Inflammasomes: Intracellular Regulators of Host Defense & Inflammation

Inflammasome-mediated Caspase-1 Activation Regulates the Secretion of IL-1β & IL-18

Hot-like receptors (TLRs) are a subset of pattern recognition receptors (PRRs) that are essential for detecting invading pathogens and activating the innate immune response. NLRs are activated by a variety of bacterial, fungal, and viral molecules that contain pathogen-associated molecular patterns (PAMPs). NLRs can sense intracellular danger signals (DAMPs) released from damaged cells. Upon activation, these NLRs oligomerize to form multiprotein inflammasome complexes that serve as platforms for the recruitment, cleavage, and activation of inflammatory caspase-1. Inflammasome-regulated caspase-1 requires two signals, a priming signal that results in the NLRs and/or NLRP1-dependent translocation of Pro-Caspase-1 and Pro-Caspase-5 and a second signal that promotes induced activation of the inflammasome. A subfamily consisting of NLRs and NLRP1-like receptors, cytokine receptors (CRs), or the AIM2 (Apoptosis-associated Speck-like protein containing a CARD) sensor, can also induce inflammasome-mediated caspase-1 activation. Similar to TLRs, inflammasome caspase-1 signaling, both IL-1β and IL-18 activate the NLRP3, ASC, and pyrin NLR signaling pathways to induce the expression of pro-inflammatory proteins and secondary mediators that promote the recruitment of innate cells to the site of infection. In addition, IL-1β enhances the cytolytic activity of natural killer (NK) cells and promotes Th1 and Th17 response. Four inflammasome complexes (NLRP1, NLRP3, NLRP4, and ASC) have been partially characterized to date. These complexes contain a specific NLR family protein or AIM2, the ASC and/or Cardinal adaptor proteins, and Pro-Caspase-1.

Although the secretion of IL-1β and IL-18 are intended to combat infection, constitutive inflammasome activation and the subsequent overproduction of IL-1β or IL-18 can have detrimental effects that are associated with autoinflammatory and autoimmune disorders. For these reasons, mechanisms that inhibit IL-1β and IL-18 signaling are of interest. Down-or up-regulated receptors that require 5-10 nM signal, 2-10 antagonists, and disruption of IL-1 receptor heterodimerization are intrinsic pathways that inhibit IL-1β signaling. Similarly, recently occurring IL-1β-binding protein (IL-1BP) can prevent IL-1β binding to its receptor. Further research in this necessary to characterize how inflammasome complexes are activated, the mechanisms by which IL-1β and IL-18 signaling are regulated, and further beneficial and detrimental effects associated with the inflammasome pathway. These findings may have therapeutic implications for inflammatory-related disorders, including autoinflammatory disorders, Crohn’s disease, type-2 diabetes, gout, psoriasis, arthritis, and Alzheimer’s disease.