 34e-42	330	mitotic cell cycle
GO:1903047	1.56097321590833e-38	287	mitotic cell cycle process
GO:0016043	1.65996314574992e-37	1317	cellular component organization
GO:0090304	1.72047041942808e-35	1090	nucleic acid metabolic process
GO:0016071	2.57821497815117e-34	256	mRNA metabolic process
GO:0006396	3.034775174389 44e-32	287	RNA processing
GO:0006397	1.14109994741034e-30	185	mRNA processing
GO:0006259	1.85036854738346e-30	298	DNA metabolic process
GO:0051726	9.88970584428661e-30	337	regulation of cell cycle
GO:0006139	1.24006166168171e-29	1155	nucleobase-containing compound metabolic process
GO:0010564	2.31375737756075e-29	239	regulation of cell cycle process
GO:0008380	3.33207739881544e-27	160	RNA splicing
GO:0046483	3.50377402894593e-27	1164	heterocycle metabolic process
GO:0006725	1.86254620679647e-26	1167	cellular aromatic compound metabolic process
GO:0044772	2.52200670274403e-26	181	mitotic cell cycle phase transition
GO:0007346	1.26594441199036e-25	202	regulation of mitotic cell cycle
GO:0006325	7.63159317333001e-25	242	chromatin organization
GO:0043170	8.85551530703141e-25	1673	macromolecule metabolic process
GO:0006974	1.12979348124682e-24	252	cellular response to DNA damage stimulus
GO:1901360	1.77653230009588e-24	1184	organic cyclic compound metabolic process
GO:1901990	1.97834177706072e-24	140	regulation of mitotic cell cycle phase transition
GO:0044770	3.07019185375495e-24	185	cell cycle phase transition
GO:0034641	7.26348033869992e-24	1226	cellular nitrogen compound metabolic process
GO:0016070	8.9734341111787e-24	945	RNA metabolic process
GO:0000375	2.8498727517767 4e-22	128	RNA splicing, via transesterification reactions
GO:1901987	2.89810606626485e-22	143	regulation of cell cycle phase transition
GO:0098813	4.19972505393276e-22	109	nuclear chromosome segregation
GO:0044085	4.71103174106874e-22	706	cellular component biogenesis
GO:0006281	5.09385682690612e-22	175	DNA repair
GO:0007059	5.15986925548619e-22	124	chromosome segregation
GO:0000377	1.33958913502289e-21	126	RNA splicing, via transesterification reactions with bulged adenosine as nucleophile
GO:0000398	1.33958913502289e-21	126	mRNA splicing, via spliceosome
GO:0000819	2.24655361491694e-21	88	sister chromatid segregation
GO:0071103	2.51479693671229e-21	103	DNA conformation change
GO:0010467	5.485741019759 62e-21	1054	gene expression
GO:0006260	1.07982607603046e-20	112	DNA replication
GO:0016032	1.46610937499 16e-20	214	viral process
GO:0051301	1.48896789302623e-20	191	cell division
GO:0000280	4.31711627870403e-20	145	nuclear division
GO:0080090	1.23831761410825e-19	1141	regulation of primary metabolic process
GO:0051171	1.66877551712948e-19	1114	regulation of nitrogen compound metabolic process
GO:0031323	1.82348460155531e-19	1161	regulation of cellular metabolic process
GO:0033044	2.15805687327294e-19	127	regulation of chromosome organization
GO:0044419	2.50190960341486e-19	225	interspecies interaction between organisms
GO:0019222	3.04720842698118e-19	1236	regulation of metabolic process
GO:0033043	4.60597111811139e-19	335	regulation of organelle organization
GO:0044260	4.81706738817321e-19	1479	cellular macromolecule metabolic process
GO:0048285	5.4510525924428e-19	153	organelle fission
GO:0044238	7.91842139639589e-19	1786	primary metabolic process
GO:0060255	9.61959611818535e-19	1155	regulation of macromolecule metabolic process
GO:0044403	9.76087590959811e-19	220	symbiont process
GO:0044237	1.10164493826741e-18	1805	cellular metabolic process
GO:0010605	1.13924225314245e-18	573	negative regulation of macromolecule metabolic process
GO:0007017	1.24457716666191e-18	230	microtubule-based process
GO:0140014	1.41351037166739e-18	111	mitotic nuclear division
GO:0009892	5.37489788766892e-18	609	negative regulation of metabolic process
GO:0000070	7.90894601124853e-18	74	mitotic sister chromatid segregation
GO:1903311	1.25560268170707e-17	105	regulation of mRNA metabolic process
GO:0006807	1.4803255287254e-17	1715	nitrogen compound metabolic process
GO:0010604	2.28133729081134e-17	680	positive regulation of macromolecule metabolic process
GO:0000226	3.05291145338695e-17	178	microtubule cytoskeleton organization
GO:0051128	5.83804356554847e-17	562	regulation of cellular component organization
GO:0048522	6.93637232802074e-17	996	positive regulation of cellular process
GO:0022607	7.82693575616316e-17	643	cellular component assembly
GO:0051172	9.66804877906865e-17	511	negative regulation of nitrogen compound metabolic process
GO:0031324	1.30624007073426e-16	539	negative regulation of cellular metabolic process
GO:0051173	3.20277083214258e-16	645	positive regulation of nitrogen compound metabolic process
GO:0031325	3.35784612570885e-16	667	positive regulation of cellular metabolic process
GO:0009987	3.42458768005432e-16	2411	cellular process
GO:0045786	4.03058744735046e-16	171	negative regulation of cell cycle
GO:0000075	4.20784802147454e-16	87	cell cycle checkpoint
GO:0009893	4.47010986458824e-16	716	positive regulation of metabolic process
GO:0033554	4.50238529417333e-16	443	cellular response to stress
GO:0009059	1.0930886348549e-15	958	macromolecule biosynthetic process
GO:0071704	1.10723743789775e-15	1822	organic substance metabolic process
GO:0051983	1.24400042600523e-15	54	regulation of chromosome segregation
GO:0010948	1.70960623215688e-15	102	negative regulation of cell cycle process
GO:0032268	1.72645979050841e-15	533	regulation of cellular protein metabolic process
GO:1901991	2.00082971210911e-15	74	negative regulation of mitotic cell cycle phase transition
GO:1902749	2.25481743101709e-15	74	regulation of cell cycle G2/M phase transition
GO:0007093	2.40812288556212e-15	71	mitotic cell cycle checkpoint
GO:0048523	3.62269317089064e-15	895	negative regulation of cellular process
GO:0010389	5.07009271375202e-15	69	regulation of G2/M transition of mitotic cell cycle

GO:0034645	5.1012903147281e-15	931	cellular macromolecule biosynthetic process
GO:0008152	6.501491926878 07e-15	1881	metabolic process
GO:0051246	6.97820116564584e-15	560	regulation of protein metabolic process
GO:1901988	7.370403058222e-15	77	negative regulation of cell cycle phase transition
GO:0048519	7.63457394479471e-15	979	negative regulation of biological process
GO:0010638	9.315893011775 06e-15	180	positive regulation of organelle organization
GO:0051130	9.895372239926 98e-15	306	positive regulation of cellular component organization
GO:0007052	1.08248101617767e-14	56	mitotic spindle organization
GO:1902850	1.213616553671 98e-14	63	microtubule cytoskeleton organization involved in mitosis
GO:0048518	1.284522178536 59e-14	1082	positive regulation of biological process
GO:0090068	2.506231702651 28e-14	97	positive regulation of cell cycle process
GO:0045787	3.568424385114 92e-14	122	positive regulation of cell cycle
GO:0019219	3.674878349298 14e-14	799	regulation of nucleobase-containing compound metabolic process
GO:0031570	3.695038237141 05e-14	68	DNA integrity checkpoint
GO:0007051	6.859806107732 29e-14	72	spindle organization
GO:0045935	7.581628802058 13e-14	417	positive regulation of nucleobase-containing compound metabolic process
GO:0051641	1.453855547147 85e-13	608	cellular localization
GO:0006323	1.524875306827 33e-13	66	DNA packaging
GO:0007010	1.666461424434 94e-13	338	cytoskeleton organization
GO:0051052	2.7317953743672e-13	125	regulation of DNA metabolic process
GO:2001252	2.883286494515 4e-13	70	positive regulation of chromosome organization
GO:0071824	3.153898890202 77e-13	85	protein-DNA complex subunit organization
GO:0022613	4.459549511901 687e-13	130	ribonucleoprotein complex biogenesis
GO:0016569	4.488106819174 68e-13	148	covalent chromatin modification
GO:0050794	4.535648657816 68e-13	1732	regulation of cellular process
GO:0010629	4.820863650713 18e-13	399	negative regulation of gene expression
GO:0045930	4.871785311937 06e-13	92	negative regulation of mitotic cell cycle
GO:0000077	6.819331660106 06e-13	62	DNA damage checkpoint
GO:0044839	8.042657398822 91e-13	83	cell cycle G2/M phase transition
GO:0050789	1.164741314332 96e-12	1817	regulation of biological process
GO:0006333	1.222747689786 91e-12	60	chromatin assembly or disassembly
GO:0000086	1.379776516437 16e-12	78	G2/M transition of mitotic cell cycle
GO:0050657	1.426474584556 19e-12	76	nucleic acid transport
GO:0050658	1.426474584556 19e-12	76	RNA transport
GO:0051236	1.808186333257 68e-12	77	establishment of RNA localization
GO:0050684	2.241609826436 97e-12	58	regulation of mRNA processing
GO:0006403	2.655080561621 48e-12	84	RNA localization
GO:0033045	2.740884259270 37e-12	42	regulation of sister chromatid segregation
GO:0051254	3.424302175357 77e-12	377	positive regulation of RNA metabolic process
GO:0044267	4.127886492176 18e-12	940	cellular protein metabolic process
GO:0016570	4.750960652690 14e-12	143	histone modification
GO:0051168	4.995304217219 24e-12	75	nuclear export
GO:0006338	6.738664708492 19e-12	64	chromatin remodeling
GO:0032392	8.412652370955 44e-12	41	DNA geometric change
GO:0051028	1.189653090438 66e-11	63	mRNA transport
GO:0051169	1.293113899256 23e-11	113	nuclear transport
GO:0031399	1.361530861837 45e-11	383	regulation of protein modification process
GO:0000082	1.613413273870 5e-11	82	G1/S transition of mitotic cell cycle
GO:0045934	1.621977910299 7e-11	328	negative regulation of nucleobase-containing compound metabolic process
GO:0034728	1.652597363614 6e-11	54	nucleosome organization
GO:0006261	1.657938184583 69e-11	60	DNA-dependent DNA replication
GO:0044774	2.017385703662 58e-11	48	mitotic DNA integrity checkpoint
GO:0007062	2.086063803900 59e-11	31	sister chromatid cohesion
GO:0072401	2.166672483942e-11	37	signal transduction involved in DNA integrity checkpoint
GO:0072422	2.166672483942e-11	37	signal transduction involved in DNA damage checkpoint
GO:0043933	2.302385324996 7e-11	447	protein-containing complex subunit organization
GO:0010557	2.881690761097 04e-11	398	positive regulation of macromolecule biosynthetic process
GO:0031023	2.986345546372 84e-11	59	microtubule organizing center organization
GO:2001251	3.618556732757 36e-11	58	negative regulation of chromosome organization
GO:0007098	3.650215921799 25e-11	55	centrosome cycle
GO:0042770	3.661849103087 68e-11	54	signal transduction in response to DNA damage
GO:0006913	4.146791359865 71e-11	111	nucleocytoplasmic transport
GO:0065004	4.537984932253 31e-11	71	protein-DNA complex assembly
GO:0051252	5.012500482313 09e-11	732	regulation of RNA metabolic process
GO:0072395	5.162528227848 77e-11	37	signal transduction involved in cell cycle checkpoint
GO:0006950	5.579669261803 36e-11	685	response to stress
GO:0010556	6.629208209133 79e-11	774	regulation of macromolecule biosynthetic process
GO:0007088	6.925722710649 02e-11	67	regulation of mitotic nuclear division
GO:0006611	6.928808696983 26e-11	68	protein export from nucleus
GO:0009889	7.189095841627 46e-11	805	regulation of biosynthetic process
GO:0044843	8.994376492000 03e-11	84	cell cycle G1/S phase transition
GO:0010558	9.266170896903 39e-11	329	negative regulation of macromolecule biosynthetic process
GO:0044773	9.400194374211e-11	44	mitotic DNA damage checkpoint
GO:0015931	9.584157590555 85e-11	82	nucleobase-containing compound transport
GO:0031497	1.372947320809 44e-10	48	chromatin assembly
GO:0044265	1.434489052271 19e-10	257	cellular macromolecule catabolic process
GO:0065003	1.650822732449 82e-10	390	protein-containing complex assembly
GO:0033047	1.654512020443 14e-10	36	regulation of mitotic sister chromatid segregation
GO:0034622	1.700951911857 41e-10	249	cellular protein-containing complex assembly
GO:0016072	1.859769156030 74e-10	73	rRNA metabolic process
GO:1903508	2.018556185321 27e-10	350	positive regulation of nucleic acid-templated transcription
GO:0031329	2.0972672299822e-10	199	regulation of cellular catabolic process
GO:1902680	2.187537926622 27e-10	350	positive regulation of RNA biosynthetic process
GO:0051649	2.954243539304 03e-10	459	establishment of localization in cell
GO:0010468	2.982264888215 68e-10	834	regulation of gene expression
GO:2000112	3.0343820784757e-10	750	regulation of cellular macromolecule biosynthetic process
GO:0006302	3.359458604701 83e-10	76	double-strand break repair
GO:0051321	4.280885793198 41e-10	76	meiotic cell cycle
GO:0010628	4.959545501389 96e-10	407	positive regulation of gene expression
GO:0006310	5.024058986746 68e-10	85	DNA recombination
GO:2000113	6.072152819778 4e-10	312	negative regulation of cellular macromolecule biosynthetic process
GO:0072331	6.318775391227 11e-10	72	signal transduction by p53 class mediator
GO:0010608	6.953094248966 47e-10	144	posttranscriptional regulation of gene expression
GO:0051704	7.289402274331 98e-10	434	multi-organism process
GO:0032508	7.816241544506 78e-10	35	DNA duplex unwinding
GO:1902275	8.782613806356 26e-10	66	regulation of chromatin organization
GO:0009891	1.0713970778154e-09	407	positive regulation of biosynthetic process
GO:1901576	1.139471416335 33e-09	1074	organic substance biosynthetic process
GO:0009057	1.156555469568 78e-09	294	macromolecule catabolic process
GO:0031328	1.278827920568 35e-09	402	positive regulation of cellular biosynthetic process
GO:0009894	1.306226347976 9e-09	217	regulation of catabolic process
GO:0006402	1.435756075559 6e-09	86	mRNA catabolic process
GO:0042254	1.497845831957 52e-09	77	ribosome biogenesis
GO:0006364	1.593568831493 72e-09	62	rRNA processing
GO:0031326	1.604655471088 78e-09	782	regulation of cellular biosynthetic process
GO:0009890	1.785125614035 52e-09	335	negative regulation of biosynthetic process
GO:0051253	1.817233641039e-09	294	negative regulation of RNA metabolic process
GO:0044271	1.914410913794 96e-09	881	cellular nitrogen compound biosynthetic process
GO:0031327	1.972970480113 24e-09	331	negative regulation of cellular biosynthetic process
GO:0006401	1.986178235331 87e-09	92	RNA catabolic process
GO:0072413	2.062010812795 33e-09	30	signal transduction involved in mitotic cell cycle checkpoint
GO:1902402	2.062010812795 33e-09	30	signal transduction involved in mitotic DNA damage checkpoint
GO:1902403	2.062010812795 33e-09	30	signal transduction involved in mitotic DNA integrity checkpoint
GO:0051225	2.127563822685 22e-09	46	spindle assembly
GO:0043412	2.401679204969 33e-09	801	macromolecule modification
GO:0006464	2.570644038611 37e-09	771	cellular protein modification process
GO:0036211	2.570644038611 37e-09	771	protein modification process
GO:0044783	2.607261448162 49e-09	32	G1 DNA damage checkpoint
GO:0019538	2.862544679965 4e-09	998	protein metabolic process
GO:0070727	3.099590238942 57e-09	397	cellular macromolecule localization
GO:0032774	3.617619233743 36e-09	699	RNA biosynthetic process
GO:0031056	3.731507509846 3e-09	55	regulation of histone modification
GO:0097659	4.244807783007 31e-09	696	nucleic acid-templated transcription
GO:0009058	4.292499455396 27e-09	1079	biosynthetic process
GO:0051304	4.918318030641 76e-09	40	chromosome separation
GO:0045893	4.939092784644 38e-09	326	positive regulation of transcription, DNA-templated
GO:0033046	4.997355146664 05e-09	25	negative regulation of sister chromatid segregation
GO:0051985	4.997355146664 05e-09	25	negative regulation of chromosome segregation
GO:0046907	5.255200094040 52e-09	386	intracellular transport

GO:0051783	5.733696525896 08e-09	68	regulation of nuclear division
GO:0034654	5.9640421141448e-09	776	nucleobase-containing compound biosynthetic process
GO:0072431	6.16935795242554e-09	29	signal transduction involved in mitotic G1 DNA damage checkpoint
GO:1902400	6.16935795242554e-09	29	intracellular signal transduction involved in G1 DNA damage checkpoint
GO:0034613	6.594717824914 86e-09	393	cellular protein localization
GO:0031571	7.182396976862 09e-09	31	mitotic G1 DNA damage checkpoint
GO:0044819	7.182396976862 09e-09	31	mitotic G1/S transition checkpoint
GO:0097711	8.196345960708 53e-09	43	ciliary basal body-plasma membrane docking
GO:0061013	8.423774671496 59e-09	55	regulation of mRNA catabolic process
GO:0051306	9.023253705951 24e-09	30	mitotic sister chromatid separation
GO:0006977	1.102354054167 45e-08	28	DNA damage response, signal transduction by p53 class mediator resulting in cell cycle arrest
GO:0043487	1.17175129912 38e-08	50	regulation of RNA stability
GO:0065007	1.452834803727 78e-08	1880	biological regulation
GO:0051640	1.607188021738 85e-08	178	organelle localization
GO:1905818	1.620894252932 02e-08	30	regulation of chromosome separation
GO:0044249	1.814809160385 53e-08	1048	cellular biosynthetic process
GO:2000045	1.892045858817 89e-08	51	regulation of G1/S transition of mitotic cell cycle
GO:0070507	1.973153433121 11e-08	65	regulation of microtubule cytoskeleton organization
GO:0019438	2.2176348491815e-08	781	aromatic compound biosynthetic process
GO:0008283	2.387221534542 08e-08	385	cell proliferation
GO:0032270	2.503198962902 35e-08	318	positive regulation of cellular protein metabolic process
GO:0040029	2.505990504410 37e-08	93	regulation of gene expression, epigenetic
GO:0018205	2.513160947203 46e-08	103	peptidyl-lysine modification
GO:0007091	2.577564317715 56e-08	28	metaphase/anaphase transition of mitotic cell cycle
GO:0018130	2.643397447999 2e-08	779	heterocycle biosynthetic process
GO:0030330	2.688515533033 72e-08	42	DNA damage response, signal transduction by p53 class mediator
GO:0051716	2.689694638883 22e-08	1167	cellular response to stimulus
GO:1903046	2.768301990270 02e-08	58	meiotic cell cycle process
GO:1901362	2.967123834524 37e-08	798	organic cyclic compound biosynthetic process
GO:0043488	3.052486647006 03e-08	47	regulation of mRNA stability
GO:0071158	3.266409925410 18e-08	34	positive regulation of cell cycle arrest
GO:0051247	3.703062806017 42e-08	334	positive regulation of protein metabolic process
GO:0044784	3.753884423844 04e-08	28	metaphase/anaphase transition of cell cycle
GO:0006334	3.851050300182 54e-08	38	nucleosome assembly
GO:0007050	3.902302379553 97e-08	73	cell cycle arrest
GO:0006405	4.009277512735e-08	51	RNA export from nucleus
GO:0033048	4.098327049995 74e-08	23	negative regulation of mitotic sister chromatid segregation
GO:0000723	4.263615246192 63e-08	53	telomere maintenance
GO:0008150	4.409000002697 48e-08	2542	biological_process
GO:2000134	4.510958472787 83e-08	40	negative regulation of G1/S transition of mitotic cell cycle
GO:0045841	4.769799860305 25e-08	21	negative regulation of mitotic metaphase/anaphase transition
GO:1902100	4.769799860305 25e-08	21	negative regulation of metaphase/anaphase transition of cell cycle
GO:0044089	4.877157916143 86e-08	136	positive regulation of cellular component biogenesis
GO:0071156	5.098257012905 08e-08	39	regulation of cell cycle arrest
GO:0010965	5.306130674117 45e-08	28	regulation of mitotic sister chromatid separation
GO:0006351	6.108645791317 11e-08	679	transcription, DNA-templated
GO:0070925	7.101379773256 94e-08	202	organelle assembly
GO:0007094	8.284265978938 65e-08	20	mitotic spindle assembly checkpoint
GO:0031577	8.284265978938 65e-08	20	spindle checkpoint
GO:0071173	8.284265978938 65e-08	20	spindle assembly checkpoint
GO:0071174	8.284265978938 65e-08	20	mitotic spindle checkpoint
GO:0030071	8.960147186983 11e-08	26	regulation of mitotic metaphase/anaphase transition
GO:0071166	9.167090812644 94e-08	48	ribonucleoprotein complex localization
GO:1905269	9.288906306177 43e-08	40	positive regulation of chromatin organization
GO:0051310	9.560227444713 83e-08	27	metaphase plate congression
GO:0032269	9.909539383981 01e-08	219	negative regulation of cellular protein metabolic process
GO:0034660	1.1216991897 71e-07	124	ncRNA metabolic process
GO:0140013	1.237858705957 65e-07	52	meiotic nuclear division
GO:1905819	1.249118656166 35e-07	21	negative regulation of chromosome separation
GO:2000816	1.249118656166 35e-07	21	negative regulation of mitotic sister chromatid separation
GO:0051248	1.277463048211 36e-07	229	negative regulation of protein metabolic process
GO:1902099	1.2954476050478e-07	26	regulation of metaphase/anaphase transition of cell cycle
GO:0051338	1.324611376840 21e-07	210	regulation of transferase activity
GO:0051174	1.360686096526 48e-07	340	regulation of phosphorus metabolic process
GO:0044093	1.544232326531 57e-07	355	positive regulation of molecular function
GO:1902807	1.544477176413 68e-07	40	negative regulation of cell cycle G1/S phase transition
GO:0019220	1.693150973761 51e-07	339	regulation of phosphate metabolic process
GO:0120031	1.696869747349 27e-07	145	plasma membrane bounded cell projection assembly
GO:0006412	1.699104749688 75e-07	137	translation
GO:0031058	1.773236689182 69e-07	37	positive regulation of histone modification
GO:0043044	1.802247857345 55e-07	31	ATP-dependent chromatin remodeling
GO:0006417	1.8874839386449e-07	95	regulation of translation
GO:0030031	1.912360574611 42e-07	147	cell projection assembly
GO:0032886	1.915664083268 88e-07	70	regulation of microtubule-based process
GO:0048024	1.942948587570 84e-07	38	regulation of mRNA splicing, via spliceosome
GO:0071426	2.087096317426 73e-07	47	ribonucleoprotein complex export from nucleus
GO:0033365	2.164643221226 21e-07	200	protein localization to organelle
GO:0031503	2.165787189680 77e-07	84	protein-containing complex localization
GO:0032200	2.1708186324176e-07	53	telomere organization
GO:0090307	2.220711219398 42e-07	29	mitotic spindle assembly
GO:0051493	2.356368827156 23e-07	136	regulation of cytoskeleton organization
GO:0006473	2.629496352187 03e-07	63	protein acetylation
GO:0043967	3.004043264413 51e-07	30	histone H4 acetylation
GO:0031401	3.112744415644 95e-07	248	positive regulation of protein modification process
GO:1902806	3.132411861395 18e-07	52	regulation of cell cycle G1/S phase transition
GO:0034248	3.224094493955 55e-07	106	regulation of cellular amide metabolic process
GO:0043484	3.269403311900 44e-07	48	regulation of RNA splicing
GO:0050000	3.4587247676684e-07	30	chromosome localization
GO:1903507	3.724997062394 96e-07	264	negative regulation of nucleic acid-templated transcription
GO:0043543	3.727192989698 92e-07	72	protein acylation
GO:0030705	3.982580761112 02e-07	62	cytoskeleton-dependent intracellular transport
GO:1902679	4.044061713153 59e-07	264	negative regulation of RNA biosynthetic process
GO:0018394	4.398512065053 31e-07	56	peptidyl-lysine acetylation
GO:0043043	4.450313789117 13e-07	140	peptide biosynthetic process
GO:1903312	4.622053825844 37e-07	31	negative regulation of mRNA metabolic process
GO:1903506	5.333709900781 78e-07	656	regulation of nucleic acid-templated transcription
GO:0050790	5.558190210484 39e-07	432	regulation of catalytic activity
GO:0030522	5.5840720235064e-07	82	intracellular receptor signaling pathway
GO:0051053	6.297402541430 01e-07	48	negative regulation of DNA metabolic process
GO:0051303	7.677597557915 36e-07	29	establishment of chromosome localization
GO:0140056	7.709703168538 18e-07	58	organelle localization by membrane tethering
GO:0000724	8.170354275404 44e-07	43	double-strand break repair via homologous recombination
GO:0018393	8.708808851612 71e-07	53	internal peptidyl-lysine acetylation
GO:2001141	8.717081969603 18e-07	656	regulation of RNA biosynthetic process
GO:0010639	8.903314482617 64e-07	100	negative regulation of organelle organization
GO:0022406	9.127365747022 22e-07	60	membrane docking
GO:0006886	9.313285714875e-07	238	intracellular protein transport
GO:0007080	1.032681792702 14e-06	21	mitotic metaphase plate congression
GO:0000725	1.059475646119 81e-06	43	recombinational repair
GO:0016573	1.133048535600 43e-06	52	histone acetylation
GO:0000380	1.142472659845 22e-06	31	alternative mRNA splicing, via spliceosome
GO:0006406	1.2502995724132e-06	41	mRNA export from nucleus
GO:0071427	1.2502995724132e-06	41	mRNA-containing ribonucleoprotein complex export from nucleus
GO:0000910	1.271429385243 78e-06	53	cytokinesis
GO:0045931	1.368300455057 47e-06	50	positive regulation of mitotic cell cycle
GO:0006518	1.502404170688 22e-06	162	peptide metabolic process
GO:0045005	1.605039873442 86e-06	22	DNA-dependent DNA replication maintenance of fidelity
GO:0065009	1.666517505249 69e-06	560	regulation of molecular function
GO:0008104	1.765674942475 22e-06	525	protein localization
GO:0051383	1.828641405556 63e-06	14	kinetochore organization
GO:0051984	1.844304162208 59e-06	17	positive regulation of chromosome segregation
GO:0018193	1.877754822388 58e-06	258	peptidyl-amino acid modification
GO:1903827	1.936811291139 65e-06	130	regulation of cellular protein localization
GO:0012501	2.0266787907597e-06	385	programmed cell death
GO:0071897	2.075020428616 48e-06	57	DNA biosynthetic process
GO:0045892	2.318497891136 81e-06	253	negative regulation of transcription, DNA-templated
GO:0043085	2.354565972510 09e-06	288	positive regulation of catalytic activity
GO:0006475	2.387451092066 02e-06	53	internal protein amino acid acetylation
GO:0045132	2.413679221359 23e-06	31	meiotic chromosome segregation

GO:0034655	2.57257941834315e-06	122	nucleobase-containing compound catabolic process
GO:0030518	2.85144242767381e-06	48	intracellular steroid hormone receptor signaling pathway
GO:0008608	2.9325529430949e-06	17	attachment of spindle microtubules to kinetochore
GO:0045839	3.53448743603255e-06	23	negative regulation of mitotic nuclear division
GO:0031124	3.54021839053045e-06	35	mRNA 3'-end processing
GO:0044087	3.5485060157545e-06	213	regulation of cellular component biogenesis
GO:0034502	3.737003429104 79e-06	31	protein localization to chromosome
GO:0050896	3.83284899119752e-06	1360	response to stimulus
GO:0032784	3.88074202891813e-06	21	regulation of DNA-templated transcription, elongation
GO:0034330	4.33666865619734e-06	88	cell junction organization
GO:0034508	4.74703390940082e-06	21	centromere complex assembly
GO:0043604	5.60218198435953e-06	161	amide biosynthetic process
GO:0090224	5.70171844716515e-06	21	regulation of spindle organization
GO:0031123	6.11366304547596e-06	42	RNA 3'-end processing
GO:0051784	6.123654916622152e-06	24	negative regulation of nuclear division
GO:0060271	6.4890985933736e-06	98	cilium assembly
GO:0006354	6.586617617243 78e-06	32	DNA-templated transcription, elongation
GO:0007064	7.49247070831138e-06	14	mitotic sister chromatid cohesion
GO:0071826	8.197956120008 08e-06	70	ribonucleoprotein complex subunit organization
GO:0031400	8.60724340827686e-06	135	negative regulation of protein modification process
GO:0022618	9.0950471240048e-06	67	ribonucleoprotein complex assembly
GO:0010563	9.39094920252922e-06	128	negative regulation of phosphorus metabolic process
GO:0031331	1.004016152586 94e-05	95	positive regulation of cellular catabolic process
GO:0035304	1.008037714929 31e-05	43	regulation of protein dephosphorylation
GO:0034724	1.020478020384 49e-05	20	DNA replication-independent nucleosome organization
GO:0046605	1.023794807002 83e-05	25	regulation of centrosome cycle
GO:0033036	1.196139504734 08e-05	575	macromolecule localization
GO:0007063	1.222781681478 61e-05	14	regulation of sister chromatid cohesion
GO:0035303	1.259564244853 72e-05	60	regulation of dephosphorylation
GO:0006289	1.310445811623 12e-05	35	nucleotide-excision repair
GO:0006890	1.352284364107 77e-05	32	retrograde vesicle-mediated transport, Golgi to ER
GO:0001701	1.43844720518 63e-05	86	in utero embryonic development
GO:0044782	1.44836676876602e-05	100	cilium organization
GO:0045936	1.45177653630768e-05	127	negative regulation of phosphate metabolic process
GO:0006355	1.48691648252505e-05	637	regulation of transcription, DNA-templated
GO:0051054	1.52637632909805e-05	61	positive regulation of DNA metabolic process
GO:0019079	1.53531195655328e-05	38	viral genome replication
GO:0031589	1.57202856504444e-05	92	cell-substrate adhesion
GO:0030261	1.64406134535214e-05	19	chromosome condensation
GO:0006270	1.65332888242604e-05	16	DNA replication initiation
GO:1903313	1.78734319364205e-05	29	positive regulation of mRNA metabolic process
GO:0002504	1.82546959750528e-05	33	antigen processing and presentation of peptide or polysaccharide antigen via MHC class II
GO:0031297	1.84675145887953e-05	17	replication fork processing
GO:0019886	1.85037368979674e-05	32	antigen processing and presentation of exogenous peptide antigen via MHC class II
GO:0043009	1.92287657284 94e-05	139	chordate embryonic development
GO:0008219	2.11277264138026e-05	401	cell death
GO:0030521	2.17917814276417e-05	28	androgen receptor signaling pathway
GO:0051129	2.30544428181948e-05	158	negative regulation of cellular component organization
GO:0006336	2.32290666269653e-05	19	DNA replication-independent nucleosome assembly
GO:0051347	2.33834884239 94e-05	143	positive regulation of transferase activity
GO:1902115	2.50051085855281e-05	58	regulation of organelle assembly
GO:0002376	2.52089742708696e-05	473	immune system process
GO:0032204	2.75279170186314e-05	30	regulation of telomere maintenance
GO:0006282	2.79592776414234e-05	36	regulation of DNA repair
GO:0031060	2.8618575322508e-05	26	regulation of histone methylation
GO:0009792	2.90707134058899e-05	142	embryo development ending in birth or egg hatching
GO:0034470	3.022064988841 67e-05	83	ncRNA processing
GO:0043486	3.022192643379 33e-05	19	histone exchange
GO:0016458	3.27801943960392e-05	69	gene silencing
GO:0010457	3.3896850414322e-05	11	centriole-centriole cohesion
GO:0002495	3.42158940569616e-05	32	antigen processing and presentation of peptide antigen via MHC class II
GO:0032502	3.49384219034027e-05	1034	developmental process
GO:0043549	3.59192407323419e-05	180	regulation of kinase activity
GO:0051298	3.8355684578175e-05	27	centrosome duplication
GO:0046700	3.8466267574995e-05	124	heterocycle catabolic process
GO:1902750	4.3415454002589e-05	22	negative regulation of cell cycle G2/M phase transition
GO:0045944	4.38076713565752e-05	241	positive regulation of transcription by RNA polymerase II
GO:0034329	4.42451748470104e-05	73	cell junction assembly
GO:0033129	4.56143477770735e-05	7	positive regulation of histone phosphorylation
GO:0061982	4.72657179680216e-05	34	meiosis I cell cycle process
GO:0032870	4.72932223806094e-05	149	cellular response to hormone stimulus
GO:0006915	4.92054922834153e-05	355	apoptotic process
GO:0007044	4.98995139050986e-05	38	cell-substrate junction assembly
GO:0031055	5.03748173851398e-05	16	chromatin remodeling at centromere
GO:0006337	5.1148959626777e-05	11	nucleosome disassembly
GO:0009896	5.11914228215472e-05	104	positive regulation of catabolic process
GO:0032206	5.63719621547354e-05	21	positive regulation of telomere maintenance
GO:0034080	5.66594883681432e-05	15	CENP-A containing nucleosome assembly
GO:0061641	5.66594883681432e-05	15	CENP-A containing chromatin organization
GO:0043401	5.66660560797629e-05	56	steroid hormone mediated signaling pathway
GO:0032465	5.75504243959958e-05	29	regulation of cytokinesis
GO:0042325	5.82079809532084e-05	290	regulation of phosphorylation
GO:0060341	6.044244270085 98e-05	194	regulation of cellular localization
GO:0010970	6.07594402499147e-05	50	transport along microtubule
GO:0099111	6.07594402499147e-05	50	microtubule-based transport
GO:0034446	6.18687738761516e-05	31	substrate adhesion-dependent cell spreading
GO:0046777	6.21456462671915e-05	67	protein autophosphorylation
GO:0019080	6.32266811572653e-05	24	viral gene expression
GO:0002478	6.39767953053029e-05	36	antigen processing and presentation of exogenous peptide antigen
GO:0060236	6.40055859011625e-05	18	regulation of mitotic spindle organization
GO:0019884	6.6750261412796e-05	37	antigen processing and presentation of exogenous antigen
GO:0071495	6.72473189271107e-05	274	cellular response to endogenous stimulus
GO:0022616	6.83717120353081e-05	13	DNA strand elongation
GO:0022414	6.85812796741422e-05	251	reproductive process
GO:0000245	6.86011945423916e-05	23	spliceosomal complex assembly
GO:0044270	7.31233521439506e-05	123	cellular nitrogen compound catabolic process
GO:0000003	7.33879531074641e-05	251	reproduction
GO:2001020	7.5704976909 9097e-05	55	regulation of response to DNA damage stimulus
GO:0043603	8.28718371857058e-05	196	cellular amide metabolic process
GO:1901983	8.47153195930089e-05	26	regulation of protein acetylation
GO:0001932	8.89702579009155e-05	268	regulation of protein phosphorylation
GO:0017148	8.93065080826453e-05	44	negative regulation of translation
GO:0031572	9.06043021293616e-05	15	G2 DNA damage checkpoint
GO:1901800	9.24773909073169e-05	33	positive regulation of proteasomal protein catabolic process
GO:0010810	9.29542873283764e-05	59	regulation of cell-substrate adhesion
GO:0007127	9.41887108853605e-05	32	meiosis I
GO:0032786	9.56877797789015e-05	14	positive regulation of DNA-templated transcription, elongation
GO:0033182	9.68400157358671e-05	8	regulation of histone ubiquitination
GO:0018023	9.87346334628397e-05	19	peptidyl-lysine trimethylation
GO:0000726	9.88855151326826e-05	28	non-recombinational repair
GO:0045815	0.0001004728342221416	22	positive regulation of gene expression, epigenetic
GO:0007568	0.0001005906330 79337	73	aging
GO:1903829	0.0001044538500 82795	83	positive regulation of cellular protein localization
GO:0016571	0.0001110962071 04799	43	histone methylation
GO:0090231	0.0001126647606 21455	9	regulation of spindle checkpoint
GO:0090266	0.0001126647606 21455	9	regulation of mitotic cell cycle spindle assembly checkpoint
GO:1903504	0.0001126647606 21455	9	regulation of mitotic spindle checkpoint
GO:0080135	0.0001164004002 26223	148	regulation of cellular response to stress
GO:0031330	0.0001169140823 30396	64	negative regulation of cellular catabolic process
GO:0006275	0.0001176742324 26429	35	regulation of DNA replication
GO:0071459	0.0001214486474 04852	11	protein localization to chromosome, centromeric region
GO:0006378	0.0001215150402 20702	19	mRNA polyadenylation
GO:0043631	0.0001215150402 20702	19	RNA polyadenylation
GO:0009790	0.0001239565550 20534	209	embryo development
GO:0044380	0.0001243423383 79255	24	protein localization to cytoskeleton
GO:0051098	0.0001261821527 45041	87	regulation of binding
GO:0000281	0.0001265400970 57368	30	mitotic cytokinesis
GO:0031334	0.0001268792872 87957	66	positive regulation of protein complex assembly
GO:0007018	0.0001325140976 82255	77	microtubule-based movement

GO:0032986	0.0001341952783331 64	11	protein-DNA complex disassembly
GO:0048002	0.0001354296060091 37	38	antigen processing and presentation of peptide antigen
GO:0071383	0.0001396139062679 07	67	cellular response to steroid hormone stimulus
GO:0019439	0.000141701839367 08	123	aromatic compound catabolic process
GO:0006368	0.0001444155828076 78	26	transcription elongation from RNA polymerase II promoter
GO:0050686	0.0001462034842958 46	14	negative regulation of mRNA processing
GO:0072359	0.0001475806562465 85	226	circulatory system development
GO:0045859	0.0001494007907846 66	162	regulation of protein kinase activity
GO:0071407	0.0001506188482498 71	123	cellular response to organic cyclic compound
GO:0006457	0.000155022424881605	52	protein folding
GO:1900024	0.0001551577777608854	19	regulation of substrate adhesion-dependent cell spreading
GO:0090169	0.0001584970336111 73	14	regulation of spindle assembly
GO:1902117	0.0001646531182595 37	28	positive regulation of organelle assembly
GO:0043984	0.0001718584216108 15	12	histone H4-K16 acetylation
GO:0010033	0.0001787388967860 78	541	response to organic substance
GO:0043067	0.0001883803219226 57	285	regulation of programmed cell death
GO:0010972	0.000188431616888 5	18	negative regulation of G2/M transition of mitotic cell cycle
GO:0031062	0.0001940158166520 29	17	positive regulation of histone methylation
GO:2000278	0.0001959798430249 49	33	regulation of DNA biosynthetic process
GO:0050690	0.0001963875893550 36	13	regulation of defense response to virus by virus
GO:0034501	0.0001969181101464 29	9	protein localization to kinetochore
GO:0001824	0.0001988479280578 83	21	blastocyst development
GO:0072698	0.000199128479775 44	22	protein localization to microtubule cytoskeleton
GO:0043489	0.0002009028934803 49	17	RNA stabilization
GO:1902369	0.0002031835626197 27	20	negative regulation of RNA catabolic process
GO:0034249	0.0002035595833108 01	47	negative regulation of cellular amide metabolic process
GO:0061640	0.0002072140126151 31	32	cytoskeleton-dependent cytokinesis
GO:0006303	0.0002108849693524 94	26	double-strand break repair via nonhomologous end joining
GO:0009755	0.0002245958676023 33	59	hormone-mediated signaling pathway
GO:0031498	0.0002375801712725 83	11	chromatin disassembly
GO:0010921	0.0002381899830304 03	48	regulation of phosphatase activity
GO:1905508	0.0002395818692520 52	16	protein localization to microtubule organizing center
GO:0032880	0.0002418779769309 98	195	regulation of protein localization
GO:0080182	0.0002466712135845 38	10	histone H3-K4 trimethylation
GO:0034332	0.0002532630454152 74	46	adherens junction organization
GO:0042981	0.0002533522450433 06	281	regulation of apoptotic process
GO:0010824	0.0002652889609233 97	18	regulation of centrosome duplication
GO:2001166	0.000269530648745 38	5	regulation of histone H2B ubiquitination
GO:0048856	0.0002750222600356 26	963	anatomical structure development
GO:1902373	0.0002777504356833 92	18	negative regulation of mRNA catabolic process
GO:2000779	0.0002791143595641 71	24	regulation of double-strand break repair
GO:0070192	0.0002865176623646 85	21	chromosome organization involved in meiotic cell cycle
GO:0033674	0.0002945641671765 51	123	positive regulation of kinase activity
GO:0010811	0.0002970127197085 17	36	positive regulation of cell-substrate adhesion
GO:0043666	0.0002976645187942 55	34	regulation of phosphoprotein phosphatase activity
GO:0045814	0.0002998925253334 47	33	negative regulation of gene expression, epigenetic
GO:0000733	0.0003043272056271 53	7	DNA strand renaturation
GO:0032467	0.0003092064346840 87	14	positive regulation of cytokinesis
GO:1901361	0.0003156471025710 94	126	organic cyclic compound catabolic process
GO:1903362	0.0003211782496366 28	63	regulation of cellular protein catabolic process
GO:0007507	0.0003218708583426 08	129	heart development
GO:0034968	0.000325945045015 77	36	histone lysine methylation
GO:0000018	0.0003330344418620 68	28	regulation of DNA recombination
GO:0061136	0.0003402747968153 22	49	regulation of proteasomal protein catabolic process
GO:0051653	0.0003446575917946 27	18	spindle localization
GO:0035065	0.000345726205936 84	20	regulation of histone acetylation
GO:0007095	0.0003483364347068 18	11	mitotic G2 DNA damage checkpoint
GO:0019882	0.0003486959550436 36	43	antigen processing and presentation
GO:0044818	0.0003491579466571 88	14	mitotic G2/M transition checkpoint
GO:0046825	0.0003511308105272 19	17	regulation of protein export from nucleus
GO:0033184	0.0003531391709011 98	5	positive regulation of histone ubiquitination
GO:0006468	0.0003537765015140 14	359	protein phosphorylation
GO:0120036	0.0003568959744585 07	313	plasma membrane bounded cell projection organization
GO:1901030	0.0003655122052633 01	13	positive regulation of mitochondrial outer membrane permeabilization involved in apoptotic signaling pathway
GO:0033127	0.0003684939351852 43	8	regulation of histone phosphorylation
GO:0071310	0.000368691386292 67	454	cellular response to organic substance
GO:1900026	0.0003696746006504 83	14	positive regulation of substrate adhesion-dependent cell spreading
GO:0016049	0.0003729180211823 35	109	cell growth
GO:0009725	0.0003904828630134 04	187	response to hormone
GO:0032799	0.0003968430786441 27	11	low-density lipoprotein receptor particle metabolic process
GO:0030010	0.0004182321937346 32	42	establishment of cell polarity
GO:0000381	0.0004203628362530 63	23	regulation of alternative mRNA splicing, via spliceosome
GO:0032479	0.0004401721178141 35	34	regulation of type I interferon production
GO:0010833	0.0004487173939578 14	27	telomere maintenance via telomere lengthening
GO:0009719	0.0004536734269530 12	305	response to endogenous stimulus
GO:0031440	0.0004571203019826 88	13	regulation of mRNA 3'-end processing
GO:1904356	0.0004590496862220 47	22	regulation of telomere maintenance via telomere lengthening
GO:1903050	0.0004623367587458 82	55	regulation of proteolysis involved in cellular protein catabolic process
GO:0006271	0.0004646138572322 82	9	DNA strand elongation involved in DNA replication
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GO:0062033	0.0004800281771179 16	10	positive regulation of mitotic sister chromatid segregation
GO:0032606	0.000490995382459 67	34	type I interferon production
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GO:0071539	0.0005227599560710 22	15	protein localization to centrosome
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GO:0006283	0.0005661782112110 06	22	transcription-coupled nucleotide-excision repair
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GO:0035556	0.0006092532265528 87	505	intracellular signal transduction
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GO:0045876	0.0006385897960227 81	7	positive regulation of sister chromatid cohesion
GO:0042176	0.0006401173516931 88	88	regulation of protein catabolic process
GO:0007076	0.0006440645067727 56	10	mitotic chromosome condensation
GO:0048255	0.000651604614897 19	15	mRNA stabilization
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GO:0051293	0.0006751430595827 19	16	establishment of spindle localization
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GO:1901992	0.0006962844648153 75	24	positive regulation of mitotic cell cycle phase transition
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GO:0098534	0.0007274713683331 23	16	centriole assembly
GO:0030030	0.0007311852145135 85	316	cell projection organization
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GO:0040007	0.000772556211287557	201	growth
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GO:0070934	0.0007879538617723 56	5	CRD-mediated mRNA stabilization
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GO:0045184	0.0008056863259424 21	381	establishment of protein localization
GO:0009314	0.0008172165285066 08	96	response to radiation
GO:0000731	0.0008190651249071 43	18	DNA synthesis involved in DNA repair
GO:1903052	0.0008340825474820 07	34	positive regulation of proteolysis involved in cellular protein catabolic process
GO:0051382	0.0008431803284279 03	9	kinetochore assembly
GO:0016310	0.0008582530616007 24	415	phosphorylation
GO:0006695	0.0008798731986598 06	22	cholesterol biosynthetic process
GO:1902653	0.0008798731986598 06	22	secondary alcohol biosynthetic process
GO:0048869	0.0008837830562278 61	719	cellular developmental process
GO:2000756	0.0008895598381287 08	21	regulation of peptidyl-lysine acetylation

GO:0045540	0.0009236973452947 82	17	regulation of cholesterol biosynthetic process
GO:0106118	0.0009236973452947 82	17	regulation of sterol biosynthetic process
GO:0035987	0.000923779763852 99	18	endodermal cell differentiation
GO:0051170	0.0009408066668809 61	47	import into nucleus
GO:0042274	0.0009639863259371 95	18	ribosomal small subunit biogenesis
GO:0035567	0.0009694951262348 79	34	non-canonical Wnt signaling pathway
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GO:0048041	0.0009797583876463 12	29	focal adhesion assembly
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GO:0035305	0.001009677475102	31	negative regulation of dephosphorylation
GO:0070646	0.0010238243295127 8	66	protein modification by small protein removal
GO:0000470	0.0010345544882440 5	9	maturation of LSU-rRNA
GO:0006278	0.0010497354224338 1	24	RNA-dependent DNA biosynthetic process
GO:2001233	0.0010555100080050 86	82	regulation of apoptotic signaling pathway
GO:0007099	0.0010838360594995 1	15	centriole replication
GO:0019058	0.001111182771 5972	67	viral life cycle
GO:0001706	0.001113677779612	19	endoderm formation
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GO:0007569	0.001136134236833 8	31	cell aging
GO:0051571	0.0011629257818660 2	9	positive regulation of histone H3-K4 methylation
GO:0019081	0.0011709721924080 29	8	viral translation
GO:1901985	0.001172490106637 66	16	positive regulation of protein acetylation
GO:0032147	0.001176219837354 05	76	activation of protein kinase activity
GO:0035148	0.001213868835616 73	43	tube formation
GO:1903320	0.001214519796375 66	55	regulation of protein modification by small protein conjugation or removal
GO:1900364	0.001214989363517 05	6	negative regulation of mRNA polyadenylation
GO:0001933	0.001221205503821 04	89	negative regulation of protein phosphorylation
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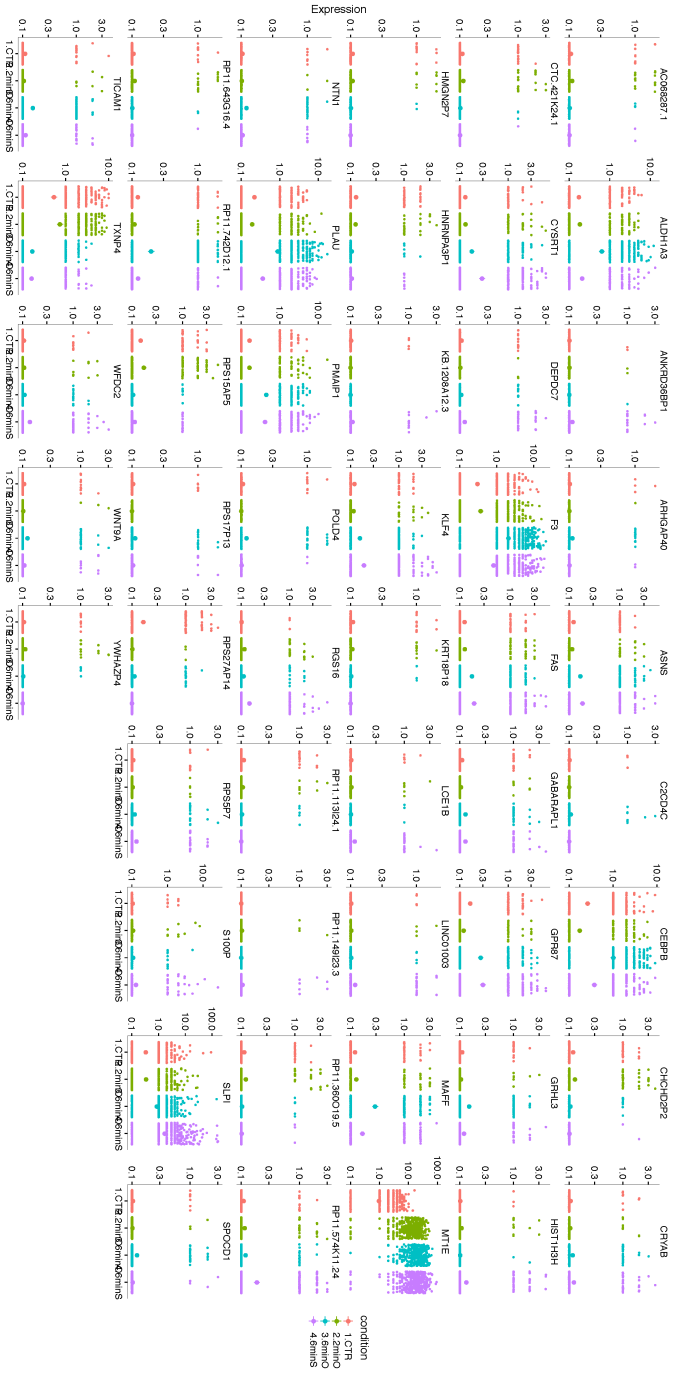
GO:0042326	0.001233466242813 34	96	negative regulation of phosphorylation
GO:0120034	0.001236887511946 59	30	positive regulation of plasma membrane bounded cell projection assembly
GO:0051302	0.001249796562116 42	42	regulation of cell division
GO:1901976	0.001251592630103 84	13	regulation of cell cycle checkpoint
GO:1901533	0.001259929950706 28	4	negative regulation of hematopoietic progenitor cell differentiation
GO:1901028	0.001290392976105 27	14	regulation of mitochondrial outer membrane permeabilization involved in apoptotic signaling pathway
GO:0007275	0.001331974987949 19	883	multicellular organism development
GO:0044257	0.001335515048101 47	156	cellular protein catabolic process
GO:0032481	0.001386859240671 37	22	positive regulation of type I interferon production
GO:0051656	0.001387429167793 05	113	establishment of organelle localization
GO:0045724	0.001396436733863 37	12	positive regulation of cilium assembly
GO:0045840	0.001396619982802 06	18	positive regulation of mitotic nuclear division
GO:1901564	0.001398943156837 25	1082	organonitrogen compound metabolic process
GO:0032210	0.001418737147150 7	19	regulation of telomere maintenance via telomerase
GO:0035521	0.001418748917638 12	4	monoubiquitinated histone deubiquitination
GO:0035522	0.001418748917638 12	4	monoubiquitinated histone H2A deubiquitination
GO:0016579	0.001428125253268 38	62	protein deubiquitination
GO:0000083	0.001444309505917 43	12	regulation of transcription involved in G1/S transition of mitotic cell cycle
GO:0007492	0.001463486302894 58	25	endoderm development
GO:0043414	0.001470671667378 68	69	macromolecule methylation
GO:0009895	0.001471361740316 48	67	negative regulation of catabolic process
GO:0006342	0.001476607111815 84	27	chromatin silencing
GO:0090316	0.001477775943656 99	44	positive regulation of intracellular protein transport
GO:0044319	0.001490391243435 56	13	wound healing, spreading of cells
GO:0090505	0.001490391243435 56	13	epiboly involved in wound healing
GO:0006413	0.001504045113218 01	38	translational initiation
GO:0002562	0.001545409060759 36	18	somatic diversification of immune receptors via germline recombination within a single locus
GO:0016444	0.001545409060759 36	18	somatic cell DNA recombination
GO:0008203	0.001552166063377 83	35	cholesterol metabolic process
GO:1901796	0.001558194301688 44	35	regulation of signal transduction by p53 class mediator
GO:1905268	0.001563580222258 04	20	negative regulation of chromatin organization
GO:0006479	0.001594312740927 65	46	protein methylation
GO:0008213	0.001594312740927 65	46	protein alkylation
GO:0030520	0.001600568970441 7	20	intracellular estrogen receptor signaling pathway
GO:1900739	0.001605295368601 04	10	regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway
GO:1900740	0.001605295368601 04	10	positive regulation of protein insertion into mitochondrial membrane involved in apoptotic signaling pathway
GO:0031532	0.001633785847537 3	29	actin cytoskeleton reorganization
GO:0006928	0.001641065395314 23	379	movement of cell or subcellular component
GO:0072175	0.001649257971704 38	39	epithelial tube formation
GO:0071478	0.001692616100756 11	46	cellular response to radiation
GO:0035735	0.001717355168833 05	16	intraciliary transport involved in cilium assembly
GO:0018022	0.001727138738591 36	36	peptidyl-lysine methylation
GO:1901989	0.001738053260576 33	26	positive regulation of cell cycle phase transition
GO:0002200	0.001741695333688 67	20	somatic diversification of immune receptors
GO:0097435	0.001765770638383 89	146	supramolecular fiber organization
GO:0090435	0.001779469521103 91	5	protein localization to nuclear envelope
GO:0070647	0.001785063357467 81	210	protein modification by small protein conjugation or removal
GO:0061458	0.001816984137763 48	93	reproductive system development
GO:0045860	0.001818486632887 33	110	positive regulation of protein kinase activity
GO:0034453	0.001872215611716 87	13	microtubule anchoring
GO:2001168	0.001873114246061 35	4	positive regulation of histone H2B ubiquitination
GO:0043254	0.001878616906294 5	100	regulation of protein complex assembly
GO:2000026	0.001946193014125 72	367	regulation of multicellular organismal development
GO:0090181	0.001962247766079 85	19	regulation of cholesterol metabolic process
GO:0030163	0.001974356309971 65	180	protein catabolic process
GO:0001844	0.002012092614214 62	11	protein insertion into mitochondrial membrane involved in apoptotic signaling pathway
GO:0048549	0.002030428646005 2	4	positive regulation of pinocytosis
GO:0016574	0.002060885629278 26	18	histone ubiquitination
GO:0016126	0.002067140977602 86	22	sterol biosynthetic process
GO:0045595	0.002103327865374 47	328	regulation of cell differentiation
GO:0006352	0.002119682183407 69	57	DNA-templated transcription, initiation
GO:0010498	0.002158402197812 58	99	proteasomal protein catabolic process
GO:0048608	0.002165340236869 05	92	reproductive structure development
GO:0042073	0.002210407954135 58	19	intraciliary transport
GO:0033143	0.002213211509563 09	25	regulation of intracellular steroid hormone receptor signaling pathway
GO:0010506	0.002238029991689 14	73	regulation of autophagy
GO:0034243	0.002240870843743 19	12	regulation of transcription elongation from RNA polymerase II promoter

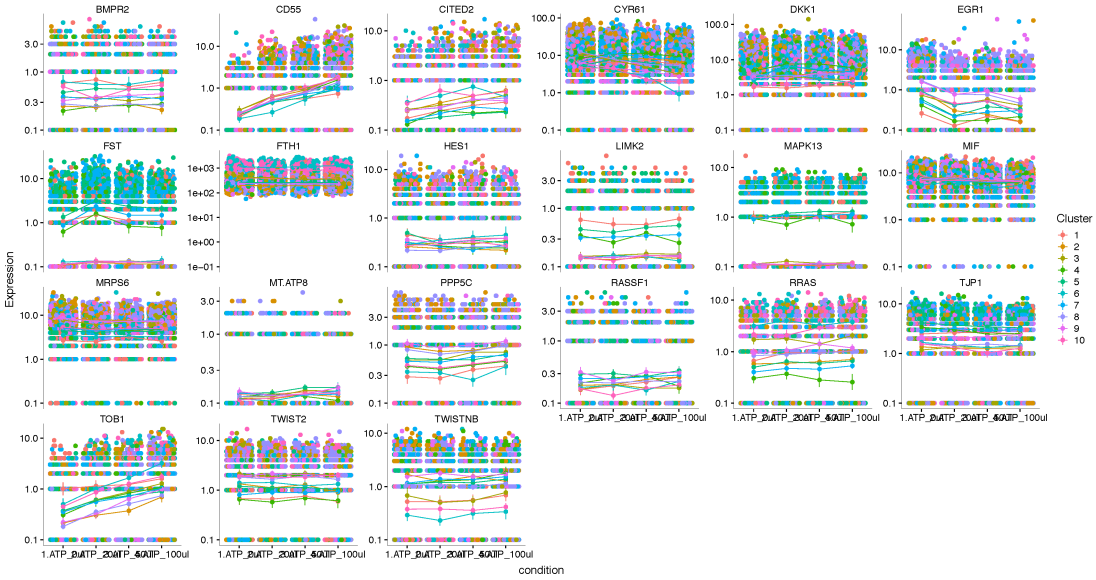
Supplement Figure S1A:

(expression profiles of 2mO, 6mO, 6mS and control for DEG)



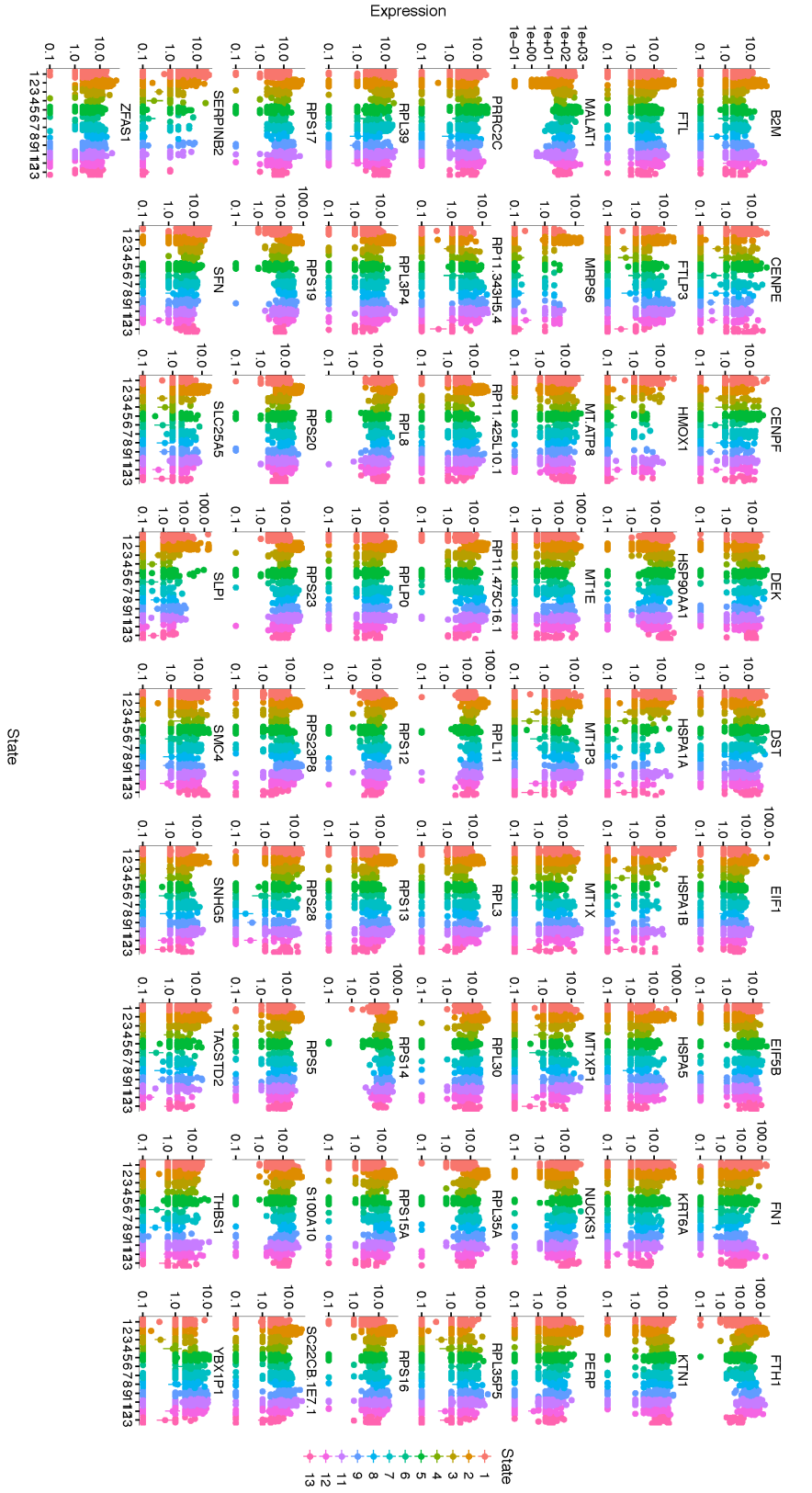
Supplement figure S1B:

(expression profiles of eATP dose response and control for DEG)



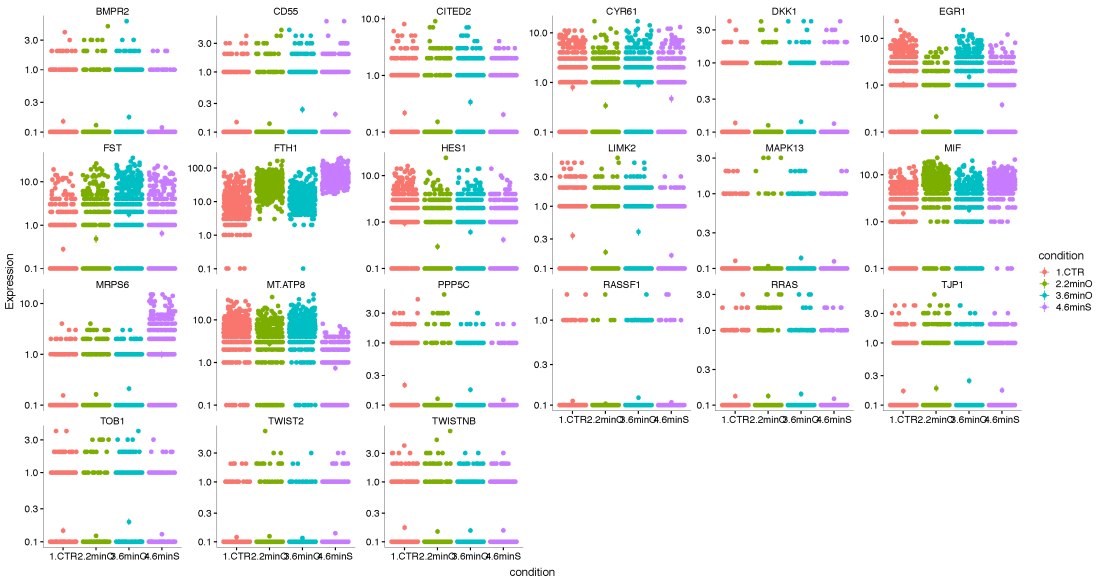
Supplement figure S2:

(expression profiles of 2mO, 6mO, 6mS and control for DEG)



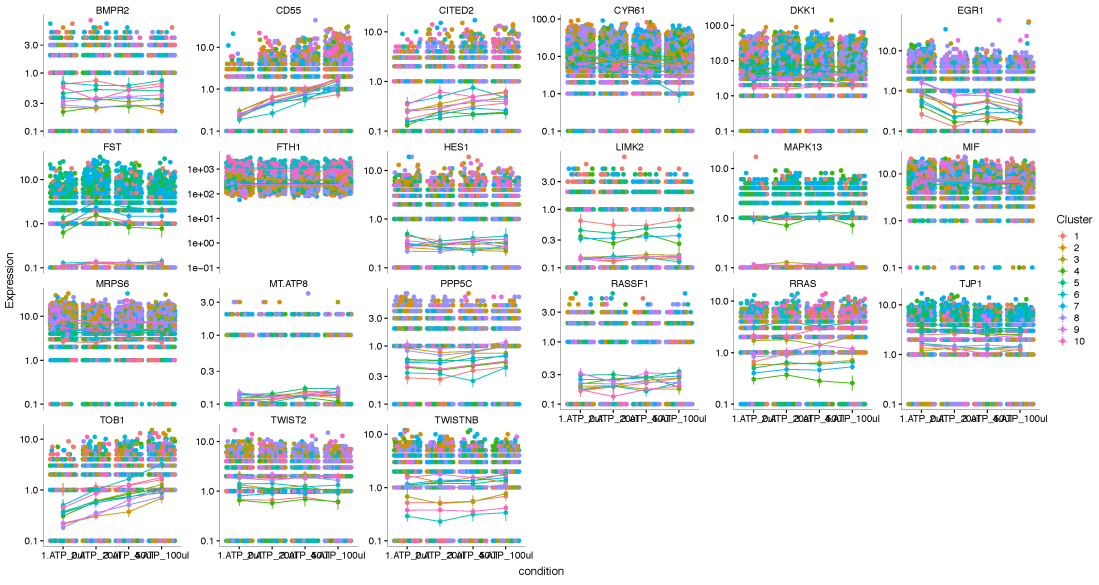
Supplement figure S3A:

(expression profiles of 2mO, 6mO, 6mS and control for DEG)



Supplement figure S3B:

(expression profiles of eATP dose response and control for DEG)



Bibliography

Abdallah, B. Y., Horne, S. D., Stevens, J. B., Liu, G., Ying, A. Y., Vanderhyden, B., … Heng, H. H. Q. (2013). Single cell heterogeneity: Why unstable genomes are incompatible with average profiles. *Cell Cycle*, *12*(23), 3640–3649. http://doi.org/10.4161/cc.26580

Aceto, N., Bardia, A., Miyamoto, D. T., Donaldson, M. C., Wittner, B. S., Spencer, J. A., … Maheswaran, S. (2014). Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. *Cell*, *158*(5), 1110–1122. http://doi.org/10.1016/j.cell.2014.07.013

Agonists, D. C., Tsien, R. W., & Beant, B. P. (1986). Mechanisms of Calcium Channel Modulation by β-Adrenergic Agents and Dihydropyridine Calcium Agonists. *J Mol Cell Cardiol*, *710*.

Allard, B., Longhi, S., & John, C. R. (2017). The ectonucleotidases CD39 and CD73 : Novel checkpoint inhibitor targets. *Immunological Reviews*, *276*, 121–144. http://doi.org/10.1111/imr.12528

Antsiferova, M., Klatte, J. E., Bodó, E., Paus, R., Jorcano, J. L., Matzuk, M., … Kögel, H. (2009). Keratinocyte-derived follistatin regulates epidermal homeostasis and wound repair. *Lab Invest*, *89*(2), 131–141. http://doi.org/10.1038/labinvest.2008.120.Keratinocyte-derived

Ashall, L., Horton, C. a, Nelson, D. E., Paszek, P., Harper, C. V, Sillitoe, K., … White, M. R. H. (2009). Pulsatile stimulation determines timing and specificity of NF-kappaB-dependent transcription. *Science (New York, N.Y.)*, *324*(5924), 242–246. http://doi.org/10.1126/science.1164860

Barriere, G., Fici, P., Gallerani, G., Fabbri, F., & Rigaud, M. (2015). Epithelial Mesenchymal Transition: a double-edged sword. *Clinical and Translational Medicine*, *4*(1), 4–9. http://doi.org/10.1186/s40169-015-0055-4

Barrière, G., Riouallon, A., Renaudie, J., Tartary, M., & Rigaud, M. (2012). Mesenchymal and stemness circulating tumor cells in early breast cancer diagnosis. *BMC Cancer*, *12*. http://doi.org/10.1186/1471-2407-12-114

Bartis, D., Mise, N., Mahida, R. Y., Eickelberg, O., & Thickett, D. R. (2014). Epithelial-mesenchymal transition in lung development and disease: Does it exist and is it important? *Thorax*, *69*(8), 760–765. http://doi.org/10.1136/thoraxjnl-2013-204608

Battich, N., Stoeger, T., & Pelkmans, L. (2015). Control of Transcript Variability in Single Mammalian Cells. *Cell*, *163*(7), 1596–1610. http://doi.org/10.1016/j.cell.2015.11.018

Baum, B., Settleman, J., & Quinlan, M. P. (2008). Transitions between epithelial and mesenchymal states in development and disease. *Seminars in Cell and Developmental Biology*, *19*(3), 294–308. http://doi.org/10.1016/j.semcdb.2008.02.001

Berridge, M. J., Lipp, P., & Bootman, M. D. (2000). The versatility and universality of calcium signalling. *Nature Reviews*, *1*(October).

Berridge, M. J., Lipp, P., & Bootman, M. D. (2000). The versatility and universality of calcium signalling. *Nature Reviews. Molecular Cell Biology*, *1*(1), 11–21. http://doi.org/10.1038/35036035

Bhowmick, N. A., Gorska, A. E., Dumont, N., Shappell, S., Washington, M. K., Neilson, E. G., & Moses, H. L. (2004). TGF-Beta Signaling in Fibroblasts Modulates the Oncogenic Potential of Adjacent Epithelia. *Science*, *303*(February), 848–851. http://doi.org/10.1126/science.1090922

Bissell, M. J., & Radisky, D. (2001). An innate anticancer mechanism. *Nature Reviews Cancer*, *1*(October), 46–54.

Bootman, M. D. (2006). Calcium Signalling and Regulation of Cell Function. *Transfusion Medicine and Hemotherapy*, *32*(2), 1–7. http://doi.org/10.1002/9780470015902.a0001265.pub3

Bootman, M. D., Berridge, M. J., & Lipp, P. (1997). Cooking with calcium: The recipes for composing global signals from elementary events. *Cell*, *91*(3), 367–373. http://doi.org/10.1016/S0092-8674(00)80420-1

Border, W. A., & Noble, N. A. (1997). CYTOKINES IN THE KIDNEY TGF-J3 in kidney

fibrosis: A target for gene therapy. *Kidney International*, *51*, 1388–1396. http://doi.org/10.1038/ki.1997.190

Braga, V. M. M., Machesky, L. M., Hall, A., Hotchin, N. A., & Hotchin, N. A. (2013). for the Establishment of The Small GTPases Rho and Rac Are Required Cell-Cell Contacts, *137*(6), 1421–1431.

Breau, M. A. (2006). Lack of 1 integrins in enteric neural crest cells leads to a Hirschsprung-like phenotype. *Development*, *133*(9), 1725–1734. http://doi.org/10.1242/dev.02346

Bruce, D. L., Macartney, T., Yong, W., Shou, W., & Sapkota, G. P. (2012). Protein phosphatase 5 modulates SMAD3 function in the transforming growth factor - β pathway. *Cellular Signalling*, *24*(11), 1999–2006. http://doi.org/10.1016/j.cellsig.2012.07.003

Büttner, S., Habernig, L., Broeskamp, F., Ruli, D., Nora Vögtle, F., Vlachos, M., … Madeo, F. (2013). Endonuclease G mediates α-synuclein cytotoxicity during Parkinson's disease. *EMBO Journal*, *32*(23), 3041–3054. http://doi.org/10.1038/emboj.2013.228

Cano, A., Diaz-Lopez, A., & Moreno-Bueno, G. (2014). Role of microRNA in epithelial to mesenchymal transition and metastasis and clinical perspectives. *Cancer Management and Research*, 205. http://doi.org/10.2147/cmar.s38156

Chawla, S., Hardingham, G. E., Quinn, D. R., & Bading, H. (1998). CBP : A Signal-Regulated Transcriptional Coactivator Controlled by Nuclear Calcium and CaM Kinase IV. *Science*, *281*(September), 1505–1510.

Chen, L., Xiao, Z., Meng, Y., Zhao, Y., Han, J., Su, G., … Dai, J. (2012). Biomaterials The enhancement of cancer stem cell properties of MCF-7 cells in 3D collagen scaffolds for modeling of cancer and anti-cancer drugs. *Biomaterials*, *33*(5), 1437–1444. http://doi.org/10.1016/j.biomaterials.2011.10.056

Chen, X., Liu, X., Lang, H., Zhang, S., Luo, Y., & Zhang, J. (2015). S100 calcium-binding protein A6 promotes epithelial-mesenchymal transition through β-catenin in pancreatic cancer cell line. *PLoS ONE*, *10*(3), 1–14.

http://doi.org/10.1371/journal.pone.0121319

Chen, Y., Tong, Y., Li, Y., Liu, R., Xu, Q., Chang, G., & Chen, G. (2016). Ferritin heavy polypeptide 1 mediates apoptosis-related gene expression of duck (Anas platyrhynchos domesticus). *Canc. J. Anim*, *625*(July), 619–625.

Cheng, N., Bhowmick, N. A., Chytil, A., Gorksa, A. E., Brown, K. A., Muraoka, R., … Moses, H. L. (2005). Loss of TGf-β type II receptor in fibroblasts promotes mammary carcinoma growth and invasion through upregulation of TGF-α-, MSP- and HGF-mediated signaling networks. *Oncogene*, *24*(32), 5053–5068. http://doi.org/10.1038/sj.onc.1208685

Coffey, R. G. (1992). Paradoxical stimulation and inhibition by protein kinase C modulating agents of lipopolysaccharide evoked production of tumour necrosis factor in human monocytes. *Immunology*, *76*, 48–54.

Cooke, H. J., Wunderlich, J., & Christofi, F. L. (2019). " The Force Be with You ": ATP in Gut Mechanosensory Transduction. *News Physioloogy*, *18*, 43–49.

Cox, A., Dunning, A. M., Garcia-Closas, M., Balasubramanian, S., Reed, M. W. R., Pooley, K. A., … Easton, D. F. (2007). A common coding variant in CASP8 is associated with breast cancer risk. *Nature Genetics*, *39*(3), 352–358. http://doi.org/10.1038/ng1981

Crabtree, G. R. (1999). Generic signals and specific outcomes: Signaling through Ca2+, calcineurin, and NF-AT. *Cell*, *96*(5), 611–614. http://doi.org/10.1016/S0092-8674(00)80571-1

Czerwinska, P., & Kaminska, B. (2015). Regulation of breast cancer stem cell features. *Contemporary Oncology*, *19*. http://doi.org/10.5114/wo.2014.47126

Dho, S. H., Lim, J. C., Kim, L. K., & Kim, L. K. (2018). Beyond the Role of CD55 as a Complement Component. *Immune Network*, *18*(1), 1–13.

Ding, J. M., Buchanan, G. F., Tischkau, S. A., Chen, D., Kuriashkina, L., Faiman, L. E., … Gillette, M. U. (1998). A neuronal ryanodine receptor mediates light-induced phase delays of the circadian clock. *Nature*, *394*(6691), 381–384.

http://doi.org/10.1038/28639

Dolmetsch, R. E., Xu, K., & Lewis, R. S. (1998). Calcium oscillations increase the efficiency and specificity of gene expression. *Nature*, *392*(6679), 933–936. http://doi.org/10.1016/1369-5266(88)80037-2

Dupont, G., Combettes, L., Bird, G. S., & Putney, J. W. (2011). Calcium oscillations. *Cold Spring Harbor Perspectives in Biology*, *3*(3), 1–18. http://doi.org/10.1101/cshperspect.a004226

El-Tanani, M., Platt-Higgins, A., Rudland, P. S., & Campbell, F. C. (2004). Ets gene PEA3 cooperates with β-catenin-Lef-1 and c-Jun in regulation of osteopontin transcription. *Journal of Biological Chemistry*, *279*(20), 20794–20806. http://doi.org/10.1074/jbc.M311131200

Elenbaas, B., Spirio, L., Koerner, F., Fleming, M. D., Zimonjic, D. B., Donaher, J. L., … Weinberg, R. a. (2001). Human breast cancer cells generated by oncogenic transformation of primary mammary epithelial cells. *Genes & Development*, *15*(1), 50–65. http://doi.org/10.1101/gad.828901.monly

Elenbaas, B., & Weinberg, R. A. (2001). Heterotypic signaling between epithelial tumor cells and fibroblasts in carcinoma formation. *Experimental Cell Research*, *264*(1), 169–184. http://doi.org/10.1006/excr.2000.5133

Erlinge, D. (1998). Extracellular ATP : A Growth Factor for Vascular Smooth Muscle Cells. *Gen. Pharmac.*, *31*(1), 1–8.

Feng Wei-gang, T. X. (2017). Identification of a new pro-invasion factor in tumor microenvironment: progress in function and mechanism of extracellular ATP. *Jurnal of Pekin University*, *49*(2).

Fernandez, I. E., & Eickelberg, O. (2012). The Impact of TGF-β on Lung Fibrosis. *Proceedings of the American Thoracic Society*, *9*(3), 111–116. http://doi.org/10.1513/pats.201203-023AW

Gab Seok Kim, Joo Eun Jung, Purnima Narasimhan, Hiroyuki Sakata, and P. H. C. (2013). Induction of thioredoxin-interacting protein is mediated by oxidative

stress, calcium, and glucose after brain injury in mice. *Neurobiologi Dis.*, *46*(2), 440–449. http://doi.org/10.1016/j.nbd.2012.02.008.Induction

Galichon, P., & Hertig, A. (2011). Epithelial to mesenchymal transition as a biomarker in renal fibrosis: Are we ready for the bedside? *Fibrogenesis and Tissue Repair*, *4*(1), 1–7. http://doi.org/10.1186/1755-1536-4-11

Geng, Y., Ju, Y., Ren, F., Qiu, Y., Tomita, Y., Tomoeda, M., & Kishida, M. (2014). Insulin Receptor Substrate 1 / 2 (IRS1 / 2) Regulates Wnt / □ -Catenin Signaling through Blocking Autophagic Degradation of Dishevelled2 *. *Journal of Biological Chemistry*, *289*(16), 11230–11241. http://doi.org/10.1074/jbc.M113.544999

Giovannelli, P., Donato, M. Di, Galasso, G., Zazzo, E. Di, & Bilancio, A. (2018). The Androgen Receptor in Breast Cancer. *Frontiers in Endocrinology*, *9*(August), 1–8. http://doi.org/10.3389/fendo.2018.00492

Goldman, S. L., MacKay, M., Afshinnekoo, E., Melnick, A. M., Wu, S., & Mason, C. E. (2019). The Impact of Heterogeneity on Single-Cell Sequencing. *Frontiers in Genetics*, *10*(March), 1–8. http://doi.org/10.3389/fgene.2019.00008

Greenman, C., Stephens, P. J., Smith, R., Dalgliesh, G. L., Hunter, C., Bignell, G. R., … Stratton, M. R. (2007). UKPMC Funders Group Patterns of somatic mutation in human cancer genomes. *Nature*, *446*(7132), 153–158. http://doi.org/10.1038/nature05610.Patterns

Grosse-Wilde, A., D'H??rou??l, A. F., McIntosh, E., Ertaylan, G., Skupin, A., Kuestner, R. E., … Huang, S. (2015). Stemness of the hybrid epithelial/mesenchymal state in breast cancer and its association with poor survival. *PLoS ONE*, *10*(5), 1–28. http://doi.org/10.1371/journal.pone.0126522

Hamada, T., Liou, S. Y., Fukushima, T., Maruyama, T., Watanabe, S., Mikoshiba, K., & Ishida, N. (1999). The role of inositol trisphosphate-induced Ca 2+ release from IP 3 - receptor in the rat suprachiasmatic nucleus on circadian entrainment mechanism. *Neuroscience Letters*, *263*(2–3), 125–128. http://doi.org/10.1016/S0304-3940(99)00111-1

Handly, L. N., Yao, J., & Wollman, R. (2017). Signal transduction at the single-cell

level: Approaches to study the dynamic nature of signaling networks. *J Mol Biol*, *428*(19), 3669–3682. http://doi.org/10.1016/j.jmb.2016.07.009.Signal

Hardingham, G. E., Chawla, S., Cruzalegui, F. H., & Bading, H. (1999). Control of Recruitment and Transcription-Activating Function of CBP Determines Gene Regulation by NMDA Receptors and L-Type Calcium Channels. *Neuron*, *22*, 789–798.

Hart, Y., Reich-zeliger, S., Antebi, Y. E., Zaretsky, I., Mayo, A. E., & Alon, U. (2014). Paradoxical Signaling by a Secreted Molecule Leads to Homeostasis of Cell Levels. *Cell*, *158*(5), 1022–1032. http://doi.org/10.1016/j.cell.2014.07.033

Hata, K., Takashima, R., Amano, K., Ono, K., Nakanishi, M., Yoshida, M., … Yoneda, T. (2013). Arid5b facilitates chondrogenesis by recruiting the histone demethylase Phf2 to Sox9-regulated genes. *Nature Communications*, *4*, 1–11. http://doi.org/10.1038/ncomms3850

He, A., He, S., Li, X., & Zhou, L. (2019). ZFAS1 : A novel vital oncogenic lncRNA in multiple human cancers. *Cell Proliferation*, *52*(June 2018), 1–9. http://doi.org/10.1111/cpr.12513

Hertig, A., Anglicheau, D., Ancel, P., Mesnard, L., Brousse, N., Baugey, E., … Rondeau, E. (2008). Early Epithelial Phenotypic Changes Predict Graft Fibrosis. *J Am Soc Nephrol 19:*, *19*, 1584–1591. http://doi.org/10.1681/ASN.2007101160

Hogan, P. G., Hogan, P. G., Chen, L., & Chen, L. (2003). Transcriptional regulation by calcium, calcineurin and NFAT. *And NFAT. Genes Dev.*, *17*(18), 2205–2232. http://doi.org/10.1101/gad.1102703.GENES

Hou, C., Lin, F., Hou, S., & Liu, J. (2014). Cyr61 promotes epithelial-mesenchymal transition and tumor metastasis of osteosarcoma by Raf-1 / MEK / ERK / Elk-1 / TWIST-1 signaling pathway. *Molecular Cancer*, *13*, 1–13.

Huang, J., & Guo, L. (2019). Knockdown of SOX9 Inhibits the Proliferation, Invasion, and EMT in Thyroid Cancer Cells. *Oncology Reserch*, *25*, 167–176.

Ihara, H., Hirukawa, K., Goto, S., & Togari, A. (2005). ATP-stimulated interleukin-6

synthesis through P2Y receptors on human osteoblasts. *Biochemical and Biophysical Research Communications*, *326*, 329–334. http://doi.org/10.1016/j.bbrc.2004.11.037

Jayaraman, S., Doucet, M., Lau, W. M., & Kominsky, S. L. (2016). CITED2 Modulates Breast Cancer Metastatic Ability Through Effects on IKKα. *Molecular Cancer Research*, *96*(8), 730–739. http://doi.org/10.1158/1541-7786.MCR-16-0081.CITED2

Jia Yin, Keping Xu, Jing Zhang, Ashok Kumar, and F.-S. X. Y. (2007). Wound-induced ATP release and EGF receptor activation in epithelial cells. *J Cell Sci*, *120*(Pt 5), 815–825.

Jiao, Y., Sun, K., Zhao, L., Xu, J., Wang, L., & Fan, S. (2011). Suppression of human lung cancer cell proliferation and metastasis in vitro by the transducer of ErbB-2 . 1 (TOB1). *Acta Pharmacologica Sinica*, *33*(2), 250–260. http://doi.org/10.1038/aps.2011.163

Kalcheim, C. (2015). Epithelial–Mesenchymal Transitions during Neural Crest and Somite Development. *Journal of Clinical Medicine*, *5*(1), 1. http://doi.org/10.3390/jcm5010001

Kalluri, R., & Weinberg, R. a. (2009). Review series The basics of epithelial-mesenchymal transition. *Journal of Clinical Investigation*, *119*(6), 1420–1428. http://doi.org/10.1172/JCI39104.1420

Klein, A. M., Mazutis, L., Weitz, D. A., Kirschner, M. W., Klein, A. M., Mazutis, L., … Peshkin, L. (2015). Droplet Barcoding for Single-Cell Transcriptomics Applied to Embryonic Stem Cells Resource Droplet Barcoding for Single-Cell Transcriptomics Applied to Embryonic Stem Cells. *Cell*, *161*(5), 1187–1201. http://doi.org/10.1016/j.cell.2015.04.044

Knight, G. E., Bodin, P., Groat, W. C. D. E., & Burnstock, G. (2019). ATP is released from guinea pig ureter epithelium on distension. *Physiol Renal*, *282*.

Komin, N., & Skupin, A. (2017). Systems Biology How to address cellular heterogeneity by distribution biology. *Current Opinion in Systems Biology*, *3*,

154–160. http://doi.org/10.1016/j.coisb.2017.05.010

Kowanetz, M., Valcourt, U., Bergstro, R., & Heldin, C. (2004). Id2 and Id3 Define the Potency of Cell Proliferation and Differentiation Responses to Transforming Growth Factor and Bone Morphogenetic Protein †. *Molecular and Cellular Biology*, *24*(10), 4241–4254. http://doi.org/10.1128/MCB.24.10.4241

Kroemer, G., Galluzzi, L., Kepp, O., & Zitvogel, L. (2013). Immunogenic Cell Death in Cancer Therapy. *Immunology*, *31*. http://doi.org/10.1146/annurev-immunol-032712-100008

Kwon, T., Youn, H., Son, B., Kim, D., Moon, K., Park, S., … Youn, B. (1978). DANGER is involved in high glucose-induced radioresistance through inhibiting DAPK-mediated anoikis in non-small cell lung cancer. *Oncotarget*, *7*(6).

Lauren Averett Byers, Lixia Diao, Jing Wang, J. V. H. (2011). An epithelial-mesenchymal transition (EMT) gene signature predicts resistance to EGFR and PI3K inhibitors and identifies Axl as a therapeutic target for overcoming EGFR inhibitor resistance. *Clinical Cancer Res*, *193*(1), 118–125. http://doi.org/10.1016/j.jneumeth.2010.08.011.Autogenic

Legewie, S., Herten, D.-P., Lymperopoulos, K., Eils, R., Klingmüller, U., Kallenberger, S. M., & Unger, A. L. (2017). Correlated receptor transport processes buffer single-cell heterogeneity. *PLOS Computational Biology*, *13*(9), e1005779. http://doi.org/10.1371/journal.pcbi.1005779

Lewis, C. E., & Hughes, R. (2007). Inflammation and breast cancer. Microenvironmental factors regulating macrophage function in breast tumours: Hypoxia and angiopoietin-2. *Breast Cancer Research*, *9*(3), 2–5. http://doi.org/10.1186/bcr1679

Lin, E. Y., & Pollard, J. W. (2007). Tumor-associated macrophages press the angiogenic switch in breast cancer. *Cancer Research*, *67*(11), 5064–5066. http://doi.org/10.1158/0008-5472.CAN-07-0912

Liu, C., Lv, D., Li, M., & Zhang, X. (2017). Hypermethylation of miRNA-589 promoter leads to upregulation of HDAC5 which promotes malignancy in non-small cell

lung cancer. *Jurnal of Oncology*, *50*, 2079–2090. http://doi.org/10.3892/ijo.2017.3967

Lohman, A. W., Billaud, M., & Isakson, B. E. (2012). Mechanisms of ATP release and signalling in the blood vessel wall. *Cardiovascular Research*, *95*, 269–280. http://doi.org/10.1093/cvr/cvs187

Longo, D., & Hasty, J. (2006). Dynamics of single-cell gene expression. *Molecular Systems Biology*, *2*. http://doi.org/10.1038/msb4100110

Lüer, K., & Technau, G. M. (2009). Single cell cultures of drosophila neuroectodermal and mesectodermal central nervous system progenitors reveal different degrees of developmental autonomy. *Neural Development*, *4*(1), 1–16. http://doi.org/10.1186/1749-8104-4-30

Luika A. Timmerman, Neil A. Clipstone, Steffan N. Ho, J. P. N. & G. R. C. (1996). Rapid shuttling of NF-AT in discrimination of Ca2+ signals and immunosuppression. *Nature*, *383*.

Macosko, E. Z., Basu, A., Satija, R., Nemesh, J., Shekhar, K., Goldman, M., … McCarroll, S. A. (2015). Highly parallel genome-wide expression profiling of individual cells using nanoliter droplets. *Cell*, *161*(5), 1202–1214. http://doi.org/10.1016/j.cell.2015.05.002

Mathew, S. O., Chaudhary, P., Powers, S. B., Jamboor, K., & Mathew, P. A. (2016). Overexpression of LLT1 (OCIL , CLEC2D) on prostate cancer cells inhibits NK cell-mediated killing through LLT1-NKRP1A (CD161) interaction. *Oncotarget*, *7*(42).

Mathis, L., & Nicolas, J. F. (2002). Cellular patterning of the vertebrate embryo. *Trends in Genetics*, *18*(12), 627–635. http://doi.org/10.1016/S0168-9525(02)02806-8

Mimitou, E., Cheng, A., Montalbano, A., Hao, S., Stoeckius, M., Legut, M., … Smibert, P. (2018). Expanding the CITE-seq tool-kit: Detection of proteins, transcriptomes, clonotypes and CRISPR perturbations with multiplexing, in a single assay. *bioRxiv*, 466466. http://doi.org/10.1101/466466

Moosavi, A., & Ardekani, A. M. (2016). Role of Epigenetics in Biology and Human Diseases. *Biomedical J*, *20*(November), 246–258. http://doi.org/10.22045/ibj.2016.01

Morel, A.-P., Lièvre, M., Thomas, C., Hinkal, G., Ansieau, S., & Puisieux, A. (2008). Generation of Breast Cancer Stem Cells through Epithelial-Mesenchymal Transition. *PLoS ONE*, *3*(8), e2888. http://doi.org/10.1371/journal.pone.0002888

Moris, N., Pina, C., & Arias, A. M. (2016). Transition states and cell fate decisions in epigenetic landscapes. *Nature Publishing Group*, *17*(11), 693–703. http://doi.org/10.1038/nrg.2016.98

N. M. Woods, K.S. Cuthbertson, P. H. C. (1986). Repetitive transient rises in cytoplasmic free calcium in hormone-stimulated hepatocytes. *Nature*, *319*.

Nair, R., Teo, W. S., Mittal, V., & Swarbrick, A. (2014). ID Proteins Regulate Diverse Aspects of Cancer Progression and Provide Novel Therapeutic Opportunities. *Molecular Therapy*, *22*(8), 1407–1415. http://doi.org/10.1038/mt.2014.83

Nelson, D. E. (2004). Oscillations in NF-kB Signaling Control the Dynamics of Gene Expression. *Science*, *306*(October), 704–708. http://doi.org/10.1126/science.1099962

Ng, K., Chan, L., Chai, S., Tong, M., Guan, X., Lee, N. P., … Ma, S. (2017). TP53INP1 Downregulation Activates a p73- Dependent DUSP10 / ERK Signaling Pathway to Promote Metastasis of Hepatocellular Carcinoma. *Cancer Research*, *77*(16), 4602–4613. http://doi.org/10.1158/0008-5472.CAN-16-3456

Nieto, M. A., Huang, R. Y. Y. J., Jackson, R. A. A., & Thiery, J. P. P. (2016). Emt: 2016. *Cell*, *166*(1), 21–45. http://doi.org/10.1016/j.cell.2016.06.028

Nishida, H. (2005). Specification of embryonic axis and mosaic development in ascidians. *Developmental Dynamics*, *233*(4), 1177–1193. http://doi.org/10.1002/dvdy.20469

North, R. A. (2019). Molecular Physiology of P2X Receptors. *Physiol Rev.*, 1013–1067.

Novak, I. (2003). ATP as a Signaling Molecule : the Exocrine Focus. *News Physioloogy*, *18*, 0–5.

Parekh, A. B. (2011). Decoding cytosolic Ca2+ oscillations. *Trends in Biochemical Sciences*, *36*(2), 78–87. http://doi.org/10.1016/j.tibs.2010.07.013

Patsialou, A., Wang, Y., Lin, J., Whitney, K., Goswami, S., Kenny, P. A., & Condeelis, J. S. (2012). Selective gene-expression profiling of migratory tumor cells in vivo predicts clinical outcome in breast cancer patients. *Breast Cancer Research*, *14*(5). http://doi.org/10.1186/bcr3344

Polyak, K. (2007). Science in medicine Breast cancer : origins and evolution. *The Journal of Clinical Investigation*, *117*(11), 3155–3163. http://doi.org/10.1172/JCI33295.group

Pote, M. (2012). Endonuclease G interacts with histone H2B and DNA topoisomerase II alpha during apoptosis. *Molecular and Cellular Biochemistry*, *363*, 301–307. http://doi.org/10.1007/s11010-011-1182-x

Press Release, W. (2018). Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018, (September), 13–15.

Purvis, J. E., & Lahav, G. (2013). Review Encoding and Decoding Cellular Information through Signaling Dynamics. *Cell*, *152*(5), 945–956. http://doi.org/10.1016/j.cell.2013.02.005

Putney, J. W., Poggioli, J., & Weiss, S. J. (1981). Receptor regulation of calcium release and calcium permeability in parotid gland cells. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *296*(1080), 37–45. http://doi.org/10.1098/rstb.1981.0169

Qiang Li, Diana L. Ramírez-Bergeron, Sally L. Dunwoodie, and Y.-C. Y. (2012). Cited2 Gene Controls Pluripotency and Cardiomyocyte Differentiation of Murine Embryonic Stem Cells through Oct4 Gene. *Journal of Biological Chemistry*, *287*(34), 29088–29100. http://doi.org/10.1074/jbc.M112.378034

Roberts, A. B., Tian, F., Byfield, S. D. C., Stuelten, C., Ooshima, A., Saika, S., &

Flanders, K. C. (2006). Smad3 is key to TGF-β-mediated epithelial-to-mesenchymal transition, fibrosis, tumor suppression and metastasis. *Cytokine and Growth Factor Reviews*, *17*(1–2), 19–27. http://doi.org/10.1016/j.cytogfr.2005.09.008

Rorison, P., Thomlinson, A., Hassan, Z., Roberts, S. A., Ferguson, M. W. J., & Shah, M. (2010). Longitudinal changes in plasma Transforming growth factor beta-1 and post-burn scarring in children. *Burns*, *36*(1), 89–96. http://doi.org/10.1016/j.burns.2009.03.008

Saitoh, M. (2018). Involvement of partial EMT in cancer progression. *Biochem J*, *164*(4), 257–264. http://doi.org/10.1093/jb/mvy047

Shan, L., Song, Y., Su, D., Liu, Y., Shi, X., & Lu, S. (2015). Early Growth Response Protein-1 Involves in Transforming Growth factor-β1 Induced Epithelial-Mesenchymal Transition and Inhibits Migration of Non-Small-Cell Lung Cancer Cells. *Asian Pacific Journal of Cancer Prevention*, *16*, 4137–4142.

Simino, J., Wang, Z., Bressler, J., Chouraki, V., Yang, Q., & Mosley, H. (2017). Whole exome sequence-based association analyses of plasma amyloid- β in African and European Americans ; the Atherosclerosis Risk in Communities-Neurocognitive Study. *PLoS ONE*.

Sjöblom, T., Jones, S., Wood, L. D., Parsons, D. W., Lin, J., Barber, T. D., … Velculescu, V. E. (2006). Supporting Online Material for “The consensus coding sequences of human breast and colorectal cancers”. *Science (New York, N.Y.)*, *314*(September), 1–11. http://doi.org/10.1126/science.1133427

Skupin, A., Kettenmann, H., & Falcke, M. (2010). Calcium signals driven by single channel noise. *PLoS Computational Biology*, *6*(8), 17–19. http://doi.org/10.1371/journal.pcbi.1000870

Smedler, E., & Uhlén, P. (2014). Frequency decoding of calcium oscillations. *Biochimica et Biophysica Acta - General Subjects*, *1840*(3), 964–969. http://doi.org/10.1016/j.bbagen.2013.11.015

Sonnen, K. F., & Aulehla, A. (2014). Seminars in Cell & Developmental Biology

Dynamic signal encoding — From cells to organisms. *Seminars in Cell and Developmental Biology*, *34*, 91–98. http://doi.org/10.1016/j.semcdb.2014.06.019

Stacey, S. N., Manolescu, A., Sulem, P., Rafnar, T., Gudmundsson, J., Gudjonsson, S. A., … Stefansson, K. (2007). Common variants on chromosomes 2q35 and 16q12 confer susceptibility to estrogen receptor–positive breast cancer. *Nature Genetics*, *39*(7), 865–869. http://doi.org/10.1038/ng2064

Suarez-carmona, M., Lesage, J., Cataldo, D., & Gilles, C. (2017). EMT and inflammation : inseparable actors of cancer progression. *Molecular Oncology*, *11*, 805–823. http://doi.org/10.1002/1878-0261.12095

Sun, T., Du, S. Y., Armenia, J., Qu, F., Fan, J., Wang, X., … Kantoff, P. W. (2018). Expression of lncRNA MIR222HG cotranscribed from the miR-221/222 gene promoter facilitates the development of castration-resistant prostate cancer. *Oncogenesis*, *7*(3). http://doi.org/10.1038/s41389-018-0039-5

Syn, W. K. I. N., Jung, Y., Omenetti, A., Abdelmalek, M., Guy, C. D., Yang, L. I. U., … Diehl, A. M. A. E. (2009). Hedgehog-Mediated Epithelial-to-Mesenchymal Transition and Fibrogenic Repair in Nonalcoholic Fatty Liver Disease. *GASTROENTEROLOGY*, *137*(4), 1478–1488.e8. http://doi.org/10.1053/j.gastro.2009.06.051

Thevenod, F., Streb, H., Ullrich, K. J., & Schulz, I. (1986). Inositol 1,4,5-trisphosphate releases Ca2+ from a nonmitochondrial store site in permeabilized rat cortical kidney cells. *Kidney International*, *29*(3), 695–702. http://doi.org/10.1038/ki.1986.54

Thurley, K., Tovey, S. C., Moenke, G., Prince, V. L., Meena, A., Thomas, A. P., … Falcke, M. (2014). Reliable encoding of stimulus intensities within random sequences of intracellular Ca2+ spikes. *Science Signaling*, *7*(331), ra59. http://doi.org/10.1126/scisignal.2005237

Trapnell, C., & Cacchiarelli, D. (2017). Monocle : Cell counting , differential expression , and trajectory analysis for single-cell RNA-Seq experiments, 10. Retrieved from https://bioconductor.org/packages/release/bioc/html/monocle.html

Ulrich, C. M., Bigler, J., & Potter, J. D. (2006). Non-steroidal anti-inflammatory drugs for cancer prevention: Promise, perils and pharmacogenetics. *Nature Reviews Cancer*, *6*(2), 130–140. http://doi.org/10.1038/nrc1801

Valladares, D., Almarza, G., Contreras, A., Pavez, M., Buvinic, S., Jaimovich, E., & Casas, M. (2013). Electrical stimuli are anti-apoptotic in skeletal muscle via extracellular ATP. Alteration of this signal in Mdx mice is a likely cause of dystrophy. *PLoS ONE*, *8*(11). http://doi.org/10.1371/journal.pone.0075340

Vallejos, C. A., Risso, D., Scialdone, A., Dudoit, S., & Marioni, J. C. (2017). Normalizing single-cell RNA sequencing data: challenges and opportunities. *Nature Methods*, *14*(6), 565–571. http://doi.org/10.1038/nmeth.4292

Virgilio, F. Di, Ben, D. D., Sarti, A. C., Giuliani, A. L., & Falzoni, S. (2017). Review The P2X7 Receptor in Infection and Inflammation. *Immunity*, *47*(1), 15–31. http://doi.org/10.1016/j.immuni.2017.06.020

Volk, S. W., Iqbal, S. A., & Bayat, A. (2013). Interactions of the Extracellular Matrix and Progenitor Cells in Cutaneous Wound Healing. *Advances in Wound Care*, *2*(6), 261–272. http://doi.org/10.1089/wound.2012.0417

Wang, J., Moreira, K. M., Campos, B., Kaetzel, M. A., & John, R. (1996). Targeted neutralization of calmodulin in the nucleus blocks DNA synthesis and cell cycle progression. *Biochemical and Biophysical Research Communications*, *1313*, 223–228.

Wang, J., Sun, D., Wang, Y., Ren, F., Pang, S., Wang, D., & Xu, S. (2014). FOSL2 Positively Regulates TGF-b1 Signalling in Non-Small Cell Lung Cancer. *PLoS ONE*, *9*(11), 1–7. http://doi.org/10.1371/journal.pone.0112150

Wang, S., Ren, T., Jiao, G., Huang, Y., & Bao, X. (2017). BMPR2 promotes invasion and metastasis via the RhoA-ROCK- LIMK2 pathway in human osteosarcoma cells. *Oncotarget*, *8*(35), 58625–58641.

Wen-hong, L., Llopis, J., Whitney, M., Zlokarnik, G., & Tsien, R. Y. (1998). Cell-permeant caged InsP3 ester shows that Ca2+ spike frequency can optimize gene expression. *Nature*, *414*(November), 204–208.

http://doi.org/10.1038/nature02336.1.

Wen, J. D. O., Trieter, R. S., Urdick, M. B., Aghnegahdar, H. H., Anney, L. N., & Randt, R. S. H. (1997). Enhanced tumor-forming capacity for immortalized melanocytes expressing melanoma growth stimulatory activity/growth-regulated cytokine β and γ proteins. *International Journal of Cancer*, *103*(February), 94–103.

Wesley, U. V, Bove, P. F., Mccarthy, S., & Der, A. Van. (2007). Airway Epithelial Cell Migration and Wound Repair by ATP-mediated Activation of Dual Oxidase 1 *. *Biol. Chem.*, *282*. http://doi.org/10.1074/jbc.M606533200

Whitaker, M. (2006). Calcium at fertilization and in early development. *Physiol Rev.*, *86*(1), 25–88. http://doi.org/10.1152/physrev.00023.2005.Calcium

Wiley, H. S. (2017). Previews Decoding Signal Processing at the Single-Cell Level. *Cell Systems*, *5*, 542–543. http://doi.org/10.1016/j.cels.2017.12.003

Wojtowicz, A. M., Oliveira, S., Carlson, M. W., Zawadzka, A., Rousseau, C. F., & Baksh, D. (2014). The importance of both fibroblasts and keratinocytes in a bilayered living cellular construct used in wound healing. *Wound Repair and Regeneration : Official Publication of the Wound Healing Society [and] the European Tissue Repair Society*, *22*(2), 246–255. http://doi.org/10.1111/wrr.12154

Xu, G., Chen, J., Jing, G., & Shalev, A. (2012). Preventing β-Cell Loss and Diabetes With Calcium Channel Blockers. *Diabetes*, *61*(April). http://doi.org/10.2337/db11-0955

Xu, L., Zhang, Y., Guo, R., Shen, W., Qi, Y., & Wang, Q. (2017). HES1 promotes extracellular matrix protein expression and inhibits proliferation and migration in human trabecular meshwork cells under oxidative stress. *Oncotarget*, *8*(13), 21818–21833.

Yang, J. M., Bhattacharya, S., West-Foyle, H., Hung, C. F., Wu, T. C., Iglesias, P. A., & Huang, C. H. (2018). Integrating chemical and mechanical signals through dynamic coupling between cellular protrusions and pulsed ERK activation. *Nature*

Communications, *9*(1), 1–13. http://doi.org/10.1038/s41467-018-07150-9

Yang, Y., Pan, X., Lei, W., Wang, J., & Song, J. (2006). Transforming growth factor-1 induces epithelial-to-mesenchymal transition and apoptosis via a cell cycle-dependent mechanism Transforming growth factor- b 1 induces epithelial-to-mesenchymal transition and apoptosis via a cell cycle-dependent mechanism. *Oncogene*, *25*(December 2006). http://doi.org/10.1038/sj.onc.1209712

Yoon, K., Kim, S. H., Lee, S. Y., & You, H. J. (2015). Tight junction protein 1 is regulated by transforming growth factor- β and contributes to cell motility in NSCLC cells. *BMB Reports*, *48*(2), 115–120.

Youk, H., Lim, W. A., Biology, S., Francisco, S., Francisco, S., & Francisco, S. (2014). Sending Mixed Messages for Cell Population Control. *Cell*, *158*(5), 973–975. http://doi.org/10.1016/j.cell.2014.08.013.Sending

Zeisberg, M., Hanai, J., Sugimoto, H., Mammoto, T., Charytan, D., Strutz, F., & Kalluri, R. (2003). BMP-7 counteracts TGF- β 1 – induced epithelial-to- mesenchymal transition and reverses chronic renal injury. *Nature Medicine*, *9*(7), 964–968.

Zeng, J., Zhang, N., Zhao, G., Xu, L., Yang, Y., Xu, X., & Chen, M. (2018). MT1G is Silenced by DNA Methylation and Contributes to the Pathogenesis of Hepatocellular Carcinoma. *Journal of Cancer*, *9*. http://doi.org/10.7150/jca.25680

Zhu, L., Luo, Y., Chen, T., Chen, F., Wang, T., & Hu, Q. (2008). Ca2+ oscillation frequency regulates agonist-stimulated gene expression in vascular endothelial cells. *Journal of Cell Science*, *121*, 2511–2518. http://doi.org/10.1242/jcs.031997

Zhu, L., Song, S., Pi, Y., Yu, Y., She, W., Ye, H., … Hu, Q. (2011). Cumulated $Ca2^{+}$ spike duration underlies $Ca2^{+}$ oscillation frequency-regulated NFκB transcriptional activity. *Journal of Cell Science*, *124*(Pt 15), 2591–2601. http://doi.org/10.1242/jcs.082727