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THE PLASMA MEMBRANE CALCIUM ATPases AND THEIR ROLE AS MAJOR NEW PLAYERS IN HUMAN DISEASE

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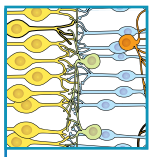

Stafford N, Wilson C, Oceandy D, Neyses L, Cartwright EJ. The Plasma Membrane Calcium ATPases and Their Role as Major New Players in Human Disease. *Physiol Rev* 97: 1089–1125, 2017. Published May 31, 2017; doi:10.1152/physrev.00028.2016.—The Ca^{2+} extrusion function of the four mammalian isoforms of the plasma membrane calcium ATPases (PMCAs) is well established. There is also ever-increasing detail known of their roles in global and local Ca^{2+} homeostasis and intracellular Ca^{2+} signaling in a wide variety of cell types and tissues. It is becoming clear that the spatiotemporal patterns of expression of the PMCAs and the fact that their abundances and relative expression levels vary from cell type to cell type both reflect and impact on their specific functions in these cells. Over recent years it has become increasingly apparent that these genes have potentially significant roles in human health and disease, with PMCAs1-4 being associated with cardiovascular diseases, deafness, autism, ataxia, adenoma, and malarial resistance. This review will bring together evidence of the variety of tissue-specific functions of PMCAs and will highlight the roles these genes play in regulating normal physiological functions and the considerable impact the genes have on human disease.

I. INTRODUCTION

The presence of an ATP-dependent Ca^{2+} transporter located in the plasma membrane was first identified in erythrocytes half a century ago (327). The plasma membrane calcium ATPase (PMCA) has since been classified as a member of the P-type transport ATPase family, due to the covalent intermediate state that is formed upon phosphorylation of a highly conserved aspartate residue during its catalytic cycle (285). The pumps are high affinity (0.2–0.5 μM under optimal conditions) Ca^{2+} extruders, binding a single intracellular Ca^{2+} ion which is then deposited to the extracellular space following conformational changes which first allow transport of the ion through the plasma membrane and finally dissociation from the pump through lowering its Ca^{2+} affinity (44, 225). This means that compared with the related ATPase of the sarco(endo)plasmic reticulum (SERCA), the PMCA has a lower capacity for Ca^{2+} clearance, removing only one Ca^{2+} ion per ATP molecule hydrolyzed as opposed to two (143). PMCA's export of Ca^{2+} occurs in conjunction with the import of one or more protons (H^+), with reports ranging from an electrogenic <1 to ~3 H^+ per Ca^{2+} in barnacle skeletal muscle to an electroneutral $1Ca^{2+}$:$2H^+$ stoichiometry in human erythrocyte membrane preparations and snail neurons (93, 264, 371).

There are four known PMCA isoforms, encoded by separate genes *ATP2B1-4* located at human chromosomal loci 12q21-q23, 3p25-p26, Xq28, and 1q25-q32, respectively (358). In the mouse, a model which has been extensively used to understand the functional roles of the PMCAs, these four genes are located on chromosomes 10, 6, X, and 1, respectively. In both humans and mouse, the PMCAs 1–4 exhibit differential spatial patterns of expression, with isoforms 1 and 4 being more or less ubiquitous, while PMCA2 and 3 expression is restricted to specific cell types, most notably in the nervous system. In addition, a total of over 25 splice variants have been identified, including the more or less ubiquitous full-length "b" variants deemed to play housekeeping functions, and many others which show cell specific distributions (147, 353, 358). This has led to the consensus that each isoform and variant may perform unique functions.

II. PMCAs: THE RELATIONSHIP BETWEEN STRUCTURE AND FUNCTION

This review article focuses its attention on the PMCAs in human health and disease and our current understanding of their physiological and pathophysiological roles. By way of introducing the PMCAs, we provide an overview of the structure of the PMCA isoforms and their regulation, but for more extensive and detailed information, we refer the

reader to a number of excellent published reviews (51, 94, 358).

A. The Structure of PMCA

The general structure of the PMCA, like other members of the P-type ATPase family, consists of 10 hydrophobic transmembrane (TM) domains flanked by cytosolic NH_2 and COOH terminals, and with two large intracellular loops (94, 358). More specifically, the PMCAs belong to the type II subset of P-type ATPases which include a number of proteins of physiological/pathophysiological importance in vertebrates due to their roles in the movement of a variety of ions across membranes. The NH_2 terminal of the PMCA contains the most variation among isoforms in its 80–90 amino acids. The two intracellular loops span TM domains 2–3 and 4–5, and each contains an autoinhibitory region that interacts with a calmodulin-binding site located on the long COOH terminal rendering the PMCA in a closed conformation in the absence of calmodulin and greatly reducing its Ca^{2+} affinity (116, 117). The second intracellular loop contains the catalytic core of the pump, featuring conserved aspartate and lysine residues critical for catalytic phosphorylation and ATP binding, respectively.

The determination of the complete nucleotide sequence for the PMCA by two groups in the late 1980s began to clarify the structure of the enzyme (346, 387). The gene products among these isoforms share ~75–85% identity, while ~85–90% of the primary sequence is conserved (356). Importantly, rodent and human isoforms share ~99% sequence homology making rodents a suitable model in which to study PMCA function. The regions of the PMCA displaying least identity among isoforms are the NH_2 and COOH terminals (58, 357), which may be of note as the COOH terminal is especially rich in interaction partners (see sect. II*D*).

B. Regulation of PMCA Activity

The major regulator of pump activity is calmodulin (CaM), which upon binding to its domain releases autoinhibition and raises pump Ca^{2+} affinity to sub-micromolar levels rendering it active at cellular concentrations and increasing pump activity four- to sixfold (107, 112). CaM affinity is 5- to 10-fold higher in neuronal isoforms PMCA2 and 3 compared with the ubiquitous PMCA1 and 4 (44), while PMCA2 displays unusually high basal ATPase activity in the absence of CaM compared with other isoforms (107). Interestingly, there is evidence that the erythrocyte PMCA exists as both a CaM-activated monomer as well as in a Ca^{2+}-dependent dimeric form which is fully activated in the absence of CaM (64, 190, 191). To date, there are no reports as to whether the self-activated oligomeric form is present in other cell types.

Further mediators of pump activation have also been identified including the action of acidic phospholipids, unsaturated fatty acids, and trypsin-mediated partial proteolysis of the enzyme (263). In addition, a rise in basal activity has been witnessed upon phosphorylation of the PMCAs by protein kinase C (PKC) (113) and, in the case of PMCA1, protein kinase A (PKA) (142).

C. PMCAs and Regulation of Global and Local Intracellular Ca^{2+}

Every cell type has unique requirements for optimal Ca^{2+} homeostasis to perform their respective physiological functions. This can range from the maintenance of a low resting intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) to prevent the activation of Ca^{2+}-mediated cell death to dynamic control of beat-to-beat Ca^{2+} levels in cardiomyocytes enabling muscle contraction and relaxation. In nonexcitable cells where the resting intracellular Ca^{2+} levels remain low, the PMCA is generally the principal Ca^{2+} removal system (423); however, excitable cells such as myocytes and neurons with their more complex needs for Ca^{2+} extrusion demand higher capacity systems for cytosolic Ca^{2+} clearance. In excitable cells, the three main pathways for removal of cytosolic Ca^{2+} are via reuptake into the sarco(endo)plasmic reticulum via SERCA (221), and extrusion from the cell via the PMCA and the high capacity sodium-calcium exchanger (NCX) (45, 96), as illustrated in **FIGURE 1*A***. The relative contributions of these three pathways to Ca^{2+} clearance vary depending on cell type. In bladder smooth muscle for example, these are roughly 2:1:1 in favor of the NCX (138), whereas in cardiomyocytes, 70–92% of Ca^{2+} (dependent on species) is returned to the internal store via SERCA with the remainder largely extruded via the NCX, leaving the PMCA along with a small amount of mitochondrial reuptake, together coined the "slow systems," to contribute little more than 1% to global Ca^{2+} clearance (26).

The PMCA is not only involved in global Ca^{2+} homeostasis however, but also in the regulation of local intracellular Ca^{2+} dynamics. Similarly to transient receptor potential canonical (TRPC) channels and inositol 1,4,5-trisphosphate receptors ($InsP_3Rs$), which have been shown to activate Ca^{2+}-dependent effectors through generating high Ca^{2+} microdomains at the subplasmalemmal and perinuclear compartments, respectively (104, 406), the PMCA is able to regulate downstream signaling pathways. In the case of the PMCA, this is achieved through pump activity lowering the $[Ca^{2+}]$ in its microdomain, thereby negatively regulating Ca^{2+}-dependent interaction partners as illustrated in **FIGURE 1*B***.

To gain an understanding of how the PMCA can influence local Ca^{2+} dynamics and to directly monitor PMCA activity, we have recently developed a novel fusion protein by cloning the genetically encoded Ca^{2+} indicator GCaMP2 to

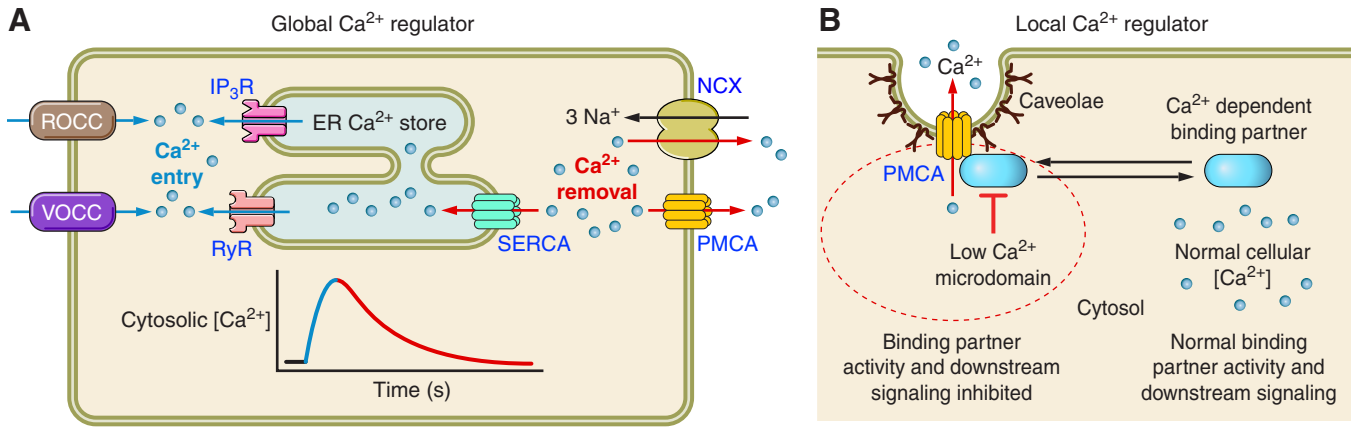

FIGURE 1. *A*: cartoon illustrating global Ca^{2+} regulation in an excitable cell. The sources of Ca^{2+} entry to the cytosol and associated rise in global intracellular Ca^{2+} are highlighted in blue, while routes for cytosolic Ca^{2+} clearance and associated decay phase of the global transient are highlighted in red. *B*: diagram demonstrating regulation of local Ca^{2+} and Ca^{2+}-dependent signaling by PMCA. PMCA activity generates a low Ca^{2+} microdomain in its vicinity, negatively regulating Ca^{2+}-dependent binding partners by attracting them to its locale in caveolae, thereby influencing downstream signaling. VOCC, voltage-operated Ca^{2+} channel; ROCC, receptor-operated Ca^{2+} channel; IP3R, inositol trisphosphate receptor; RyR, ryanodine receptor; SERCA, sarco(endo)plasmic reticulum Ca^{2+}-ATPase; PMCA, plasma membrane Ca^{2+}-ATPase; NCX, Na^{+}/Ca^{2+} exchanger.

the NH_2 terminal of PMCA4. Upon transfection into cardiomyocytes, the PMCA4-GCaMP2 fusion protein was able to detect Ca^{2+} oscillations in the subsarcolemmal compartment which could be inhibited by specific pharmacological blockade of PMCA4, thus providing us with a tool to assess Ca^{2+} dynamics in the local vicinity of PMCA4 (241). It is clear therefore that the PMCAs can regulate both global and local intracellular Ca^{2+} levels depending on tissue type and PMCA isoform, while through the import of H^{+} and hydrolysis of ATP they may also influence subplasmalemmal pH and ATP concentration (85, 93, 372). This regulation of local Ca^{2+} lends itself to the PMCA being a major mediator of Ca^{2+}-dependent signaling events (59, 267) as we will describe in the following section.

D. PMCAs as Signaling Molecules via Interactions With Protein Partners

Amidst large fluctuations in global Ca^{2+} during excitation-contraction coupling, excitable cells retain the ability to utilize Ca^{2+} as a second messenger in many signaling pathways involved in both normal physiological function and in disease progression (126). Over recent years the PMCA has emerged as a significant regulator of Ca^{2+}-dependent signaling, through protein-protein interactions and compartmentalization of the signal in the subplasmalemmal microdomain (267). A possible role in signal transduction was suggested based on evidence that PMCA4 is localized in protein-rich signaling hubs termed caveolae (128).

In subsequent years, our group and others have identified many PMCA interaction partners, some of which are common to all PMCAs and others unique to particular isoforms (FIGURE 2). Many of these interactions occur at a PDZ ligand-binding domain located at the terminal end of the carboxyl tail. Interacting partners at this domain include members of the membrane-associated guanylate kinase (MAGUK) family, calcium/calmodulin-dependent serine protein kinase (CASK), LIM family protein CLP36, homer protein Ania-3, PMCA-interacting single-PDZ pro-

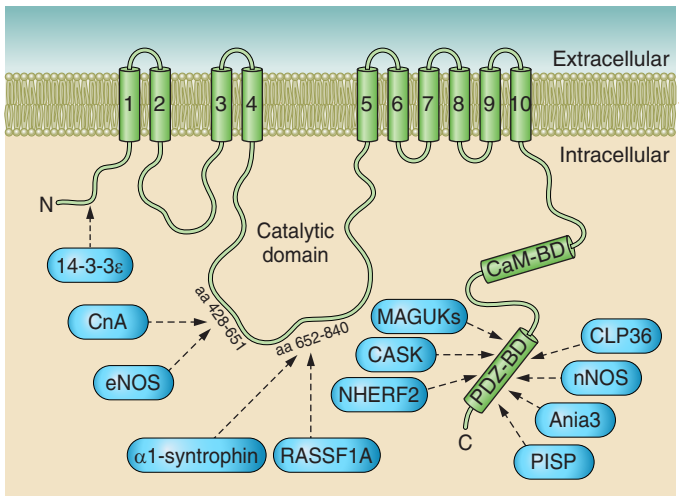

FIGURE 2. Schematic illustrating general PMCA structure, consisting of 10 transmembrane (TM) domains. The intracellular loop connecting TM 4 and 5 contains the catalytic core with phosphorylation and ATP binding sites. PMCA interaction partners are shown, with arrows detailing to which regions they bind. CnA, calcineurin A; eNOS, endothelial nitric oxide synthase; RASSF1A, Ras-associated factor 1A; NHERF2, Na/H exchanger regulatory factor 2; CASK, calcium/calmodulin-dependent serine protein kinase; MAGUK, membrane-associated guanylate kinase; PISP, PMCA-interacting single-PDZ protein; nNOS, neuronal nitric oxide synthase; PDZ-BD, PDZ protein-binding domain; CaM-BD, calmodulin-binding domain.

tein (PISP), Na/H exchanger regulatory factor 2 (NHERF2), and neuronal nitric oxide synthase (nNOS) (39, 91, 92, 137, 182, 334, 335, 339). We have found the PMCA4-nNOS interaction to occur in a macromolecular complex with α-1 syntrophin and dystrophin, through binding a linker region on α-1 syntrophin to the PMCA's second intracellular loop (395). Further interactions in this catalytic region of the PMCA occur with the Ca^{2+}-dependent phosphatase calcineurin, the tumor suppressor Ras-associated factor 1A (RASSF1A), and endothelial nitric oxide synthase (eNOS) (13, 46, 158). Meanwhile, isoform ε of the trafficking protein 14-3-3 has been found to associate with PMCA4's NH_2-terminal region (312). As we describe later in this review, some of these interactions have now been well characterized to be of functional significance, in particular those between PMCA and nNOS in the cardiovascular system, and PMCA and calcineurin in cardiovascular and breast cancer cells (61, 160).

It may in part be through the individualities of these interactions that isoforms can perform specific functions. For example, in identifying an inhibitory interaction between 14-3-3ε and PMCA4, Carafoli and colleagues noted no association with PMCA2 (312). Similarly, while Strehler and colleagues found both isoforms 2 and 4 to interact with MAGUK family proteins, some family members bound selectively to PMCA4 (92), while NHERF2 interacts only with PMCA2 (91). These differences in the biochemical properties of the pumps mean that the various PMCA isoforms perform cell-specific roles, not only in health but also in human pathophysiology. The remainder of this review will focus on the tissue-specific physiological roles and disease associations of the PMCA pumps.

III. PMCA AND ITS ASSOCIATIONS WITH HUMAN DISEASE

In recent years, the relevance of the PMCA in a number of human disease processes has come to light. Through examination of whole genomes among populations it is now possible to identify particular genetic variants associated with a certain disease. Following extensive data analysis, genome-wide association studies (GWAS) can detect particular disease-causing single nucleotide polymorphisms (SNPs) located within specific loci in the genome. Genetic mutations in the genes encoding each PMCA isoform have now been associated with human disease (**Table 1 and FIGURE 3**), highlighting the significance of this family of Ca^{2+} pumps in human health and disease.

A. PMCA1, Hypertension, and Cardiovascular Disease

Worldwide more people die from cardiovascular diseases (CVD) than any other cause. Currently, over 30% of all deaths are attributed to CVD, and despite the size of the ongoing research focus, the World Health Organisation predicts that by 2030 the number of people that will die annually from this group of diseases will rise to ~22 million (1). Hypertension, which is a major risk factor for cardiovascular disease, affects ~30% of the adult population worldwide (201) and has long been thought to be influenced by genetic factors as well as environmental ones. In the past 5 years, GWAS of systolic and diastolic blood pressure, as well as hypertension in general, have reported the most significant SNPs associated with these diseases to occur at multiple loci in and around *ATP2B1*, the gene which encodes PMCA1 (76, 173, 178, 206, 366). This finding is consistent among multiple ethnicities including those of East Asian (Japanese, Korean and Chinese), South Asian, and European origin; however, the two studies carried out in African-American populations showed no association between *ATP2B1* and hypertension. Although the effects of *ATP2B1* variants on systolic and diastolic blood pressure are small at around 1 mmHg (105), Levy et al. (206) predicted the risk of developing hypertension to increase by 17 and 37% dependent on whether one or two respective alleles are affected. This finding of an association between *ATP2B1* and hypertension is not just limited to adults as one study has determined that the *ATP2B1* SNP rs2681472 is associated with an increased risk of hypertension in Chinese children (407), while the same SNP also predisposes Chinese women to early-onset pre-eclampsia during pregnancy (389). Using a gene-centric array in which ~50,000 SNPs in 2,100 genes previously implicated in cardiovascular, metabolic, and inflammatory processes, Fontana et al. (124) demonstrated a strong association between SNP rs12817819 in *ATP2B1* and resistant hypertension, a condition in which raised blood pressure is not controlled despite the use of at least three antihypertensive drugs.

It is beginning to emerge that it may be a reduction in the expression of *ATP2B1* which leads to raised blood pressure. Human umbilical artery smooth muscle cells carrying the risk allele of the *ATP2B1* SNP rs11105378 were found to have reduced *ATP2B1* mRNA expression (364). Studies in transgenic mice are also beginning to provide functional evidence of the role of *ATP2B1* in blood pressure control, with PMCA1 silencing leading to the development of hypertension associated with an increase in intracellular Ca^{2+} and vascular remodeling (187, 343).

Hypertension is not the only cardiovascular disease to be linked by genetic association and candidate gene studies with *ATP2B1*. A number of studies have now identified SNPs in the *ATP2B1* locus to carry increased risk of developing coronary artery disease in Asian and Caucasian populations (219, 367, 394) and myocardial infarction (119), while mutations also associate with several cardiovascular disease risk factors such as salt sensitivity

Table 1. *Reported SNPs in ATP2B isoforms and their association with disease phenotypes*

SNP	Disease Association	Ethnicity	Reference Nos.
ATP2B1-PMCA1			
rs1401982	Hypertension, SBP, DBP, arterial stiffness	Chinese	391
rs2070759	Hypertension	Japanese	364
rs2681472	Hypertension, SBP, DBP	Japanese	366
	SBP, DBP	European	206
	Salt sensitivity	Korean	309
	Preeclampsia	Han Chinese	389
	Coronary artery disease	East Asian	367
rs2681492	SBP, DBP	European	206
	Hypertension, SBP, DBP, arterial stiffness	Chinese	391
	MAP, PP	East Asian	180
rs7136259	Coronary artery disease	Han Chinese	219
rs10858911	Hypertension, SBP, DBP, arterial stiffness	Chinese	391
rs11105354	SBP, DBP	European	206
	Hypertension, SBP, DBP, MAP	European	173
	Coronary artery calcification in chronic kidney disease	European/African	119
	Myocardial infarction	European/African	119
rs11105378	Hypertension	Japanese	364
rs12817819	Resistant hypertension (in patient groups with CAD or ischemic HD)	European American and Hispanics	124
rs17249754	Hypertension, SBP, DBP, arterial stiffness	Chinese	391
	Hypertension, SBP, DBP	East Asian, South Asian, African	105
	Hypertension, SBP, DBP	Korean	162
	SBP, DBP	Asian	76
	Hypertension	Chinese children	407
	Hypertension, SBP, DBP	Chinese	220
	MAP, PP	East Asian	180
	Obesity and hypertension in children	Han Chinese	408
	Coronary artery disease	European	213
	Hyperlipidemia and diabetes	Korean	152
ATP2B2-PMCA2			
rs35678	Autism	European (Italian)	52
rs241509	Autism spectrum disorders	European (Italian)	296
rs3774179	Autism	Han Chinese	414
ATP2B4 - PMCA4			
rs4951074	Malaria in children	African	373
	Severe malaria/cerebral malaria/severe malarial anemia	African	314a
rs10900585	Malaria in pregnancy	African	21
	Malaria in children	African	373
	Severe malaria/cerebral malaria/severe malarial anemia	African	314a

SNP, single nucleotide polymorphism; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; CAD, coronary artery disease; HD, heart disease.

and coronary artery calcification in chronic kidney disease (119, 309).

These data combined demonstrate the importance of PMCA1 in human health and its potential role in cardiovascular disease, and together suggest that PMCA1 may play a critical role in Ca^{2+} clearance and homeostasis in vascular smooth muscle and/or endothelial cells.

B. PMCA2, Hereditary Deafness, and Autism

Hearing loss is known to be caused by both genetic and environmental factors and likely often a combination of the two. One of many genes that have been associated with deafness is *ATP2B2*, the gene that encodes PMCA2. Mutations in PMCA2 have been identified by two studies of

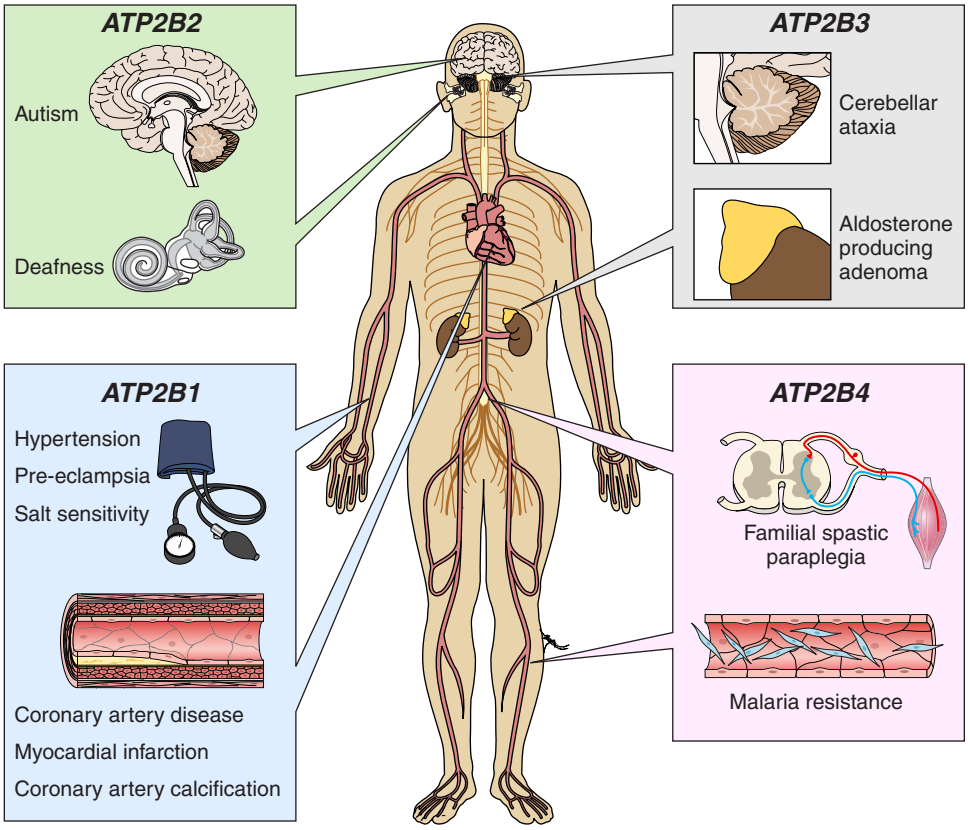

FIGURE 3. Cartoon depicting the diseases that have presently been found to be associated with genetic variants of each of the four PMCA isoforms in humans. Human disease associations of ATP2B1 are shown in blue, ATP2B2 in green, ATP2B3 in gray, and ATP2B4 in pink.

families with hereditary hearing loss (123, 336). While the mutations identified in each family were different, in both cases the mutation seems to potentiate the effects of a mutation in the cadherin23 gene, resulting in severe hearing impairment. Studies in a number of mouse mutants appear to corroborate the fact that PMCA2 is essential for normal hearing function: the first of these was a mouse line known as "deafwaddler," which as the name suggests has both deafness and motor imbalance. The mutation, which arose spontaneously, leads to a single point mutation in PMCA2 resulting in an amino acid change which affects sensory transduction in hair cells of the inner ear, in addition to neurotransmitter release from the basolateral membrane (355). A second spontaneous mutant known as "wriggle mouse sagami" also carries a PMCA2 point mutation, which differs from that of deafwaddler, and again results in hearing loss (365). Over the subsequent years other spontaneous mutations were identified, a gene knockout was generated, and a number of ethylnitrosourea (ENU) mutagenesis screens were performed which identified mutations in *Atp2b2* leading to deafness (38, 192, 236, 350, 410). The most recent of these ENU mutagenesis screens revealed two novel mutants of *Atp2b2*, one carrying a mutation in the 10th transmembrane domain and the other with a mutation in the catalytic core, both of which resulted in mild to moderate, progressive hearing loss in the heterozygous mutants and profound deafness in the homozygotes (56).

Recent links have also been made between PMCA2 and autism as a result of GWAS and candidate gene studies. Autism is a neurodevelopmental disorder with multiple genetic causes and an extremely high level of heritability. GWAS identified a number of chromosomal regions to have linkage to autism, including the region 3p25, where *ATP2B2* (as well as a number of other genes) is located (200, 235, 341). In a subsequent study comparing the gene expression profiles of lymphoblasts from autistic and nonaffected sibling pairs, *ATP2B2* was the only gene found to be differentially expressed of the 43 known genes in the identified region at 3p25 (164). Using Ingenuity Pathway Analysis, Hu et al. (164) identified that differential expression of *ATP2B2* may affect nervous system development and function via altering Purkinje cell morphology, cerebellar development, or synapse biogenesis. Intracellular Ca^{2+} levels and Ca^{2+}-signaling pathways are indeed important in the regulation of neuronal survival, differentiation, migration, and synaptogenesis, and it is likely that perturbations in these processes may play a role in the pathogenesis of autism spectrum disorders (193).

Based on this evidence, Carayol et al. (52) carried out a family-based association study that identified a number of SNPS in *ATP2B2* as having a significant association with autism in males only. Further studies have identified SNPs in *ATP2B2* as being associated with autism and autism

spectrum disorders in Italian families and in those of Han Chinese descent (296, 414).

C. PMCA3, Cerebellar Ataxia, and Adenoma

ATP2B3 mutations have been linked to two separate diseases affecting different organs. One was identified in a family with X-linked cerebellar ataxia, where three out of three descendants of a carrier female were found to be either affected (males) or a carrier (female) (420). The mutation, which was identified by exome sequencing, was found in the calmodulin binding domain of PMCA3, which was found in in vitro studies to impair Ca^{2+} clearance in cell culture. Calì et al. (50) have identified another mutation of *ATP2B3*, which results in a missense mutation and impaired Ca^{2+} extrusion, in a patient with cerebellar ataxia and developmental delay. The patient not only carried a PMCA3 mutation but also two mutations in *LAMA1*, the gene encoding laminin 1α, and it may be that the observed disease phenotype is dependent on simultaneous mutations in both of these genes.

Given the predominant expression of PMCA3 in the nervous system, including the cerebellum where it has a role in neuronal Ca^{2+} homeostasis, the association with cerebellar ataxia is not unexpected. However, what is more surprising is that two novel *ATP2B3* mutations have recently been found in tissue from a number of aldosterone-producing adenomas (APAs), a major factor in the development of primary aldosteronism which is the most common cause of secondary hypertension (27). Since Beuschlein et al.'s first report in 2013 (27), *ATP2B3* mutations have been identified in APAs present in western European, Japanese, Taiwanese, Chinese, and American populations occurring at frequencies ranging from 0.6 to 9% (6, 102, 121, 186, 272, 330, 331, 396, 404, 422). With the exception of one Taiwanese patient who exhibited a Tyr410Asp substitution (404), all mutations identified thus far involve the deletion of one or more amino acids between Thr-423 and Leu-433 lying in the M4 region of the plasma membrane, believed to be important in Ca^{2+} binding during its transport to the extracellular space. Clinically APAs containing *ATP2B3* mutations are associated with higher levels of aldosterone secretion when compared with wild-type APAs (27, 186, 397), most likely as a result of an observed increase in aldosterone synthase CYP11B2 expression (250, 254, 396). Recently these associations have been confirmed through the transfection of *ATP2B3* carrying the common Leu425_Val426 deletion into adrenocortical NCI-H295R cells, resulting in impaired Ca^{2+} clearance accompanied by elevated basal Ca^{2+}, CYP11B2 expression, and aldosterone secretion (370). This highlights a highly specialized function for this isoform in nonneuronal tissue.

D. PMCA4, Malarial Resistance, and Familial Spastic Paraplegia

The Ca^{2+}-ATPase of the membrane of erythrocytes was the first to be characterized, and has since been found to consist predominately of PMCA4 (352). Recently a GWAS identified a novel locus within *ATP2B4* where several SNPs conferred resistance to a severe form of malaria among children in a West African population (373). One of the SNPs identified in this study was also shown to confer protection against malaria and associated maternal anemia in pregnant Ghanaian women (21), which may make PMCA4 an interesting target for anti-malarial medication (246). This association between PMCA4 and malaria was strengthened by the findings of a large multi-center study in which several *ATP2B4* SNPs were analyzed in ~12,000 cases of severe malaria from 12 different locations in Africa, Asia, and Oceania (224).

A single nucleotide variant of *ATP2B4* which results in a missense mutation has been found in a Chinese family with familial spastic paraplegia, a disease leading to muscle weakness and spasticity of the lower limbs (212). In a subsequent study, the authors have demonstrated that this mutation in *ATP2B4* results in altered Ca^{2+} homeostasis, perhaps suggesting a link between disrupted Ca^{2+} regulation and familial spastic paraplegia (156).

IV. TISSUE-SPECIFIC FUNCTIONS OF THE PMCAs

It can be said that PMCA is ubiquitously expressed, with all cell types expressing at least one isoform of this gene family. The level, localization, and temporal nature of the expression of the PMCAs likely reflect their specific functional roles during embryonic development and in the adult in both health and disease.

In situ hybridization has provided evidence that PMCA1 is expressed by day 9.5 post coitum (pc) in the developing mouse embryo and is abundant and ubiquitous thereafter, although most concentrated in the heart, nervous system, skeletal muscle, and intestine (415). All four isoforms are expressed by day 12.5 pc, with PMCA2 confined to the brain and PMCA3 to the nervous system, lung, and skeletal muscle. PMCA4 expression is ubiquitous though less abundant than PMCA1, with the strongest expression found in the brain, bladder, heart, and spinal cord (415). The early and widespread nature of PMCA1 expression has led to the opinion that this isoform is the major housekeeping isoform.

The ubiquitous pattern of PMCA1 expression persists after birth and throughout adulthood in both rat and human, while PMCA4 is also present in most cells. The ratio of PMCA1 expression to that of isoform 4 is roughly 2:1 in

human adult lung, liver, kidney, stomach, and skeletal muscle (353). In the heart, however, the ratio between the two isoforms is roughly 1:1. PMCA2 demonstrates a more specific expression pattern, being prominent in Purkinje and inner ear cells, as well as in lactating mammary glands, while isoform 3 expression is restricted largely to neurons in the neonate and adult (358).

A. Role of PMCAs in the Development of the Embryo

Of the two largely ubiquitously expressed isoforms of PMCA (PMCA1 and 4), PMCA1 has been given the status of the housekeeping isoform based on the fact that it is the isoform to be expressed earliest in the development of the embryo; that it is widely expressed in both the embryo and the adult; and that its deletion leads to embryonic lethality. Other than the fact that there are no live births of PMCA1 knockout mice, we currently know little of the role of PMCA1 during development. The same is also true of the other PMCA isoforms; PMCA2 and PMCA4 knockout mice are viable, and while they are both expressed during development, their role has not been studied and we know even less of PMCA3 as a knockout mouse has never been reported.

1. PMCA and the placenta

The transport of Ca^{2+} from mother to baby via the placenta is tightly regulated during pregnancy to ensure normal fetal development and in particular skeletal mineralization. PMCAs are among many Ca^{2+} handling pumps, channels, and exchangers that move Ca^{2+} across the placenta. The syncytiotrophoblast, which is a polarized epithelium with a maternal microvillus membrane and a fetal-facing basal membrane, is a critical site involved in this transfer of Ca^{2+} from the maternal to the fetal circulation (290). During this transepithelial transfer, Ca^{2+} enters the syncytiotrophoblast on the brush-border membrane via transient receptor potential vanilloid (TRPV) channels, from where it is carried to the fetal side of the syncytiotrophoblast by Ca^{2+}-binding proteins, and then extruded by the PMCAs. The importance of the PMCAs in this process is evident, as ATP-dependent Ca^{2+} transport increases linearly across the syncytiotrophoblast basal membrane during the third trimester of pregnancy in line with the demand for fetal skeletal mineralization (360), and the level of PMCA3 gene expression correlates with the level of bone mineral content in newborn babies (232).

Given this vital role in materno-fetal Ca^{2+} transfer, it is no surprise that alterations in PMCA activity and expression have been witnessed in pregnancies complicated by a number of diseases. As already mentioned, the common SNP rs2681472 in *ATP2B1* has been associated with the risk of early-onset preeclampsia, a leading cause of maternal and fetal mortality, preterm labor, and intrauterine growth restriction present in ~5% of pregnancies (389). Myometrial and subcutaneous resistance arteries from preeclamptic women display impaired relaxation and PMCA attributable Ca^{2+} clearance (398) while preeclamptic myometrium and syncytiotrophoblasts display a 50% reduction in PMCA activity and reduced PMCA1 and 4 expression (57, 145). In addition to changes during preeclampsia, altered ATP-dependent Ca^{2+} transport has also been witnessed in the placenta in pregnancies complicated by intrauterine growth restriction and insulin-dependent diabetes mellitus (359). These observations highlight the importance of the PMCA in tightly regulating Ca^{2+} transport between the mother and fetus.

2. PMCA and the spermatozoa

As in many cell types, Ca^{2+} is essential for the regulation of a number of functions of the spermatozoa, including motility, the acrosome reaction, and fusion of sperm and egg membranes (83). The PMCA, by acting as an extrusion pump, is known to provide tight control of intracellular Ca^{2+} levels which is required for normal sperm function and hence male fertility. While both PMCA1 and PMCA4 are expressed in spermatozoa, it has been shown that PMCA4 is the predominant isoform and is localized to the principal piece of the sperm tail (269). More recently it has been shown that in mouse sperm both major PMCA4 splice variants (PMCA4a and PMCA4b) are expressed throughout the sperm maturation process (283). Gene knockout studies have provided very clear evidence of the functional role PMCA4 has in sperm motility. Two separate mouse models in which PMCA4 has been deleted, our own model which carries a null deletion resulting in lack of expression of all PMCA4 splice variants (332), and that of Okunade et al. (269) which produces a functionally inactive mutant protein, both lead to male infertility as a result of impaired motility. Homozygous PMCA4 knockout mice are born at the expected Mendelian ratio when mice carrying a heterozygous PMCA4 deletion are bred; however, breeding of male and female PMCA4 KO mice did not result in any pups being born, even though mating behavior was normal. Investigations revealed sperm and testes morphology were normal, but assessment of parameters of motility showed a lack of progressive, directional, and hyperactivated motility (269, 332). Given that PMCA1 knockout mice are embryonic lethal, it cannot be ruled out that PMCA1 also has an important role in sperm motility, but mice carrying a heterozygous deletion of PMCA1 are not known to have impaired fertility (269).

B. Role of PMCAs in the Sensory Systems

Due to the nervous system being one of the only areas of the human body where all four PMCA isoforms are expressed, numerous studies have looked at the role of PMCA in neuronal health and disease. As previously mentioned, PMCA2 and PMCA3 have been established as being clinically related to

deafness and cerebellar ataxia, respectively (134, 420). Furthermore, PMCA has been reported to be involved in other sensory roles such as vision as well as numerous neuronal conditions associated with balance dysfunction and aging.

1. PMCA and the eye

PMCA isoform expression has been reported in various regions of the eye including lens epithelial cells (all PMCA isoforms), the corneal epithelium (all isoforms), lamina cribrosa cells of the optic nerve head (PMCA1 and 4), various cell types of the inner retina (all PMCA isoforms), and the photoreceptors (PMCA1, 2, and 4) (195, 226, 237, 369). For ease of navigation, the macrostructure of the eye is depicted in **FIGURE 4*A***.

The maintenance of low $[Ca^{2+}]_i$ levels in the lens against the very high concentration in the surrounding aqueous humor requires tight regulation over Ca^{2+} homeostasis, and the PMCAs are among the mechanisms involved in ensuring this control, thus preventing lens opacity (310) **(FIGURE 4*B*)**.

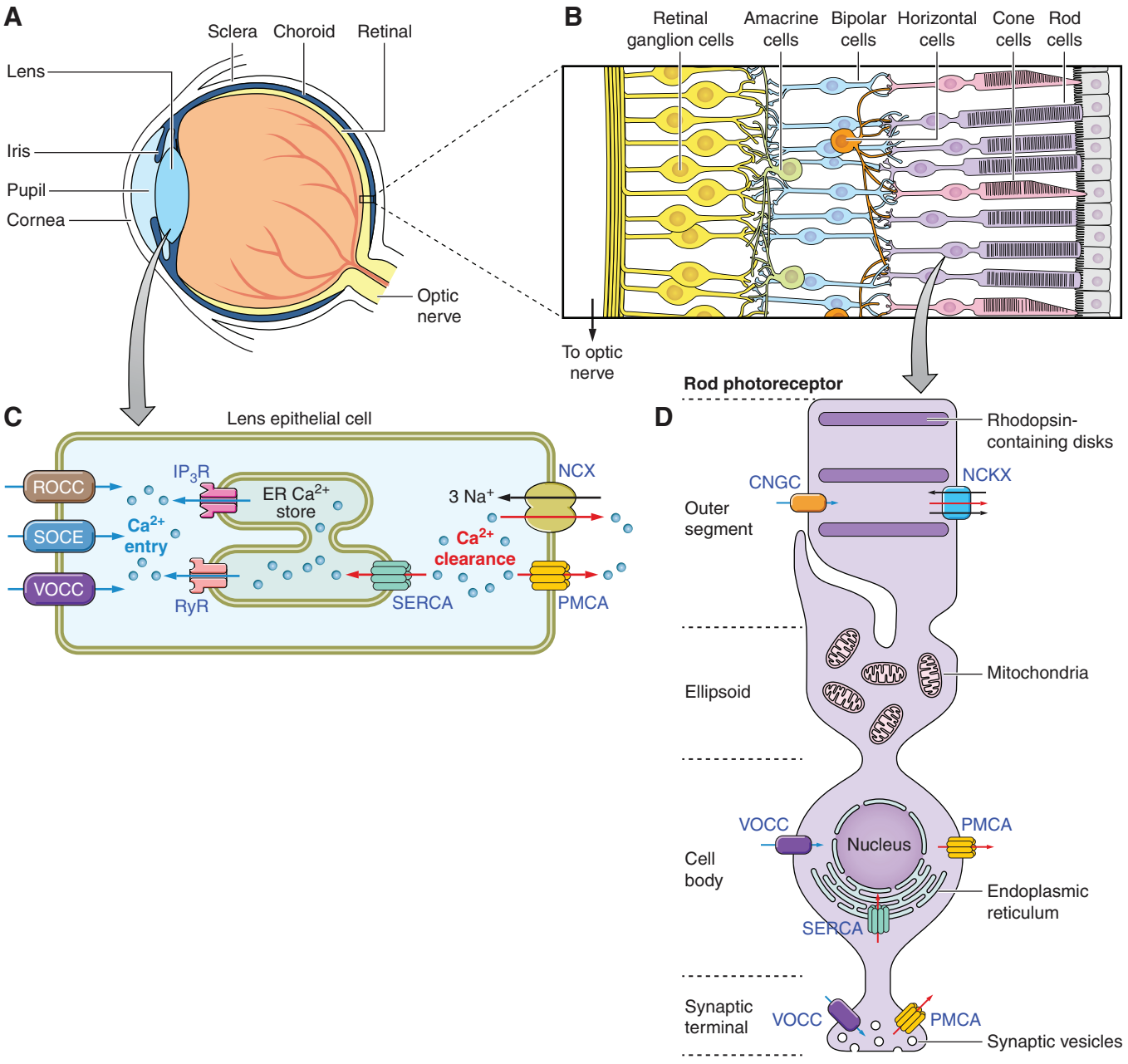

FIGURE 4. Cartoon illustrating the macrostructure of the eye (*A*) and the composition of the retina (*B*), in addition to the routes for cytosolic Ca^{2+} entry and clearance in a lens epithelial cell (*C*) and a rod photoreceptor (*D*). VOCC, voltage-operated Ca^{2+} channel; SOCE, store-operated Ca^{2+} entry; ROCC, receptor-operated Ca^{2+} channel; IP3R, inositol trisphosphate receptor; RyR, ryanodine receptor; SERCA, sarco(endo)plasmic reticulum Ca^{2+}-ATPase; PMCA, plasma membrane Ca^{2+}-ATPase; NCX, Na^+/Ca^{2+} exchanger; CNGC, cyclic nucleotide-gated Ca^{2+} channel; NCKX, $Na^+/K^+/Ca^{2+}$ exchanger.

The PMCA predominantly removes Ca^{2+} from lens epithelial cells, whereas expression is absent from fiber cells where the NCX takes on increased importance. It has been known for many years that intracellular Ca^{2+} is increased in cataractous lenses (100), and it is not surprising therefore that Ca^{2+}-ATPase activity is reduced by 50% in lenses from cataractous donors (284) despite a possibly compensatory upregulation in PMCA2 expression (227). Further evidence for a potentially protective role of the PMCA in cataract prevention has been found in cultured human lens epithelial cells exposed to two major factors involved in cataract development: an increase in PMCA1 expression was observed in response to raised $[Ca^{2+}]_i$ (228), and both PMCA1 and 2 expression increased in response to oxidative stress (229).

Altered PMCA expression has also been witnessed in glial fibrillary acid-negative protein lamina cribrosa cells of the optic nerve head obtained from donors with glaucoma, which play an integral role in characteristic extracellular matrix remodelling during this condition. Both PMCA1 and 4 expression were found to be reduced, accompanied by an elevation in $[Ca^{2+}]_i$, most likely due to increased oxidative stress (237).

All four PMCA isoforms are expressed in the human corneal epithelium, and while PMCA4 is the predominant isoform, it appears that each isoform localizes to specific cell layers, which perhaps reflects the different Ca^{2+} requirements across the epithelium (369). Isoform-specific functions in the cornea are largely unknown, although experiments using siRNA to knockdown PMCA4 in cultured human corneal epithelial cells suggest an important role in corneal wound healing (368).

Ca^{2+} plays myriad roles in the retina, the area of the eye that when hit by light begins the cascade of events which results in stimulation of the optic nerve, from light transduction in photoreceptors to subsequent neurotransmitter release from these and retinal neurons, in addition to its actions as a neuromodulatory intracellular second messenger (8). The retina is composed of rod and cone photoreceptors **(FIGURE 4*C*)**, with rod cells being of more abundance and higher sensitivity and cone cells being responsible for color vision. Early studies, in the tree shrew and salamander, suggested PMCA was crucial in regulating intracellular Ca^{2+} concentration at these photoreceptor terminals to allow the transmission of visual signals in the retina by providing the main Ca^{2+} extrusion pathway from inner segments and synaptic terminals of photoreceptor cells (194, 252) as highlighted in **FIGURE 4*D***. PMCA2 has since been identified to be heavily abundant in rod cells, but not cone cells, where it forms a complex with other proteins including membrane palmitoylated protein 4 (Mpp4) (413). Further animal studies suggested this restricted expression of PMCA2 in rod cells is related to visual signaling in this area of the eye. Mice lacking functional PMCA2 have significantly impaired rod-mediated signaling, with the level of light-evoked synaptic transmission being halved compared with control animals, possibly related to the loss of high-affinity Ca^{2+} extrusion causing synaptic delays (101). In addition, PMCA has been shown to regulate $[Ca^{2+}]_i$ in rod bipolar cell synaptic terminals both at rest and when stimulated, suggesting a role in adapting to background luminance (390). Finally, there has been a recent report that PMCA1 expression is reduced in the retina of diabetic retinopathy patients as well as fat-fed mice (69).

2. PMCA and the ear

The ear is one of the tissues in which we know most about the physiological role of the PMCA, with the cardiovascular system being the other area that has been widely studied, as will be described below. It is PMCA isoform 2 that is of great importance in hearing, with mutations in the protein or its complete loss resulting in impaired hearing or even deafness.

The inner and outer hair cells of the inner ear **(FIGURE 5*A*)** have an essential role in converting sound waves, which enter the cochlea, to electrical signals to be transmitted to the brain. The tight regulation of intracellular Ca^{2+} concentrations is governed by the mechanoelectrical transduction channels which bring Ca^{2+} into the cells and by PMCA2 which is involved in its extrusion **(FIGURE 5*B*)**. PMCA2 is expressed in specialized regions of the hair cells known as stereocilia that are present in bundles at the apical end of the cell from where they protrude into the endolymph; it is the movement of the stereocilia caused by vibration of the endolymph that leads to opening of the mechanoelectrical transduction channels and subsequent Ca^{2+} entry into the cell (as reviewed in Ref. 135). By extruding Ca^{2+} from the stereocilia to the endolymph, PMCA2 has a dual role: *1*) in maintaining the low $[Ca^{2+}]_i$ concentration required within the stereocilia and *2*) in supplying essential Ca^{2+} to the endolymph which influences the mechanical response of the stereocilia to vibrations (135). PMCA2 is localized to the stereocilia of both the inner and outer hair cells, where its expression progresses along the length of stereocilia in a temporal manner. At birth its expression is localized just to the base, then over a period of several days expression extends along the stereocilia all the way to the apex. This changing pattern of expression mirrors the maturation of the mechanoelectrical transduction channels (73). Using immunogold labeling, Chen et al. (73) were also able to determine that while PMCA2 was expressed on the inner hair cells it was present at a considerably higher density in all three layers of outer hair cells. PMCA2 is not the only isoform to be expressed in the sensory hair cells; the ubiquitously expressed PMCA1 is also expressed. It does however have a pattern of expression distinct from PMCA2 and has been found to be localized to the basolateral plasma membrane of the hair cells, suggesting specialized functions for the two isoforms within the hair cell (99, 139).

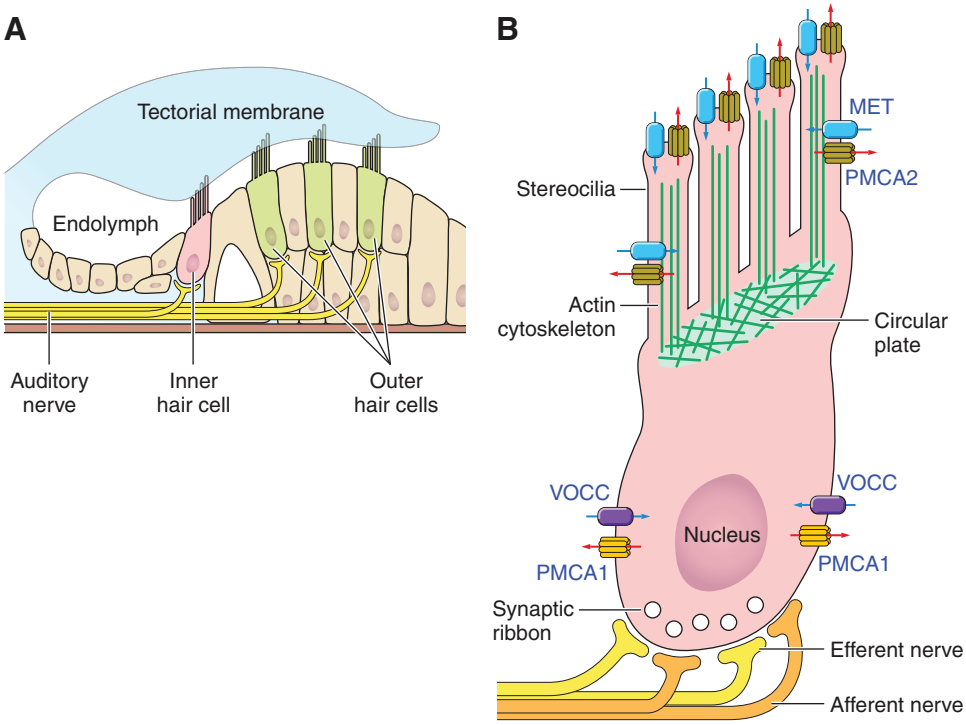

FIGURE 5. Cartoon illustrating the position of the hair cells of the cochlea within an organ of Corti (*A*) and sites of Ca^{2+} entry and PMCA-mediated extrusion in an inner hair cell (*B*), namely via PMCA2 in the stereocilia and PMCA1 at the basolateral membrane. VOCC, voltage-operated Ca^{2+} channel; MET, mechano-electrical transduction channel; 1, PMCA1; 2, PMCA2.

As has been described above, mutations in PMCA2 have been linked to deafness and hearing loss in humans and in genetically modified mice carrying a variety of PMCA2 mutations. Together this provides substantial support that PMCA2 is crucial in maintaining tight control of the Ca^{2+} concentrations required for the hair cells to perform their essential role in the hearing process (38, 123, 336, 355, 365, 392).

3. PMCA and the olfactory system

Initiation of excitation in olfactory sensory neurons (OSN; **FIGURE 6*A***) occurs upon binding of odorants to G protein-coupled receptors in the cilia, allowing Ca^{2+} entry through cAMP-gated channels and subsequent activation of Ca^{2+}-activated Cl^- channels (238) **(FIGURE 6*B*)**. Signal transduction occurs as the rise in $[Ca^{2+}]_i$ travels through the neuron from dendritic knob to dendrite to cell body, and subsequent removal of Ca^{2+} to basal levels terminates the signal (321). The PMCAs, in addition to NCX and the ER Ca^{2+} pump, are responsible for this Ca^{2+} clearance, and all four PMCA isoforms have been found to be expressed throughout mouse OSNs with the exception of PMCA3 which is absent from cilia and PMCA4 which has not been reported in the dendrite (393). Treatment of isolated toad OSNs with the PMCA inhibitor carboxyeosin significantly prolonged relaxation of whole cell current in the cilia and slowed Ca^{2+} clearance in mouse OSN knobs and cell bodies (62, 321). Saidu et al. (321) found inhibition of PMCA, SERCA, and NCX following OSN stimulation to each delay the rate constant of Ca^{2+} clearance by roughly 30%, suggesting a similar contribution for each system. While the specific function of each isoform has yet to be elucidated, OSNs isolated from PMCA2 knockout mice exhibited significantly impaired Ca^{2+} clearance following stimulation to an extent similar to total PMCA inhibition, suggesting a major role for this isoform (321).

C. Role of PMCAs in the Central Nervous System and Neurodegenerative Disease

Neuronal Ca^{2+} signaling has many unique functions, being critical to processes such as the regulation of synaptic transmission in the control of neurotransmitter release, and the formation and consolidation of memory (43). In addition, Ca^{2+} regulates processes common to other cell types such as differentiation and cell death. In vitro studies in pheochromocytoma cells have shown that knockdown of PMCA1 impairs neurite extension when stimulated with nerve growth factor (40), as does antisense oligonucleotide treatment of PMCA2 and 3 (362), suggesting a role for the PMCA in neuronal differentiation. There is also evidence for a role in the regulation of neuronal cell viability as pheochromocytoma cell survival is respectively improved or impaired by PMCA4 overexpression and knockdown under conditions of Ca^{2+} overload (131). Similarly, rat primary neurons and human SH-SY5Y neuroblastoma cells transfected with PMCA2 siRNA display increased levels of basal Ca^{2+} and impaired Ca^{2+} clearance following stimulation, and increased cell death upon exposure to excitotoxic concentrations of agents increasing $[Ca^{2+}]_i$ as well as the glutamate receptor agonist *N*-methyl-D-aspartic acid

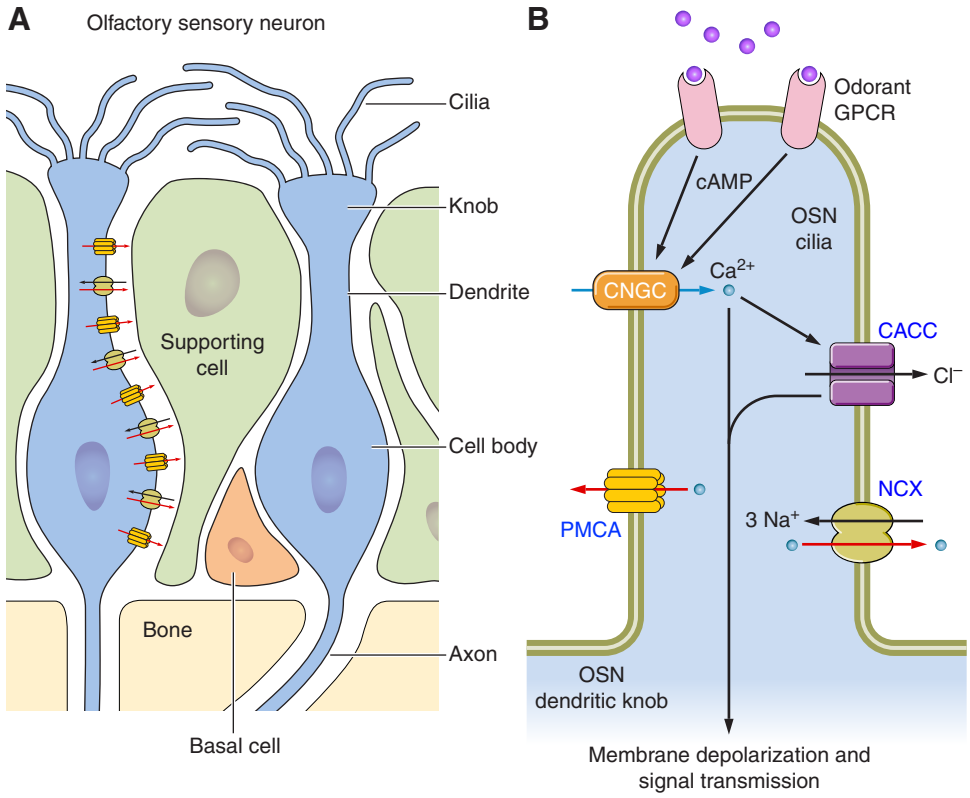

FIGURE 6. Cartoon illustrating the structure and routes for Ca^{2+} extrusion along an olfactory sensory neuron (*A*) and the mechanisms of excitation and Ca^{2+} extrusion in an OSN cilia (*B*). Following odorant binding to G protein-coupled receptors, generated cAMP activates Ca^{2+} entry via cyclic nucleotide-gated Ca^{2+} channels which in turn stimulates Ca^{2+}-activated Cl^- channels leading to membrane depolarization and signal transmission along the OSN. Extrusion of Ca^{2+} via PMCA and NCX terminates the signal.

(NMDA) (120). Furthermore, there is evidence that a number of neurotoxic agents cause proteolytic degradation of the PMCA in rat cortical cultures, highlighting a potential role in neurodegeneration caused by multiple etiologies (146). Specifically, PMCA1 and 2 expressions have been shown to be reduced in rat hippocampal pyramidal cells following kainate-induced seizures (130), and PMCA4 and 2 each shows displacement from the plasma membrane and internalization in rat hippocampal cells upon exposure to toxic concentrations of glutamate in association with reduced Ca^{2+} efflux (295). The following sections will further explore the associations of the PMCA with specific neurodegenerative diseases.

1. PMCA and cerebellar disorders

The cerebellar cortex, composed principally of Purkinje neurons, is the region of the brain predominantly involved in motor control and sensory perception. The PMCA in conjunction with NCX is responsible for precise control of local Ca^{2+} at excitatory parallel fiber-Purkinje neuron synapse terminals, thus modulating neurotransmitter release (316). Immunolocalization analysis of rat cerebellum suggests that isoforms display specific patterns of expression, with "neuronal" isoforms PMCA2 and 3 being predominately concentrated in post- and presynaptic terminals, respectively (48). In contrast, the "ubiquitous" isoforms are expressed at lower levels (47), where they may reside in lipid rafts of cerebellar granule neurons in association with NMDA receptors to regulate nitric oxide production (231).

As previously mentioned, two independent mutations in the PMCA3 gene affecting calmodulin binding and Ca^{2+} ejection, respectively, have been identified in patients presenting with cerebellar ataxia (50, 420); however, there is substantial evidence from PMCA2 mutant mice that this isoform is also critical to cerebellar function. PMCA2 is strongly expressed in Purkinje cells, and both pharmacological inhibition and genetic ablation of PMCA2 from Purkinje neurons impair dendritic growth (109, 342). Furthermore, in addition to the aforementioned hearing loss, PMCA2 null mutant mice display overt cerebellar ataxia apparent 12 days after birth accompanied by a severe inability to maintain balance and reduction in body weight (192). Similarly, the *wriggle mouse sagami* strain, which has a point mutation in the PMCA2 gene, displays involuntary dystonic movements of the extremities, writhing and wriggling of the trunk and neck, and difficulty maintaining an upright posture (166, 376). Mice with heterozygous inactivation of the gene, however, appear outwardly normal at rest, but experience abnormal coordination of the hindlimbs upon exercise (111).

Studies in these transgenic mice have identified a number of defects in cerebellar neuronal function and Ca^{2+} homeostasis. Cerebellar slices from *wriggle mouse sagami* for example display a smaller rise in $[Ca^{2+}]_i$ and impaired clearance following stimulation (376) in addition to a reduction in synaptic connections between parallel fibers and Purkinje dendritic spines (166). Purkinje neurons from PMCA2 knockouts meanwhile exhibit lower presynaptic Ca^{2+} ex-

trusion at these junctions, together with increased basal Ca^{2+} and impaired clearance, and increased firing of postsynaptic inhibitory neurons which contributes to reduced and irregular firing of action potentials in the Purkinje cells (108–110). The phenotype of the PMCA2 knockout mouse may be further exacerbated by the identification of a novel association with the metabotropic glutamate receptor 1 (mGluR1), known to play essential roles in motor coordination, synaptic plasticity, and associative learning, which is downregulated in the knockout cerebellum along with subsequent downstream signaling (197). While the phenotype in heterozygous null mutants is less overt, there are reports of impaired neuronal function in the Purkinje cells. These include increased amplitude and slower recovery times of Ca^{2+} transients, reduced firing frequency of action potentials, and loss of Purkinje cells by 20 wk of age (111, 115).

2. PMCAs in diseases of the spinal cord

There is a growing body of evidence to suggest that the PMCA may play a protective role in preventing spinal cord pathology. This may be highlighted by the finding that PMCA1 and 3 are both downregulated in brain lesions obtained from multiple sclerosis (MS) patients at autopsy (217). Work in the rat using the experimental autoimmune encephalomyelitis (EAE) model of MS, in which demyelination and subsequent ascending weakness and paralysis is induced through immunization by myelin injection into the foot, indicates a dramatic reduction in PMCA2 expression in spinal cord neurons in a pattern mirroring disease course, which becomes restored during recovery (261, 262). A similar downregulation of PMCA2 expression has also been witnessed upon exposure of spinal cord neurons to the glutamate receptor agonist kainate (198, 262).

Further evidence of a vital role for the PMCA in maintaining Ca^{2+} homeostasis and neuronal health in the spinal cord has been detected upon pharmacological inhibition in cultured rat spinal cord neurons. Kurnellas et al. (199) found the pan-PMCA inhibitor carboxyeosin delayed Ca^{2+} clearance with subsequent promotion of caspase activity and neuronal death. The authors also found PMCA2 knockout and functionally inactive *deafwaddler* mice to exhibit a significant loss of spinal cord motor neurons (199), with further exploration revealing that PMCA2 silencing in these cells reduced the expression of collapsing response mediator protein 1 (CRMP1) before neuronal degeneration (198). A recent study also suggests that PMCA2 and 3, in complex with NCX1 in lipid rafts, are critical for the function of the neuronal glycine transporter 2 (GlyT2), and hence regulating inhibitory glycinergic signaling, in brain stem and spinal cord neurons, disturbances which are known to be a major cause of the rare condition hyperekplexia (87).

3. PMCA and age-related neurological disorders

Advancing age often coincides with a progressive decline in neuronal function, thought to be largely driven by the actions of reactive oxygen species (ROS). PMCA activity and abundance declines substantially with age in synaptic plasma membranes from rats, as does the extent of PMCA activation by aged calmodulin (CaM) due to the oxidation of CaM methionine residues (172, 240, 418). Likewise, a range of oxidative agents have been shown to induce proteolytic degradation and a reduction of PMCA activity in rat synaptic membranes and cortical neurons (417, 419), as well as causing PMCA internalization and loss of expression in primary hippocampal neurons (184). Given the critical importance of the PMCA in maintaining $[Ca^{2+}]_i$, neuronal function, and viability, it is therefore highly likely that ROS-induced inactivation of the PMCA may contribute to age-related neurodegeneration.

In addition to the aging brain, PMCA expression and activity have also been shown to be reduced in the cortex of brains excised post mortem from patients with Alzheimer's disease (24, 25). Alzheimer's disease is characterized by an accumulation of amyloid β-peptide (Aβ) and tau protein, and studies have found each of these to have an inhibitory effect on PMCA activity in membrane vesicles from human hippocampus and cerebral cortex, with Aβ specifically affecting the PMCA4 isoform (24, 25, 230). Recent data suggest that PMCA activity may also be impaired in human brain tissue from Parkinson's disease patients (416), a disease characterized by loss of neurons in the substantia nigra region of the midbrain leading to insufficient dopamine secretion. This observation is supported by studies using the Parkinsonian mimetic 1-methyl-4-phenylpyridinium (MPP^+), which causes an increase in $[Ca^{2+}]_i$ and reduction in PMCA2 expression in SH-SY5Y cells and rat primary midbrain neurons (42). Interestingly Brendel et al. (42) also demonstrated that transfection of PMCA2 siRNA reduced neuronal viability while overexpression rendered cells resistant to MPP^+-induced toxicity.

Overall, there is a substantial body of evidence to suggest that multiple PMCA isoforms play a vital role in maintaining neuronal viability and synaptic function through precise regulation of Ca^{2+} homeostasis and local signaling. It may be that future therapies for excitotoxic and age-related neurodegeneration may look to stabilizing or restoring PMCA expression and function to prevent neuronal loss.

D. Role of PMCAs in the Cardiovascular System

1. PMCA and the heart

It is now well established that Ca^{2+} has a dual role in the heart: *1*) it is the driving force for myofilament contraction

and relaxation, and 2) it has the ability to regulate the intracellular signaling events, several of which dictate pathological cardiac remodeling associated with hypertrophy and heart failure.

With the bulk of intracellular Ca^{2+} being extruded from the cytosol into the sarcoplasmic reticulum (SR) of the cardiomyocyte by the SERCA and out of the cell via the NCX, the PMCAs make only a minor contribution to Ca^{2+} extrusion during diastole and consequently have traditionally been considered relatively insignificant in terms of normal Ca^{2+} homeostasis in the heart (26, 77, 266, 405).

The presence of two isoforms (PMCA1 and PMCA4) suggests specialized functions, and in recent years, through the use of genetically modified mice, a role has emerged for PMCA4 in the regulation of signal transduction processes. In contrast, there is still little known of the role of PMCA1.

With its 10 transmembrane domains and large intracellular loops, PMCA acts as a structural protein providing a scaffold to anchor interacting proteins at the plasma membrane. Within the heart, these interacting proteins include nNOS and α1-syntrophin which interact with both PMCA4 and PMCA1, calcineurin A, and Ras-associated factor 1 (RASSF1) (13, 46, 335, 395). While the precise function is not yet known of some of these interactions, others have been well characterized to be of functional significance.

Of particular note in the cardiovascular system, the binding of PMCA4 and nNOS at its PDZ domain has been shown to influence basal contractility and β-adrenergic responsiveness as well as, as will be discussed in the next section, to have an influence on vascular tone (60, 61). This interaction with nNOS was first identified in cultured cells, where PMCA4 overexpression resulted in a reduction of nNOS activity, postulated to occur due to the decreased availability of local Ca^{2+}, while a mutant nNOS molecule lacking its PDZ domain was unaffected (335). A functional interaction was subsequently identified in the heart, where PMCA4 overexpression was found to attenuate the inotropic response to β-adrenergic stimulation to an extent comparable to that seen following nNOS-specific inhibition in controls, but not in mice overexpressing a mutant form of PMCA4 unable to interact with nNOS (266). This pathway has since been characterized to affect local cGMP and hence cAMP levels, thus modulating PKA activity at the SR (244, 245). Interestingly, the latter of these studies found PMCA4 knockout mice to display a similar attenuation of the β-adrenergic response, but have enhanced basal contractility correlating with an increase in systolic Ca^{2+} due to phosphorylation of the RyR at PKA-dependent serine residues. Furthermore, the PMCA4-nNOS interaction may also have disease implications following myocardial infarction, when nNOS in association with its adaptor protein CAPON (COOH-terminal PDZ ligand of NOS1), have been shown to be recruited to the sarcolemma to bind to PMCA4 (22).

α1-Syntrophin is a cytoskeletal protein which like nNOS has a PDZ binding domain; however, although α1-syntrophin interacts directly with PMCA1 and PMCA4, it does so by binding to a domain on the catalytic second intracellular loop of PMCA. In the heart PMCA4 can form a ternary complex with nNOS and α1-syntrophin which results in a synergistic inhibition of nNOS-mediated NO production (395).

RASSF1 also binds to the same domain on the second intracellular loop of PMCA. A function of this interaction became apparent when PMCA4 was overexpressed in cultured HEK293 cells which resulted in the reduced activity of RASSF1A, and inhibition of the activation of Ras-mediated signaling (13). At the time RASSF1A, although a potential upstream regulator of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling, was not known to be associated with the hypertrophic process. However, RASSF1 knockout hearts have since been shown to have an exacerbated response to pressure overload, through mediating ERK1/2 signaling (268). More recently, it has been demonstrated that RASSF1 mediates the TNF-α-induced contractile response and signaling in the heart; however, it is not yet known whether these roles of RASSF1 in the heart are directly influenced by its interaction with PMCA4 (247, 268).

An association between the PMCA and calcineurin has been witnessed in multiple isoforms in a number of cell types. The interaction was first witnessed in PMCA4 overexpressing HEK cells and mapped to the catalytic subunit of calcineurin A, with consequential attenuation of calcineurin-nuclear factor of activated T cells (NFAT) signaling (46). Calcineurin has since been noted to also interact with PMCA2 and 4 in breast cancer cells and PMCA1, 2, and 4 in endothelial cells (158, 159), as well as with PMCA4 in the PC12 pheochromocytoma cell line (189). Calcineurin-NFAT signaling is one of the best characterized pathways in the development of pathological hypertrophy and remodeling (248), and thus this has prompted research into the function of this interaction during the hypertrophic process. PMCA4 overexpression was found to significantly reduce the extent and progression of pathological remodeling through the attenuation of NFAT signaling (405), and interestingly, we have recently found that deletion of PMCA4 also attenuates hypertrophic remodeling, through a calcineurin-independent mechanism (242).

Using a number of mouse models in which PMCA4 was deleted globally, or specifically from the cardiomyocytes or from the fibroblasts, we demonstrated that PMCA4 is involved in the development of pathological cardiac hypertrophy by regulating Ca^{2+} signaling in cardiac fibroblasts

which in turn is essential in the regulation of cardiac hypertrophy (242). Total PMCA4 knockout and deletion of PMCA4 specifically from the fibroblasts protected the animals against pressure overload-induced cardiac hypertrophy, but this protection was not evident when PMCA4 was deleted specifically from the cardiomyocytes. Ablation of PMCA4 from cardiac fibroblasts led to an increase in $[Ca^{2+}]_i$ which subsequently increased secreted frizzled related protein 2 (sFRP2) transcription, an inhibitor of the Wnt signaling pathway known to be protective against injury of the myocardium (151, 242). Secretion of sFRP2 from PMCA4 ablated fibroblasts then acted in a paracrine fashion to reduce cardiomyocyte hypertrophy and confer protection against the development of heart failure.

Cardiac hypertrophy almost invariably precedes the development of heart failure, and as an important determinant of disease progression and clinical outcome in heart failure patients, cardiac hypertrophy presents a clear target for disease prevention and treatment. With this in mind we set out to identify a pharmacological inhibitor of PMCA4 to use as an anti-hypertrophic agent. There is precedent that as an ATPase the PMCA would make a suitable drug target in that two of our most clinically successful drugs over the past years have been the cardiovascular drug ouabain and the antacid omeprazole, inhibitors of the Na^+-K^+-ATPase and the H^+-K^+-ATPase, respectively. The ease with which the inhibition of the ATPase activity of PMCA4 (and other ATPases) can be measured lends itself to drug screening and led to the identification of aurintricarboxylic acid (ATA) as a potent inhibitor of PMCA4 (58, 241, 243, 246). ATA was found to inhibit PMCA4 at low concentrations (having an IC_{50} of 150 nM) and to have minimal effect on PMCA1, the other isoform of PMCA present in the heart (241). This novel and potent inhibitor of PMCA4 was successfully used to both prevent the development of pathological cardiac hypertrophy in an in vivo mouse model, and of greater potential clinical relevance it was shown to have the ability to reverse established cardiac hypertrophy in the mouse (242). To add further weight to the notion of essaying PMCA4 inhibition as an anti-hypertrophic therapy, it has recently been shown that crossing PMCA4 null mice with mice expressing a mutant form of α-tropomyosin prevents the development of spontaneous hypertrophic cardiomyopathy which would otherwise occur (297).

2. PMCA and the vasculature

In addition to its regulatory roles in contractile and hypertrophic processes in the heart, several roles have been identified for the PMCA in noncardiac cell types in the cardiovascular system (59). In contrast to cardiac muscle, it has been demonstrated that the PMCA accounts for the bulk of Ca^{2+} extrusion from vascular smooth muscle, and its inhibition prolongs aortic relaxation to a similar extent to that of SERCA while NCX inhibition has little effect (298), and in myometrial resistance arteries PMCA inhibition mimics the phenotype of preeclamptic vessels (398). As described in section IIIA, PMCA1 has been identified in numerous studies as a leading candidate gene for the development of hypertension. It is perhaps not surprising therefore that both PMCA1 and 4 have been shown to influence vascular tone (129, 141, 187, 333, 343) and that they have been identified as potential targets for the treatment of essential hypertension (214).

Both PMCA1 and PMCA4 have been identified in vascular smooth muscle cells from a variety of species including mouse, rat, and pig (4, 187, 269, 276, 326, 363). Both have also been identified in endothelial cells (276, 363). Adding extra weight to the potential significance of the expression of the PMCAs in the vasculature is the fact that functional interactions between PMCA1 and 4 and eNOS, the major producer of the vasodilator NO in the vasculature, have been identified in endothelial cells (158). However, it is again through the study of a number of mouse models carrying genetic mutations in either PMCA1 or PMCA4 that we have gained our understanding of the role of these genes in the regulation of vascular tone and blood pressure.

There is an accumulation of evidence that PMCA1 is important in arterial contractility and blood pressure regulation and that modified expression results in hypertension. Three different mouse models, all of which exhibit reduced expression of PMCA1, develop raised blood pressure. Hypertension in a model in which PMCA1 was specifically deleted from the vascular smooth muscle cells was found to correlate with increased intracellular Ca^{2+} (187), global heterozygous deletion of PMCA1 also resulted in raised blood pressure (129), and PMCA1 knockdown by siRNA led to an elevation in blood pressure (343) associated with structural changes to the walls of the resistance arteries.

Although to date there is no GWAS data linking PMCA4 with hypertension, there is evidence from mouse models that it is important in the regulation of vascular tone and blood pressure. Mice overexpressing PMCA4 in smooth muscle cells have been shown to have elevated blood pressure (141, 333). While this may appear counterintuitive as increased expression of a Ca^{2+} extrusion pump would potentially lead to lower intracellular Ca^{2+} levels and subsequent vascular relaxation, it is in fact through the negative regulation of nNOS that PMCA4 acts to regulate vascular contractility (141, 333).

E. Role of PMCAs in Hematopoietic Cells

With PMCA first discovered and isolated in human erythrocytes (327), numerous studies have looked at the role of the pump in hematopoetic cells. Perhaps more than any other cell population, the PMCA is the predominant Ca^{2+} extrusion system in blood cells (erythrocytes, leukocytes, and platelets) where maintenance of intracellular Ca^{2+} lev-

els is essential for the regulation of cellular function, signaling, metabolism, and blood rheology (33, 211, 313). Variations in PMCA activity can impact Ca^{2+} homeostasis in blood cells and have been associated with numerous aspects of health and disease, as we will highlight below.

1. PMCA in erythrocytes

Aside from some internal buffering capacity, the PMCA is the sole mechanism responsible for the maintenance of free cytosolic [Ca^{2+}] in erythrocytes (122, 210). Coupled with the relative ease with which patient samples can be obtained, this has made red blood cells and red blood cell ghosts (erythrocytes which do not contain hemoglobin or other cytoplasmic components but retain their shape) a popular choice in which to study the biochemical properties of human PMCA. Using these models, researchers have been able to identify abnormalities in PMCA activity in a number of disease states (28, 291). In addition, purified preparations of human erythrocyte PMCA have been widely used to identify molecular and pharmacological modulators of the pumps' activity such as F- and G-actin, acidic phospholipids, diacylglycerol, the bidentate chromium (III) ATP complex, the phytoalexin resveratrol, and inhibitory peptide caloxin1c2 (251, 263, 277, 278, 289, 383).

In erythrocytes, Ca^{2+} regulates numerous parameters such as cell volume and rheological properties, metabolic activity, redox state, and cell clearance (33). Human erythrocyte PMCA is composed primarily of PMCA4, with PMCA1 expression also having been identified (188, 352). PMCA activity declines as red blood cells age in line with increasing glycated hemoglobin, which may make them prone to Ca^{2+} overload and earmark them for clearance (207).

Elevated $[Ca^{2+}]_i$ is a feature of a number of diseases of the erythrocyte associated with hemolytic anemia such as sickle cell disease (SCD), β-thalassaemia, and familial phosphofructokinase (PFK) deficiency (103, 315, 340). In SCD- and PFK-deficient cells, Ca^{2+} accumulates via increased entry through the red cell membrane, in a stochastic fashion in the case of sickled cells (209), likely causing a reduction in deformability (the ability for cells to change shape in response to flow) and leaving them prone to hemolysis (114, 315). Interestingly, in SCD a reduction in PMCA activity is likely to contribute to this Ca^{2+} accumulation (114), whereas in PFK deficiency a compensatory increase in PMCA activity to clear the Ca^{2+} leads to ATP depletion (315). There is also a suggestion that in an effort to prevent Ca^{2+} overload, both SCD and β-thalassaemia erythrocytes are able to store Ca^{2+} in endocytic inside-out vesicles, pumping it in via the PMCA (35, 208).

Hypertension is also associated with a decrease in red blood cell deformability, where it may contribute to an increased risk of vascular occlusion (78, 249). PMCA activity is reduced in erythrocytes from hypertensive patients and appears directly correlated with erythrocyte deformability. Studies suggest deformability reduces by 55% upon PMCA inhibition and increases upon PMCA activation with neutral or acidic phospholipids (249). Similarly, a 50% reduction in erythrocyte PMCA activity has been reported in women suffering from preeclampsia (259), and this has been ascribed to changes in lipid composition, specifically an increase in the level of lipid peroxidation (273).

2. PMCA in leukocytes

Ca^{2+} signaling in leukocytes is required for processes such as lymphocyte activation, granule secretion in granulocytes, and the regulation of cell motility and death (211, 328). The presence of a PMCA, thought to be predominately isoform 4, has been demonstrated in all classes of lymphocytes, as well as neutrophils, monocytes, macrophages, and mast cells (67, 132, 177, 211, 329, 338).

The PMCA represents the major route for Ca^{2+} clearance from human T cells, where it regulates $[Ca^{2+}]_i$ in conjunction with the main Ca^{2+} entry channels, calcium release-activated channels (CRAC, encoded by ORAI) (211). To facilitate T-cell activation, there is a redistribution of the PMCA to maximize Ca^{2+} entry through CRAC (299), and decreased PMCA-mediated efflux through an interaction with stromal interacting molecule-1 (STIM1) (314) which together increase cytosolic Ca^{2+} thus activating NFAT. In contrast, defective PMCA signaling, for example through decreased expression following exposure to ROS, can promote T-cell apoptosis (286). There is also evidence that through an interaction with CD147, PMCA4 is able to modulate the immune response in T cells by inhibiting the production of interleukin-2 (361). A rise in Ca^{2+} in B-lymphocytes meanwhile is important for their proliferation, differentiation, and antibody production, and studies have shown that through positive and negative PMCA regulation, respectively, CD22 and myc transcription factors are able to either inhibit or stimulate these processes (71, 144).

PMCA activity has also been shown to be altered in disease states in neutrophils. Both hepatocytes and neutrophils from patients with alcoholic liver disease exhibit elevated basal Ca^{2+} and impaired PMCA-mediated efflux (16), while the ability of PMCA inhibition to attenuate neutrophil apoptosis is lost in patients with uremia (80).

3. PMCA in platelets

Tight regulation of platelet Ca^{2+} homeostasis is essential for maintaining low resting Ca^{2+} levels and also allowing steep rises to enable platelet activation, platelet aggregation, and thrombus formation at sites of injury; underactive platelets are associated with bleeding disorders, while hyperactivation can result in thromboembolism (88, 313). As

is the case in erythrocytes and leukocytes, the PMCA is the major Ca^{2+} extrusion system in platelets (318), with expression studies showing PMCA4 to be the predominant isoform (281). Studies have found that PMCA4 is recruited to the cytoskeleton during platelet activation through an interaction with the LIM family protein CLP36 to facilitate clot formation (39). The critical role of the PMCA during aggregation has been highlighted by studies using platelets from PMCA4 knockout mice, which display impaired platelet aggregation when stimulated with collagen (174). Similar results were obtained upon incubation of platelets with the PMCA inhibitor carboxyeosin, which led to elevated resting Ca^{2+}, but smaller increases in Ca^{2+} upon stimulation alongside reduced aggregation (174).

Altered platelet PMCA activity has been witnessed in a number of disease states associated with an increased risk of clot formation or bleeding. As we will discuss in the following section, platelet PMCA4 expression is elevated during diabetes, but this is accompanied by an overall reduction in PMCA activity in type 2 diabetic platelets as a result of increased tyrosine phosphorylation (66, 168, 317). A similar reduction in PMCA activity has been reported in platelets from hypertensive patients in a manner that correlates with increasing diastolic blood pressure, again despite increased expression of PMCA4 (82, 89). As in diabetes, this occurs as a result of tyrosine phosphorylation, leaving platelets with elevated $[Ca^{2+}]_i$ and in a potentially hyperactivated state prone to spontaneous aggregation and thrombus formation (30). Increased PMCA4 expression has also been reported in a family with type 2B von Willebrand disease, where it is associated with the production of immature megakaryocytes and severe thrombocytopenia (265), while increased PMCA activity has been found in platelets from obese patients associated with increased anisotropy (302).

F. Role of PMCAs in Pancreatic β-Cell Function and Diabetes

An increase in cytosolic Ca^{2+} is required to stimulate insulin release from pancreatic β-cells in response to a rise in glucose (401), and as such, disturbances in the regulation of $[Ca^{2+}]_i$ can have profound effects upon β-cell function and may be a potential mechanism leading to the development of type 2 diabetes. In addition, Ca^{2+} signaling is important in regulating β-cell mass, apoptosis, and proliferation, key events in the cytokine and nutrient-induced destruction of pancreatic islets which occur in type 1 and type 2 diabetes, respectively (79, 154).

Ca^{2+} clearance from pancreatic β-cells is regulated by the SERCA, NCX and PMCA, with relative contributions estimated to occur at around a 2:1:1 ratio among these three systems in mice (72). Surprisingly for nonneuronal cells, all four PMCA isoforms are expressed at the mRNA and protein level in rat islets, including up to eight splice variants (175), suggesting highly specialized functions. Unusually, the "neuronal" isoforms PMCA2 and 3 may have particular importance in β-cells as their expression is downregulated upon exposure of insulin-producing RINm5F cells to the inflammatory cytokine interleukin-1β, thought to be a major cause of autoimmune death in type 1 diabetes (349). In addition, glucose has been shown to decrease PMCA activity, suggesting a possible link to altered β-cell function in type 2 diabetes (153).

Gain- and loss-of-function studies have shown that altered expression of either NCX1 or PMCA2 is sufficient to modulate insulin secretion, β-cell mass, proliferation, and survival (155). PMCA2 overexpression in insulin-secreting BRIN-BD11 cells leads to reduced increases in intracellular Ca^{2+} in response to depolarization and glucose accompanied by increased glucose metabolism and insulin secretion (176), while depleting cytosolic, mitochondrial, and ER $[Ca^{2+}]$ and triggering apoptosis via the mitochondrial pathway (171). In contrast, pancreatic islet cells isolated from mice with heterozygous PMCA2 deletion were found to display increased Ca^{2+} stores and glucose-induced insulin release, along with having higher rates of β-cell proliferation with greater mass, viability, and islet size (275).

Diabetes is of course a major risk factor for the development of various diseases, and PMCA activity has been found to be altered in numerous nonpancreatic cell types both clinically and in experimental models of diabetes. A number of studies have found abnormal PMCA function in hematopoietic, vascular smooth muscle, or endothelial cells which may contribute to the increased risk of cardiovascular complications such as thrombus formation and atherosclerosis in diabetic patients.

An examination of Ca^{2+} clearance proteins in platelets from diabetic patients has shown PMCA4 expression to be increased in both insulin-dependent and -independent diabetes, and this can be corrected upon insulin treatment in type 1 diabetics (66). In line with the increased expression, platelets from insulin-dependent diabetic patients have previously been found to have higher PMCA activity (234), while incubation of platelets from healthy donors with low-density lipoprotein (LDL) isolated from type 1 diabetic patients also increased PMCA activity along with resting $[Ca^{2+}]$ and platelet aggregation responses (300). On the contrary, PMCA activity appears to be reduced in platelets from type 2 diabetic patients likely due to increased tyrosine phosphorylation as a result of oxidative stress (168, 317), as well as in lymphocytes which may contribute to higher basal $[Ca^{2+}]$ in these cells (19).

Similar to the situation seen in platelets, human aortic endothelial cells incubated with type 1 diabetic patient LDL were found to have increased basal $[Ca^{2+}]_i$ and higher

PMCA activity, along with alterations in the plasma membrane structure which could lead to an atherogenic phenotype (301). Meanwhile, coronary smooth muscle cells isolated from swine following induction of diabetic dyslipidemia have been found to have increased basal $[Ca^{2+}]_i$ due to reduced PMCA-mediated efflux, a phenomenon which can be prevented through exercise training (399, 400).

Altered PMCA activity may also lead to disturbances in Ca^{2+} homeostasis in other cell types during diabetes. For example, basolateral membrane vesicles isolated from syncytiotrophoblast of insulin-dependent diabetic patients display increased PMCA activity (359), while reduced PMCA activity or expression has been identified in parotid and submandibular salivary glands, kidney, and brain synaptosomes of streptozotocin-induced diabetic rats (260, 347, 421).

G. Role of PMCAs in Visceral Smooth Muscle

Smooth muscle contraction is triggered by the influx of extracellular Ca^{2+} following membrane depolarization through Ca^{2+} channels at the sarcolemma, or via IP_3-mediated SR Ca^{2+} release following agonist-induced activation of G protein-coupled receptors. Through its binding of calmodulin, the rise in cytosolic Ca^{2+} activates myosin light chain kinase (MLCK) leading to phosphorylation of the myosin light chain (MLC), thus increasing actin-myosin crossbridge formation and stimulating contraction. Relaxation is brought about by a decrease in cytosolic Ca^{2+} via SERCA-mediated SR reuptake and sarcolemmal extrusion through the PMCA and NCX, with inactivation of MLCK and activation of MLC phosphatase leading to the dephosphorylation of the MLC. The physiological role of the PMCA in this process in visceral smooth muscle will be discussed below.

1. PMCA in uterine smooth muscle

The contractile state and function of the myometrium influences reproductive processes such as implantation and parturition and can contribute to a number of disease states including spontaneous miscarriage, preterm labor, dysmenorrhea, and endometriosis (5).

Experiments in rat uterine smooth muscle cells have determined that Ca^{2+} extrusion at the plasma membrane is required for full recovery of transients induced by both membrane depolarization and Ca^{2+} release from internal stores (345). In the nonpregnant myometrium, it is believed that the PMCA is responsible for producing ~85% of relaxation and 70% of Ca^{2+} extrusion, while work in PMCA4 ablated mice has identified that ~80% of the PMCA contribution can be attributed to this isoform (233). In the endometrium however, PMCA1 appears to be the dominant isoform, and its expression has been found to increase along with TRPV6 during the proliferative phase of the menstrual cycle (412).

In contrast to nonpregnant myometrium, it has been suggested that up to 70% of Ca^{2+} efflux occurs via the NCX in the pregnant rat uterus (344). This switch in mode of Ca^{2+} extrusion may be explained by an examination of the effects of physiological concentrations of oxytocin on human myometrium taken at term, which found the hormone to strongly inhibit Ca^{2+}-ATPase activity and thus induce contraction (294), a phenomenon which has also been reciprocated at late stages of gestation in the rat (222). Surprisingly, oxytocin's inhibitory actions on PMCA and SERCA activity at term occur despite an increase in expression of both pumps in the human myometrium during active labor (374).

2. PMCA in bladder smooth muscle

Tight regulation of $[Ca^{2+}]_i$ in detrusor smooth muscle of the urinary bladder is critical to allow for relaxation while filling and storing urine, and contraction during micturition. Disturbances in these processes can lead to lower urinary tract symptoms such as urgency, frequency, and incontinence, which primarily manifest themselves with increasing age (10). Indeed, studies in guinea pig smooth muscle have found Ca^{2+} extrusion to be impaired in aged animals as a result of decreased PMCA activity (138).

With the use of inhibitors to SERCA and NCX in PMCA gene-ablated mice, the relative contribution of the PMCA to relaxation of bladder smooth muscle rings was estimated to be ~25–30%, slightly greater than that of SERCA and with the NCX responsible for up to 70% of relaxation (216). This is largely compatible with data from isolated guinea pig detrusor smooth muscle cells which, using inhibitors to each system, estimated the relative contributions of PMCA, NCX, and SERCA to Ca^{2+} clearance to be 27, 55, and 31%, respectively (138). Interestingly, Liu et al. (216) also found PMCA ablation to impair the rate of contraction, and in a further study in which contraction and $[Ca^{2+}]_i$ were measured simultaneously, it was determined that the loss of PMCA4 significantly inhibited the force and rate of contraction, as well as the rates of increase and decrease of $[Ca^{2+}]_i$ following cholinergic stimulation (215). In contrast, the authors found heterozygous PMCA1 deletion to elicit larger increases in $[Ca^{2+}]_i$ and rate and force of contraction following KCl stimulation, suggesting a greater role for this isoform in overall Ca^{2+} extrusion.

H. Role of PMCAs in Epithelial Ca^{2+} Absorption and Tissue Mineralization

Regulated Ca^{2+} absorption is critical in maintaining serum $[Ca^{2+}]$ at desirable levels for a wide range of normal physiological functions, in addition to the mineralization of cal-

cified tissues such as bone and enamel. In mammals, the bulk of Ca^{2+} transport occurs in the small intestine and kidney, either paracellularly directly from the lumen to the extracellular space via tight junctions, or transcellularly through epithelial cells (157) **(FIGURE 7)**. The PMCA, along with NCX1, performs the final step in transcellular Ca^{2+} absorption, extruding Ca^{2+} from the epithelia to the interstitial space at the basolateral membrane following its entry from the lumen via TRPV5/6 channels and subsequent diffusion through the cytosol bound to calbindin. The importance of PMCA1, the major isoform in epithelial absorption, in maintenance of serum ionic balance can be highlighted by the genome-wide association of the SNP rs7965584 in the region of *ATP2B1* with serum Mg^{2+} concentration (239). This section discusses the role of the PMCA in intestinal and renal Ca^{2+} absorption, how it is affected by disease states, and the implications this can have on skeletal and dental mineralization.

1. PMCA and intestinal Ca^{2+} absorption

In the intestine, the majority of transcellular Ca^{2+} absorption occurs in the duodenum (181), where it is primarily extruded from enterocytes via the PMCA (95). In addition, it has been demonstrated that the PMCA plays an active role in Ca^{2+} transport in the large bowel, with basolateral membrane vesicles isolated from human colon able to uptake Ca^{2+} in a Mg^{2+}/ATP-dependent calmodulin-regulated manner (323).

Expression studies have shown that PMCA1 is the predominant isoform in both human and rat duodenal mucosa, and therefore, this isoform is likely to be largely responsible for Ca^{2+} absorption in the intestine (163). Indeed, PMCA1 expression levels positively correlate with both intestinal Ca^{2+} absorption and bone mineral density in mice (11, 308). In rabbit and mouse small intestine it has been shown that PMCA1 expression is higher proximally in the duodenum than in the jejunum or ileum, and in the large bowel higher in the cecum and ascending colon than in the descending colon (9, 125). Alexander et al. (9) also found that PMCA1 was the only isoform present in enterocytes throughout human and mouse intestine, whereas PMCA4 was the predominant isoform in smooth muscle layers, increasing in expression distally from small to large bowel.

As with most components of the transcellular pathway for Ca^{2+} absorption, duodenal PMCA1 expression is primarily regulated by the vitamin D metabolite $1,25\text{-}(OH)_2D_3$. Data from rat intestine indicate that PMCA1 expression decreases substantially in aged animals in line with serum $1,25\text{-}(OH)_2D_3$ concentration (12). Treatment of human duodenal mucosal explants with $1,25\text{-}(OH)_2D_3$, as well as its in vivo administration in mice and chickens, has been shown to significantly increase PMCA1 expression (20, 49, 202, 388). Along with the upregulation of TRPV6 and calbindin-D_{9K}, this enables the gut to increase Ca^{2+} absorption in an attempt to maintain Ca^{2+} balance under experimental conditions of dietary Ca^{2+} deficiency, as well as a dietary depletion or excess of phosphorus and chronic metabolic acidosis (49, 65, 70, 179).

There is also evidence for a role in the regulation of duodenal PMCA1 expression by estrogens, with ovariectomized rats and mice displaying reduced PMCA1 mRNA (97, 379). This experimental model results in negative Ca^{2+} balance and displays many characteristic features of postmenopausal osteoporosis. In support of this role, intestinal PMCA1 expression is increased in pregnant and lactating mice, and in response to 17β-estradiol treatment in ovariectomized rats (378, 379).

The potential link between aberrant duodenal PMCA1 expression and inadequate bone mineralization can also be highlighted by recent data showing enterocyte-specific PMCA1 deletion in mice to lead to growth restriction and reduced bone mineral density (320). Furthermore, intestinal PMCA1 expression was found to be downregulated in ulcerative colitis patients and in mice fed on a high-fat diet, the latter finding also correlating with reduced bone mineral density (402, 409), and both inflammatory bowel disease and obese patients have a higher risk for the development of

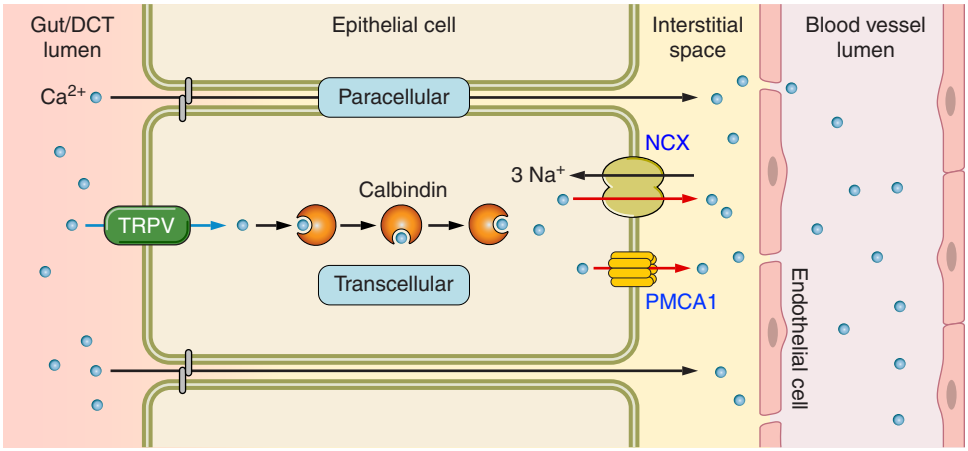

FIGURE 7. Cartoon illustrating transepithelial Ca^{2+} absorption into the blood. Ca^{2+} moves passively from gut/kidney lumen through tight junctions between epithelial cells to the interstitial space (paracellular) or is actively transported across the epithelial cell (transcellular). Ca^{2+} enters the cell via transient receptor potential vanilloid channels, is transported across the cytoplasm bound to calbindins, and exits via the NCX and PMCA1 to the interstitial space.

bone-related disorders including osteoporosis (140, 150). In addition, duodenal PMCA1 levels are lower in pregnant hypoxic rats than normoxic controls which may contribute towards growth restriction in preeclamptic offspring (411).

2. PMCA and renal Ca^{2+} reabsorption

In excess of 98% of the Ca^{2+} filtered through the glomeruli is reabsorbed into the plasma along the nephron. Approximately two-thirds of this transport occurs passively in the proximal convoluted tubule, 20% in the thick ascending loop of Henle, and 10 and 5% in the distal convoluted tubule (DCT) and connecting tubule, respectively, the main sites for active Ca^{2+} absorption (127, 157). Unlike in the intestine, it is NCX1 that is believed to reabsorb the majority of transcellular Ca^{2+} at the basolateral membrane, with the PMCA responsible for the remaining one-third (29).

The presence of a Mg^{2+}-dependent Ca^{2+}-ATPase was demonstrated throughout the rabbit nephron in the early 1980s, with activity highest in the DCT and cortical collecting tubule (98). Since then, mRNA for all four PMCA isoforms has been found with site-specific distribution along the nephron. Interestingly, PMCA3 expression appears to be restricted mainly to the thin descending loop of Henle in the rat nephron, whereas isoforms 1, 2, and 4 show more general distribution along the nephron (53, 55). PMCA1 and 4 predominate in mouse DCT cells where they appear targeted to the basolateral membrane (223), and immunohistochemical staining of the mouse nephron shows PMCA expression to peak in the late DCT and connecting tubule where transcellular Ca^{2+} transport occurs, before expression tapers off towards the collecting duct (218).

In contrast to intestinal absorption, recent data suggest that PMCA4 may be the major isoform involved in renal active Ca^{2+} transport, where it shows strong localization to distal tubular regions in human and mouse kidney (9). In a cultured murine model of the distal convolution, PMCA4, but not PMCA1, was found to be enriched when compared with total cortical expression along with the other components of renal transcellular transport TRPV5, calbindin-D_{28k}, and NCX1 (381). Given this evidence regarding the expression of PMCA4 it was then interesting to note that in vivo deletion of PMCA4 from the mouse does not affect renal Ca^{2+} handling, with the mice displaying normal serum Ca^{2+} levels and urinary Ca^{2+} excretion (242, 382). As is the case in the digestive tract, active Ca^{2+} transport is primarily regulated via 1,25-$(OH)_2D_3$ in the distal tubule, and it has been shown that vitamin D_3 treatment of Madin-Darby canine kidney cells leads to significant upregulation of basolateral PMCA4 expression in line with an increase in apical-to-basolateral membrane Ca^{2+} flux (185).

Interestingly, the pathways regulating PMCA expression in the renal cortex appear to show isoform specificity; whereas PMCA4 expression is induced by 1,25-$(OH)_2D_3$, and PMCA1 expression is dramatically reduced in the kidney of ovariectomized rats and estrogen-deficient aromatase knockout mice (97, 274). In contrast, a low phosphate diet induces PMCA2 and 3 downregulation and a corresponding increase in urinary Ca^{2+}, while PMCA1 expression is unaltered by dietary Ca^{2+} levels (54, 97).

Associations have been identified between abnormal PMCA activity and a number of disease states involving the kidney. Patients with idiopathic hypercalciuria, an inherited condition associated with an increased risk of kidney stones, display significantly higher erythrocyte PMCA activity than healthy controls (28). In contrast, red blood cell PMCA activity is reduced in line with an increase in cytosolic Ca^{2+} in both children and adults with chronic kidney disease (CKD) (253, 293). In children, erythrocyte PMCA activity and Ca^{2+} balance deteriorates as CKD progresses and can be only partially and transiently rescued by hemodialysis (291, 292). There is also evidence from the rat that gestational diabetes induced by streptozotocin (STZ) can impact on PMCA expression and urinary Ca^{2+} output in neonatal male offspring which persists into adulthood (34), while STZ-induced diabetes in the adult rat reduces renal PMCA1 expression and increases urinary Ca^{2+} excretion (421). In both these cases, the disturbance in Ca^{2+} balance ultimately leads to reduced trabecular bone formation, a likely mechanism contributing towards the development of diabetes-induced osteoporosis.

3. PMCA and bone mineralization

As detailed in the previous sections, it is clear that perturbations in duodenal and renal PMCA expression may impact on bone mineral density (12, 34, 320, 409, 421). Furthermore, altered maternal PMCA expression also appears to influence bone formation in offspring. This is evident both in the placenta, where PMCA3 levels correlate strongly with neonatal bone area and mineral content (232), as well as during lactation where a decrease in PMCA2 expression in mammary epithelial cells from 1,25-$(OH)_2D_3$-deficient dams is associated with reduced cortical bone volume in pups (170). In fact, PMCA1, 2, and 4 mRNA and total PMCA protein each increases dramatically during lactation in rat mammary tissue, most notably that of PMCA2 which is upregulated some 1,500- and 100-fold at the RNA and protein levels, respectively (303, 304). The importance of this increase in PMCA2 expression in transport of Ca^{2+} from mammary epithelial cells into milk has since been verified through studies in transgenic mice, which show a 60–70% reduction in milk [Ca^{2+}] produced by PMCA2 null or functionally inactive *Deafwaddler* mice (306, 385).

In addition to serum and milk [Ca^{2+}], the degree of bone mineralization depends on optimal Ca^{2+} homeostasis within the bone forming and resorbing cell types of the tissue itself, namely, the osteoblasts and osteoclasts. Bone is

a highly dynamic tissue that undergoes constant turnover. Osteoblasts lay down new osteoid through matrix, Ca^{2+}, and phosphate secretion, forming a specialized connective tissue hardened by hydroxyapatite. Meanwhile, osteoclasts simultaneously digest this osteoid, and the balance of these two processes impacts on bone growth and strength (84).

PMCAs are expressed in both cell types, although their precise functions are incompletely understood. PMCA1, 2, and 4 have all been found to be present in human osteoblasts (41, 196, 380). In human and rat osteoblasts, the PMCA appears targeted to the osteoidal domain, suggesting a role in the mineralization process (258, 380), although chick osteoblasts show localization to the apical and lateral membranes facing away from bone so there may be some interspecies variation in this respect (7, 351). In support of a role in basolateral Ca^{2+} transport, PMCA inhibition using ortho-vanadate has been shown to decrease mineralization of murine osteoblast precursor cultures (257), while patients suffering from adult idiopathic scoliosis appear to have a reduction in PMCA4 expression (41).

It has been reported that PMCA1 and 4 are expressed during osteoclast differentiation from human peripheral blood mononuclear cells, and each acts to inhibit osteoclastogenesis through regulation of Ca^{2+} oscillations, NFATc1, and in the case of PMCA4, NO-dependent osteoclast fusion (183). In mature human, mouse, and chick osteoclasts, the PMCA appears localized to the basolateral membrane facing away from bone (7, 183, 380). In addition to PMCA's role during osteoclastogenesis, they also appear to prevent apoptosis in mature cells, while both PMCA1 heterozygous mice and PMCA4 ablated mice exhibit reduced bone mineral density and trabecular bone volume associated with increased osteoclast number (183). Interestingly, this study also found a correlation between PMCA4 expression and higher peak bone mass in Chinese women.

4. PMCA and dental mineralization

Enamel is the hardest substance in the human body, being composed primarily of calcium phosphate in the form of hydroxyapatite. It is laid down during tooth development by ameloblasts, and constantly remineralized thereafter via Ca^{2+} and phosphate secreted in saliva (161).

PMCA has been shown to be localized to the enamel facing Tomes' processes and plasma membrane of human ameloblasts, indicating a likely role in enamel mineralization, and indeed PMCA1 and 4 expressions have been shown to increase in parallel with the onset and progression of enamel development (37). The importance of PMCA1 in the mineralization process may be highlighted by work using morpholino knockdown of the zebrafish *Atp2b1a* gene, which leads to inadequate calcification of developing pharyngeal teeth (136), while PMCA4 expression is reduced in matrix metalloproteinase-20 (MMP20) null mice in which enamel thickness is reduced by 50% (375).

Regulation of salivary Ca^{2+} levels is critical in preventing the incidence of dental caries and formation of calculus, and the PMCA is the principal route via which Ca^{2+} is extruded from acini into the salivary ducts. PMCA1, 2, and 4 are each expressed in the human parotid and submandibular glands, where they appear localized to the apical membrane of acinar cells (161). PMCA2 was also found to be present in the secretory canaliculi between the cells, while labeling of all three isoforms was found in the cytoplasm of the interlobular and intralobular ducts of rabbit submandibular glands (36).

I. Role of PMCAs in Cell Proliferation, Differentiation, and Death

Ca^{2+} is known to be a widespread intracellular messenger, controlling numerous cellular processes from cell growth to cell death. When the level of cytosolic Ca^{2+} changes, a multitude of downstream signaling pathways driving these processes become activated and therefore the regulation of intracellular Ca^{2+} is a key element of cellular physiology (23). With the PMCA being the major regulator of $[Ca^{2+}]_i$ in many cell types, it therefore plays a critical role in directing Ca^{2+}-mediated signaling, and as discussed elsewhere in this review can influence such processes as megakaryocyte, osteoclast, and neuronal differentiation (40, 41, 66, 82, 183, 362); the proliferation of B-lymphocytes and pancreatic β-cells (71, 144, 275); and apoptosis of β-cells, osteoclasts, and neurons (120, 131, 171, 183). Indeed, microarray analysis of PC12 cells following antisense-mediated suppression of PMCA2 or PMCA3 revealed altered expression patterns of many genes involved in the regulation of cell cycle, proliferation, migration, differentiation, and apoptosis (31). Furthermore, cellular proliferation, differentiation, and survival are key determinants in tumor progression which we will discuss in further detail in section IV*J*.

1. PMCA during differentiation

Direct evidence that the PMCA may play a role in regulating the differentiation process has been demonstrated upon overexpression of human PMCA4 in rat L6 myoblasts, which led to reduced $[Ca^{2+}]_i$, increased myotube formation, and hence accelerated differentiation (148). A spike in intracellular Ca^{2+} is required for the maturation of a number of precursor cell types (23), while low resting cytosolic Ca^{2+} is a feature in most mature cells. Studies of *Xenopus* oocytes indicate that PMCA internalization, preventing PMCA-mediated efflux, contributes towards the sustained increase in cytosolic $[Ca^{2+}]$ necessary for egg activation during maturation (106). A similar spike in Ca^{2+} is thought to be required for neuronal cell differentiation, and it has been shown that PMCA activity increases substantially in

line with PMCA2, 3, and 4 expressions as IMR-32 neuroblastoma cells become differentiated, postulated to allow for optimal Ca^{2+} signaling in mature cells (377). In contrast, PMCA expression is highly abundant in megakaryoblastoid precursor cells (primarily PMCA4) compared with mature platelets (281), while expression and activity also decrease during the differentiation process in keratinocytes (75).

Hence, the PMCA may play a complex role in cellular maturation, and there is a suggestion that cell-specific patterns of PMCA expression may provide a signature for terminal differentiation among different cell types. This has been put forth following studies examining the expression of alternate splice variants during differentiation of myogenic and neuronal cells alongside fibroblasts, smooth muscle, and endothelial cells, which have shown a switch from the "b" splice variants of PMCA1 and 4 during differentiation to also express isoforms 1c, 1d, and 4a and that this is unique to the excitable cell types (86, 147).

2. PMCA during proliferation

A role for the PMCAs in proliferation has now been identified in a number of cell types. Of these, perhaps the best defined is in the regulation of the vascular smooth muscle cell (VSMC) cycle. Husain and colleagues (3, 165) have shown that repression of PMCA1 expression in rat VSMCs through the binding of transcription factor c-Myb to its promoter region leads to a subsequent reduction in the rate of PMCA-mediated Ca^{2+} efflux, which results in the increase in intracellular Ca^{2+} required for G_1/S stage transition in the cell cycle. Moreover, the authors (165) showed that PMCA1 overexpression inhibited S phase entry and reduced the rate of proliferation. The authors (4) have since found an opposing role for PMCA4 in cell cycle progression, with VSMCs from PMCA4 knockout mice displaying G_1 phase arrest which could be rescued upon electroporation of either PMCA4a or 4b splice variants. Each of these splice variants appeared to regulate independent pathways with PMCA4a suppressing the anti-proliferative AP-2β and 4b downregulating the cyclin-dependent kinase inhibitor p15, while an isoform switch occurred from a 50:50 ratio in normal vessels to PMCA4b being the predominant variant following arterial injury (4). Interestingly studies of canine VSMCs have found PMCA4a to be present only in proliferating cell populations (2). Meanwhile, in contrast to VSMCs, PMCA4 has been shown to be downregulated in proliferating airway SMCs and inhibition to enhance proliferation, whereas nonselective inhibition (and thus additionally of PMCA1) had the opposite effect (74).

In addition to its roles in arterial smooth muscle cells, the actions of PMCA4 have recently been shown to mediate VEGF-induced angiogenic signaling in vascular endothelial cells (17). Baggott et al. (17) found PMCA4 to inhibit endothelial cell migration and blood vessel formation through suppression of calcineurin/NFAT signaling while also demonstrating that PMCA4 knockout mice had improved hindlimb perfusion following femoral artery ligation.

3. PMCA in cell death

Ca^{2+} signaling plays a critical role in cell viability; a rise in basal Ca^{2+} can lead to mitochondrial dysfunction and activate pro-apoptotic factors, while Ca^{2+} overload may cause cells to undergo necrosis (23, 271). As regulators of global $[Ca^{2+}]_i$ and Ca^{2+}-mediated signaling, the PMCAs have been implicated in both necrotic and programmed cell death in numerous cell types.

In some instances PMCA-mediated apoptosis is required for normal physiological functions. For example, mice exhibit a 95% reduction in PMCA2 expression in mammary epithelial cells (which as we discuss elsewhere is greatly elevated during lactation) as early as 24 h after weaning, thus leaving the cells in a state of high Ca^{2+}, triggering apoptosis and ultimately mammary gland involution (305, 384). Improper control of this process however, as evidenced by PMCA2 mutant *deafwaddler* mice, results in apoptosis of mammary epithelial cells during pregnancy (384). PMCA-dependent promotion of cell survival has also been demonstrated in follicular granulosa cells, which through a basic fibroblast growth factor-mediated increase in PKCδ activity are able to upregulate PMCA1 expression and Ca^{2+} efflux, thus preventing apoptosis in response to elevated $[Ca^{2+}]_i$ (287, 288). In line with this protective role, antisense-mediated inhibition of PMCA1 and PMCA2, respectively, in rat VSMCs and PC12 cells induces apoptosis (32, 326).

PMCA's role in regulating cell death is somewhat complex however. A mutant form of PMCA4 which demonstrated greatly reduced expression in L929 fibrosarcoma cells conferred resistance to tumor necrosis factor-induced cell death despite elevated cytosolic Ca^{2+}, thought to result from the promotion of exocytosis of acidic lysosomes accumulating in the cytoplasm (270). In addition, the PMCA is particularly vulnerable to proteolysis, and it has consistently been shown that in the early stages of apoptosis the autoinhibitory COOH-terminal is cleaved from PMCA4 by caspase-3 leaving a properly targeted 120-kDa fragment active even in the absence of calmodulin (279, 280, 282). In theory, this would then increase Ca^{2+} extrusion and protect cells from overload; however, it appears that cleavage can eventually impair PMCA activity. This has been witnessed in hepatocytes transfected with hepatitis B virus X protein, which undergo apoptosis associated with increased PMCA4 cleavage by caspase-3, higher $[Ca^{2+}]_i$, and mitochondrial abnormalities (68). The same is true during ischemic brain injury in rats and in glutamate-treated cerebellar granule neurons, which demonstrate caspase-1-induced cleavage of PMCA2 leading to impaired activity and apoptosis (337). Schwab et al. (337) also determined that PMCA4 cleavage in nonex-

citable CHO cells resulted in impaired Ca^{2+} handling, Ca^{2+} overload, and secondary necrosis.

The mechanisms through which the PMCA pump becomes inactivated under these circumstances are unclear. One simple hypothesis would be that further cleavage would result in proteolytic degradation and reduced expression. There is also the suggestion that ATP depletion via mitochondrial dysfunction impairs PMCA activity resulting in Ca^{2+} overload and necrosis, as evidenced in pancreatic acinar cells exposed to palmitoleic acid in a model of acute pancreatitis (324). Further evidence that Ca^{2+} overload and necrosis occur as a result of reduced PMCA activity following ATP depletion has been identified in epithelial cells exposed to oxidative stress, where increased Na^+-K^+-ATPase activity induced by elevated $[Na^+]_i$ effectively "steals" ATP from the PMCA rendering the pump inactive (63). Similarly, UVB irradiation-induced oxidative stress in human lens epithelial cells has been shown to reduce PMCA1 expression and activity resulting in increased Ca^{2+} and necrosis (403). Thus it appears the PMCA plays a complex role in directing cell death via apoptotic or necrotic pathways. This can be highlighted by its regulation by the anti-apoptotic protein Bcl-2; pancreatic acinar cells isolated from Bcl-2 knockout mice demonstrate enhanced PMCA-mediated Ca^{2+} clearance and a resistance to oxidation or Ca^{2+}-induced necrosis, but increased apoptosis. Bcl-2 overexpression meanwhile was shown to impair Ca^{2+} extrusion while PMCA inhibition led to increases in necrosis in pancreatic cells (118).

J. Role of PMCAs in Cancer

Regulation of the Ca^{2+} signal can impact on many of the typical hallmarks of cancer such as sustained proliferation, resistance to cell death, and induction of angiogenesis (149, 354). This had led to the study of Ca^{2+} handling components during tumor development becoming an active field of research in recent years, with the TRP channel family leading the way, and may offer a number of novel pharmaceutical targets for the treatment of cancer (325). As we highlighted in the previous section, there is substantial evidence that PMCA expression and activity, like that of TRP channels, also impacts on many of the cellular processes defining tumorigenesis and progression. Indeed, first evidence for a potential role for the PMCA came from analysis of the expression of PMCA1 and 4 in human skin and lung fibroblastic cell lines following exposure to the oncogenic simian virus 40 (SV40), both of which were found to be downregulated (307). In this section we describe the expression changes and roles of the PMCA to have currently been identified in various cancers.

1. PMCA and breast cancer

As we discussed elsewhere in this review, changes in PMCA expression and particularly that of isoform 2 are inextricably linked to mammary epithelial cell physiology, showing a dramatic upregulation during lactation and its immediate downregulation being essential for mammary gland involution upon weaning (303–305, 384). This highlights a potentially critical role for the pumps in regulating cell survival. PMCA isoforms 1, 2, and 4 are all expressed in a variety of human breast cancer cell lines (203), with PMCA2 levels being up to 100-fold higher in tumorigenic versus nontumorigenic human breast epithelial cell lines (204). Similarly, PMCA1 demonstrates an approximately threefold increase in expression in serum-starved MCF-7 breast cancer cells compared with control MCF-10A mammary epithelial cells, while PMCA4 levels appear lower in some cancerous cell lines compared with controls (203, 204).

Clinically, high levels of PMCA2 expression in breast tumors correlate with increased tumor grade, resistance to the chemotherapeutic drug docetaxel, and reduced 5-yr survival rates in breast cancer patients (169, 384). Each of these studies examined the effects of PMCA2 overexpression in breast cancer cells, reporting decreases in $[Ca^{2+}]_i$ and apoptosis as well as higher incidence, reduced latency, and accelerated tumor growth when grown as xenografts in immunocompromised mice (169, 384). In agreement with this, crossing PMCA2-inactive mutant *deafwaddler* mice with mouse mammary tumor virus (MMTV)-Neu mice inhibited tumor formation (169). Mechanistically, these effects may well be multifaceted. Jeong et al. (169) found PMCA2 expression to correlate with human epidermal growth factor receptor 2 (HER2) in breast tumors, and through a physical interaction to regulate HER2 signaling as well as its internalization and degradation upon PMCA2 knockdown. In addition, PMCA2 has been found to interact with calcineurin in breast cancer cells, with overexpression leading to a reduction in NFAT transcriptional activity (159) and disruption of the complex causing NFAT activation with a consequential upregulation in proapoptotic Fas ligand expression, apoptosis, and increased cytotoxicity to the chemotherapeutic agent paclitaxel (18).

There is evidence that PMCA1 and 4 may also play important roles in signal regulation in breast cancer cells and that these are isoform specific. Upregulation of PMCA4 has been witnessed during induced differentiation of MCF-7 breast cancer cells alongside an increased rate of Ca^{2+} clearance (386). PMCA4 expression also increases during proliferation in these cells, and antisense PMCA inhibition was shown to result in reduced rates of proliferation while increasing $[Ca^{2+}]_i$ and impairing PMCA-mediated Ca^{2+} clearance (205). Fewer cells were found to be in the S phase and more in the G_2/M phase of the cell cycle upon PMCA inhibition, with the authors concluding slower transition through this stage. Further experiments by the group, this time in the MDA-MB-231 breast cancer cell line, have identified that PMCA1 primarily regulates bulk Ca^{2+} extrusion

in these cells and that knockdown of this isoform leaves cells vulnerable to Ca^{2+}-induced necrotic cell death (81). PMCA4 silencing, on the other hand, was found to enhance apoptosis induced by Bcl-2 inhibition, likely through regulation of NFκB signaling.

Hence, there is evidence to suggest that inhibition of any of the three PMCA isoforms expressed in breast cancer cells may have the potential to be used as an anti-cancer therapy. This may be highlighted by research conducted using a new platinum-based compound [Pt(O,O0-acac)(g-acac)(DMS)], which is highly cytotoxic to cisplatin-resistant MCF-7 cells through inhibition of PMCA activity, thus raising $[Ca^{2+}]_i$ and activating apoptotic pathways (255, 256). This may be a promising avenue to explore, particularly in tumors resistant to currently available chemotherapeutic agents.

2. PMCA and colorectal cancer

The finding that PMCA expression was altered during breast cancer tumorigenesis prompted the question as to whether this was also the case in other neoplastic cell types. Both PMCA1 and 4 have been shown to be expressed in a variety of human colon cancer cell lines, with isoform 1 predominating in undifferentiated cells (14, 311). During induced or postconfluent differentiation however, there is a marked upregulation of PMCA4 expression as well as enhanced PMCA-mediated Ca^{2+} efflux (14, 15, 311). In contrast, differentiated colon tumors exhibit significantly lower PMCA4 expression compared with healthy surrounding tissue (15). Aung et al. (15) then went on to determine that siRNA inhibition of PMCA4 did not alter HT-29 colon cancer cell viability following apoptotic stimulation, while overexpression led to a decrease in cell proliferation suggesting that the postdifferentiation downregulation of PMCA4 may facilitate tumor growth. In agreement with these findings, an examination of PMCA4 protein in normal mucosa compared with varying grades of colon tumor has found reduced levels only in high grade adenoma, adenocarcinoma, and lymph node metastasis indicating a potential role in tumor progression (319). Meanwhile, rectal tumors display elevated PMCA4 expression compared with normal mucosa (133).

3. PMCA and other cancers

In addition to the more extensively defined roles in breast and colon cancer, an association has also been found between the PMCAs and tumors in a number of other tissues. PMCA1 has been found to be downregulated in oral squamous cell carcinoma and premalignant lesions, a possible result of increased methylation (322). Conversely, PMCA expression appears higher in mouse AS-30D hepatoma cells compared with normal liver, a pattern similar to that seen in regenerating hepatic cells (90). In addition, evidence that the PMCAs may be a potential therapeutic target for chemotherapy-resistant cancers has been found in two further cell types. First, PMCA1 expression is increased in cisplatin-resistant human ovarian adenocarcinoma cells compared with cisplatin-sensitive cells (348), and second, the resistance to cell death conferred upon pancreatic cancer cells by a switch in metabolism from mitochondrial to glycolytic pathways can be reversed by inhibiting glycolysis, an effect which leads to PMCA inhibition, Ca^{2+} overload, and cell death (167). Hence, although the field is still in its infancy, the identified roles for different PMCA isoforms in regulating tumorigenesis, progression, and survival in various tissues may lend themselves towards targeting for the treatment of cancers in specific cell types.

V. CONCLUSIONS

The ubiquitous nature of PMCA expression combined with the tissue-specific distribution of the four isoforms provide an adaptable toolkit to control intracellular Ca^{2+} dynamics throughout the body. As regulators of bulk Ca^{2+} transport they are critical in the maintenance of desirable serum ionic balance for tissue mineralization from embryonic development through to adulthood, as well as influencing processes such as fertilization, smooth muscle tone, and cell survival. Meanwhile, as binding partners they are able to direct Ca^{2+}-dependent signaling to regulate a plethora of physiological processes from sensory transmission to cellular growth. Through genome-wide screening and the use of animal models, specific roles for each isoform have now been defined in the development and progression of a large number of human diseases affecting the cardiovascular, nervous, and musculoskeletal systems as well as in the fields of cancer, endocrinology, and infectious disease. Given the widespread spatiotemporal expression pattern of the PMCAs, it is perhaps surprising that mutating or knocking out a particular isoform reveals a role localized to a particular tissue. However, it is likely that the specificity of action is dictated through a combination of isoform/splice variant, interaction partner, and local Ca^{2+} requirements. It is the cell-specific functions of these pumps combined with their nature as membrane-bound ATPases that may therefore make them suitable and druggable targets for the development of novel therapeutic strategies in wide-ranging fields including contraception, hypertension, cardiac hypertrophy, neurodegeneration, malaria, and cancer.

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