**The TNF Family of Ligands and Receptors: Communication Modules in the Immune System and Beyond**

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**Abstract**

The tumor necrosis factor (TNF) and TNF receptor (TNFR) superfamilies (TNFSF/TNFRSF) include 19 ligands and 29 receptors that play important roles in the modulation of cellular functions. The communication pathways mediated by TNFSF/TNFRSF are essential for numerous developmental, homeostatic, and stimulus-responsive processes in vivo. TNFSF/TNFRSF members regulate cellular differentiation, survival, and programmed death, but their most critical functions pertain to the immune system. Both innate and adaptive immune cells are controlled by TNFSF/TNFRSF members in a manner that is crucial for the coordination of various mechanisms driving either co-stimulation or co-inhibition of the immune response. Dysregulation of these same signaling pathways has been implicated in inflammatory and autoimmune diseases, highlighting the importance of their tight regulation. Investigation of the control of TNFSF/TNFRSF activities has led to the development of therapeutics with the potential to reduce chronic inflammation or promote anti-tumor immunity. The study of TNFSF/TNFRSF proteins has exploded over the last 30 yr, but there remains a need to better understand the fundamental mechanisms underlying the molecular pathways they mediate to design more effective anti-inflammatory and anti-cancer therapies.