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BIObrief

TAKE-AWAY REFERENCE TOOL

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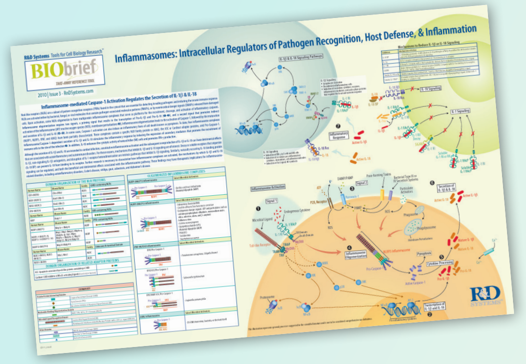

Inflammasomes: Intracellular Regulators of Pathogen Recognition, Host Defense, & Inflammation

Pattern recognition receptors (PRRs) expressed by macrophages, monocytes, dendritic cells, neutrophils, and epithelial cells play a critical role in activation of the innate immune response. Nod-like receptors (NLRs) are cytoplasmic PRRs that detect intracellular microbial components or endogenous danger signals. Following activation, some NLRs form inflammasome complexes that induce the cleavage and activation of Caspase-1, leading to the subsequent processing and secretion of IL-1β and IL-18. IL-1β and IL-18 induce the expression of secondary mediators that attract immune cells to the site of the infection. Although IL-1β and IL-18 have a beneficial role in promoting inflammation and eliminating infectious pathogens, mutations that result in constitutive inflammasome activation and the overproduction of IL-1β and IL-18 have been linked to autoinflammatory and autoimmune disorders. Further research is necessary to identify factors that regulate inflammasome activation, to characterize the cell type-specific effects of NLR-/inflammasome-dependent signaling pathways, and to determine how defects in these signaling pathways contribute to the development and progression of inflammation-related pathological conditions.

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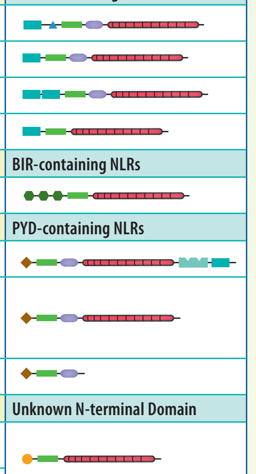
Inflammasomes: Intracellular Regulators of Pathogen Recognition, Host Defense, & Inflammation

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

Nod-like receptors (NLRs) are a subset of pattern recognition receptors (PRRs) found in the cytosol that are essential for detecting invading pathogens and initiating the innate immune response. NLRs are activated either by bacterial, fungal, or viral molecules that contain pathogen-associated molecular patterns (PAMPs), or by nonmicrobial danger signals (DAMPs) released from damaged cells. Upon activation, some NLRs oligomerize to form multiprotein inflammasome complexes that serve as platforms for the recruitment, cleavage, and activation of inflammatory caspases. Inflammasome oligomerization requires two signals, a priming signal that results in the transcription of Pro-IL-1β and Pro-IL-18 (❶-❷), and a second signal that promotes indirect activation of the inflammasome, such as ion or membrane perturbations, reactive oxygen species (ROS), or ATP (❸). Inflammasome oligomerization leads to the activation of Caspase-1, followed by the maturation and secretion of IL-1β and IL-18 (❹-❻), and in some cases, an inflammatory form of cell death known as pyroptosis. Inflammasome/Caspase-1-dependent secretion of IL-1β and IL-18 stimulates the inflammatory response by inducing the expression of secondary mediators that promote the recruitment of immune cells to the site of the infection (❼). In addition, IL-18 enhances the cytolytic activity of natural killer (NK) cells and promotes IFN-γ production. To date, four inflammasome complexes (NLRP1, NLRP3, IPAF, and AIM2) have been partially characterized. 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. Decoy or soluble receptors that sequester IL-1β, non-signaling IL-1β antagonists, and disruption of IL-1 receptor heterodimerization are intrinsic pathways that inhibit IL-1β signaling. Similarly, naturally occurring IL-18 binding protein (IL-18 BP) can prevent IL-18 from binding to its receptor. Further research is necessary to characterize how inflammasome complexes are activated, the mechanisms by which IL-1β and IL-18 signaling can be regulated, and both the beneficial and detrimental effects associated with the inflammasome pathway. These findings may have therapeutic implications for inflammasome-related disorders, including autoinflammatory disorders, Crohn's disease, vitiligo, gout, asbestosis, and Alzheimer's disease.

DOMAIN ORGANIZATION OF THE NLR PROTEINS



Human Name	Mouse Name	Family	CARD-containing NLRs
CIITA (NLRA)	CIlta (Nlra)	NLRA	
NOD1 (NLRC1)	Nod1 (Nlrc1)	NLRC	
NOD2 (NLRC2)	Nod2 (Nlrc2)	NLRC	
IPAF (NLRC4)	Ipaf (Nlrc4)	NLRC	
Human Name	**Mouse Name**	**Family**	**BIR-containing NLRs**
NAIP	Naip1-7	NLRB	
Human Name	**Mouse Name**	**Family**	**PYD-containing NLRs**
NLRP1 (NALP1)	Nlrp1a-c (Nalp1)	NLRP	
NLRP2-9 (NALP2-9), NLRP11-14 (NALP11-14)	Nlrp2, Nlrp3 (Nalp3), Nlrp4a-g (Nalp4a-g), Nlrp5, Nlrp6, Nlrp9a-c (Nalp9a-c), Nlrp12 (Nalp12), Nlrp14 (Nalp14)	NLRP	
NLRP10 (NALP10)	Nlrp10 (Nalp10)	NLRP	
Human Name	**Mouse Name**	**Family**	**Unknown N-terminal Domain**
NLRC3 (NOD3), NLRC5 (NOD27)	Nlrc3, Nlrc5	NLRC	
NLRX1 (NOD9)	Nlrx1	NLRX	

DOMAIN ORGANIZATION OF RELATED ADAPTOR PROTEINS

ASC: Apoptosis-associated speck-like protein containing a CARD	
Cardinal: CARD inhibitor of NFκB-activating ligands (found only in humans)	

DOMAIN KEY

Protein-Protein Interacting Domains	
	Caspase Recruitment Domain (CARD)
	Pyrin Domain (PYD)
	Baculovirus Inhibitor of Apoptosis Repeat Domain (BIR)
	Unknown N-terminal Domain
Nucleotide-Binding/Oligomerization Domain	
	NAIP, CIITA, HET-E, TP-1 Domain (NACHT)
Microbial Ligand Recognition Domain	
	Leucine-Rich Repeat Domain (LRR)
	Hematopoietic Interferon-inducible Nuclear Protein with a 200 a.a. repeat (HIN200)
Other Domains	
	NACHT-Associated Domain (NAD)
	Function to Find Domain (FIIND)
	Activation Domain (AD)

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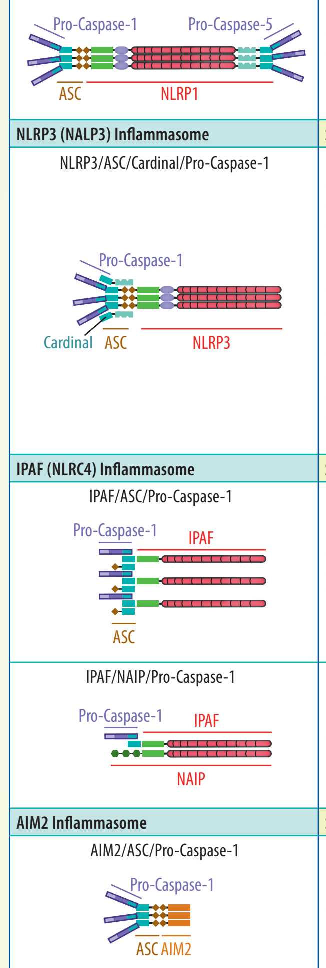
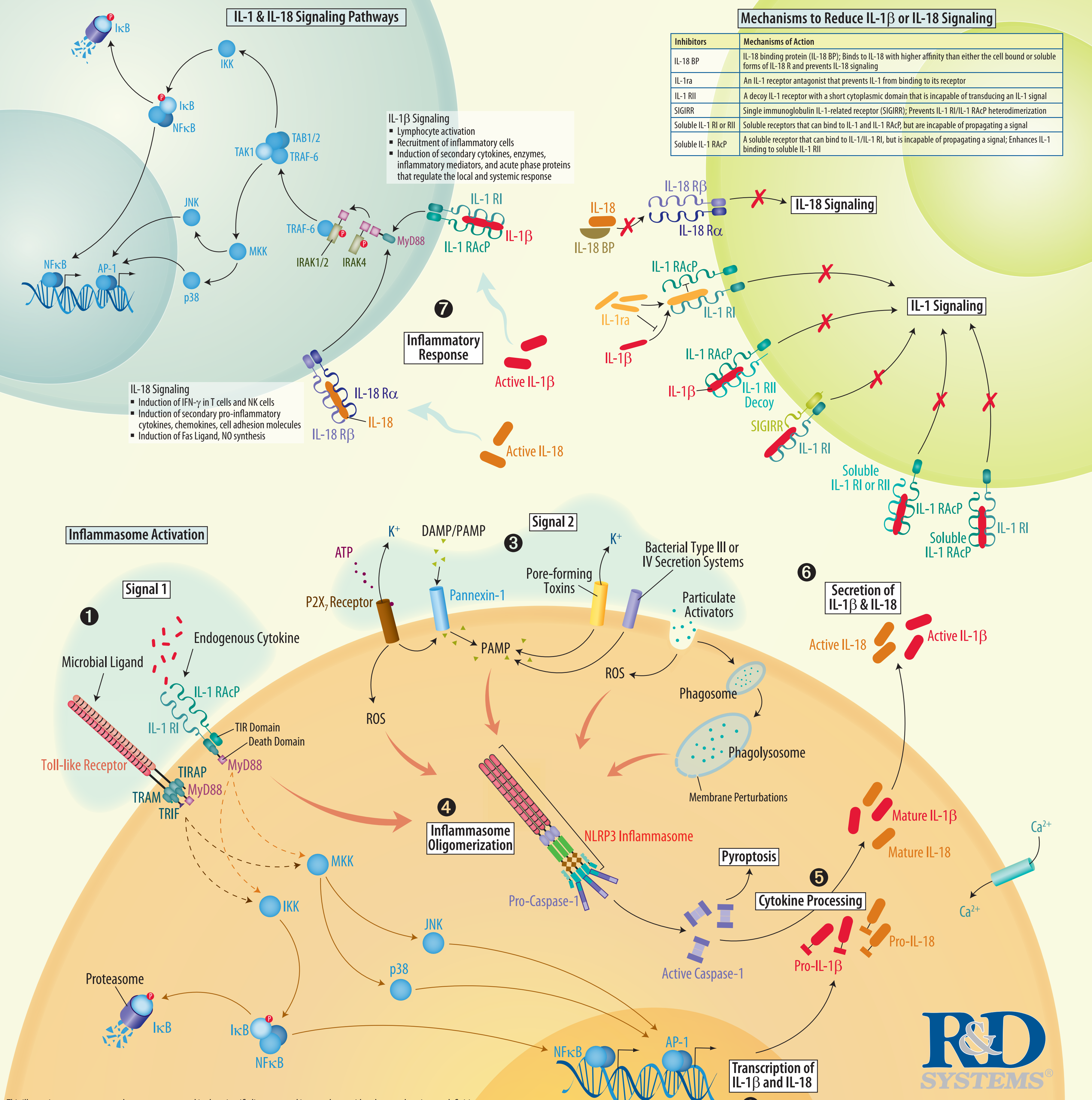
OLIGOMERIZED INFLAMMASOME COMPLEXES



NLRP1 (NALP1) Inflammasome	Select Microbial Activators
NLRP1/ASC/Pro-Caspase-1/Pro-Caspase-5	· *Bacillus anthracis* lethal toxin · Muramyl dipeptide (MDP)
NLRP3 (NALP3) Inflammasome	**Select Microbial Activators**
NLRP3/ASC/Cardinal/Pro-Caspase-1	· Adenovirus, Bacterial RNA · *Candida albicans/Saccharomyces cerevisiae* · Danger signals: ATP, NAD^+, β-amyloid and particulates such as calcium pyrophosphate dihydrate and monosodium urate · Xenogenous compounds: Silica, asbestos, and alum · Influenza virus · *Listeria monocytogenes* · Lipopolysaccharide (LPS) · Muramyl dipeptide (MDP) · Sendai virus · *Staphylococcus aureus*
IPAF (NLRC4) Inflammasome	**Select Microbial Activators**
IPAF/ASC/Pro-Caspase-1	· *Pseudomonas aeruginosa* · *Salmonella typhimurium* · *Shigella flexneri*
IPAF/NAIP/Pro-Caspase-1	· *Legionella pneumophila*
AIM2 Inflammasome	**Select Microbial Activators**
AIM2/ASC/Pro-Caspase-1	· DS-DNA from virus, bacteria, or the host itself

Oligomerized inflammasome complexes may consist of more subunits than what is shown.



This illustration represents general processes suggested in the scientific literature and is not to be considered comprehensive nor definitive.

Mechanisms to Reduce IL-1β or IL-18 Signaling

Inhibitors	Mechanisms of Action
IL-18 BP	IL-18 binding protein (IL-18 BP); Binds to IL-18 with higher affinity than either the cell bound or soluble forms of IL-18 R and prevents IL-18 signaling
IL-1ra	An IL-1 receptor antagonist that prevents IL-1 from binding to its receptor
IL-1 RII	A decoy IL-1 receptor with a short cytoplasmic domain that is incapable of transducing an IL-1 signal
SIGIRR	Single immunoglobulin IL-1-related receptor (SIGIRR); Prevents IL-1 RI/IL-1 RAcP heterodimerization
Soluble IL-1 RI or RII	Soluble receptors that can bind to IL-1 and IL-1 RAcP, but are incapable of propagating a signal
Soluble IL-1 RAcP	A soluble receptor that can bind to IL-1/IL-1 RI, but is incapable of propagating a signal; Enhances IL-1 binding to soluble IL-1 RII