Review
InvivoGen

Inflammasomes

The nucleotide-binding oligomerization domain-like receptor (NLR) family of proteins is involved in the regulation of innate immunity responses.

These proteins sense pathogen-associated molecular patterns (PAMPs) in the cytosol as well as the host-derived signals known as damage-associated molecular patterns (DAMPs).

Certain NLRs induce the assembly of large caspase-1-activating complexes called inflammasomes [1,2].

Activation of caspase-1 through autoproteolytic maturation leads to the processing and secretion of the proinflammatory cytokines interleukin-1β (IL-1β) and IL-18. So far, four inflammasomes have been identified and defined by the NLR protein that they contain; the NLRP1/NALP1b inflammasome [3]; the NLRC4/IPAF inflammasome [4,5]; the NLRP3/NALP3 inflammasome [6]; and the AIM2 (absent in melanoma 2) containing inflammasome [7,8].

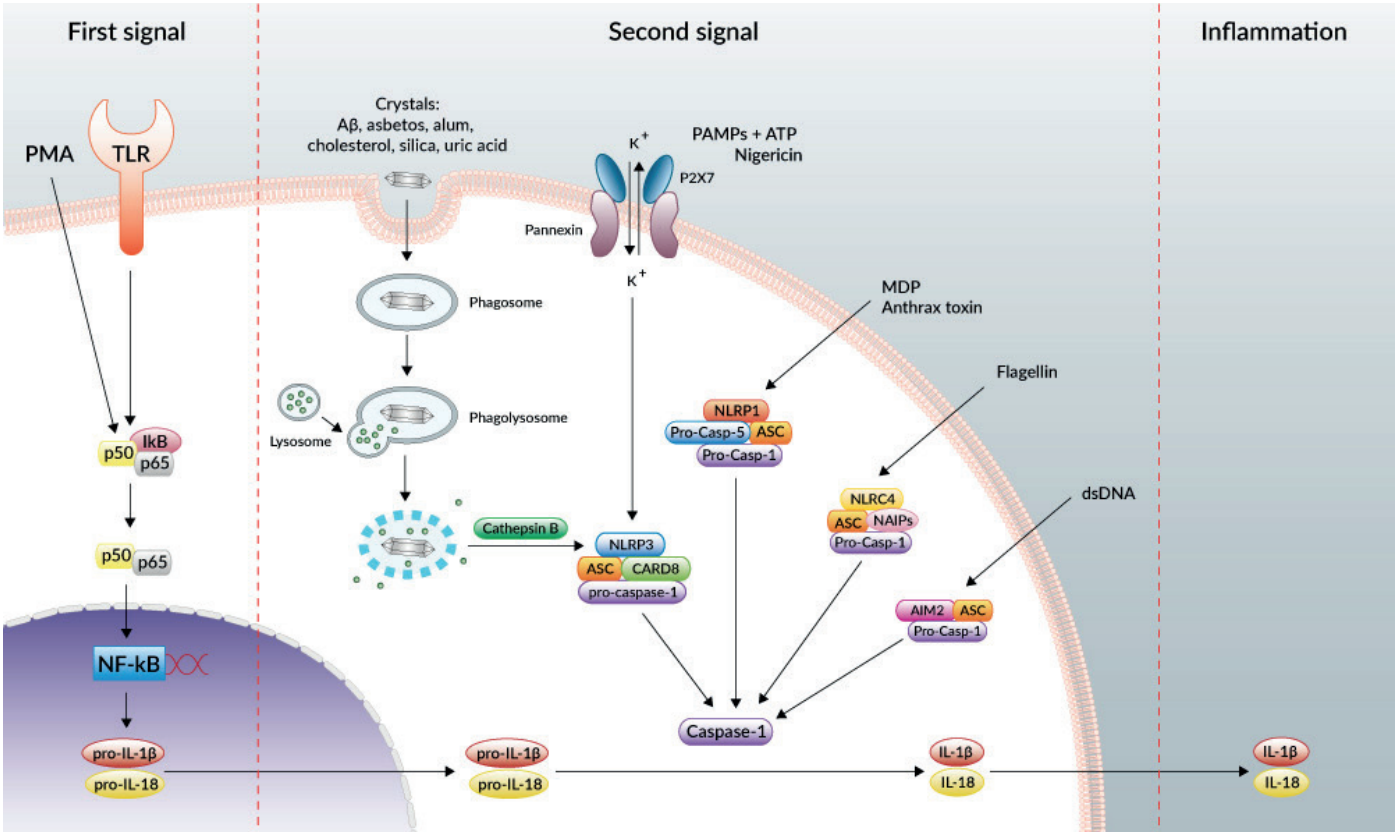
IL-1β AND IL-18

IL-1βand IL-18 are related cytokines that cause a wide variety of biological efffects associated with infection, inflammation and autoimmune processes.

IL-1β participates in the generation of systemic and local responses to infection and injury by generating fever, activating lymphocytes and by promoting leukocyte infiltration at sites of infection or injury. IL-18 induces IFN-γ production and contributes to T-helper 1 (Th1) cell polarization.

Maturation of IL-1β and IL-18 by cleavage with caspase-1 is a prerequisite for inducing the immune responses. Caspase-1 itself is synthesized as an inactive 45 kDa zymogen (pro-caspase-1) that undergoes autocatalytic processing following an appropriate stimulus. The active form of the enzyme comprises the subunits p20 and p10 [9]. Caspase-1 is activated within the inflammasome multiprotein complex through interaction with ASC (apoptosis-associated speck-like protein containing a carboxy-terminal CARD), a bipartite adapter protein that bridges NLRs and caspase-1 [10].

It is now generally accepted that activation and release of IL-1β requires two distinct signals.
The nature of these signals in vivo during infection or inflammation is not completely defined.
However, in vitro studies indicate that the first signal can be triggered by various PAMPs following Toll-like receptor (TLR) activation which induces the synthesis of pro-IL-1β.
The second signal is provided by the activation of the inflammasome and caspase-1 leading to IL-1β processing.



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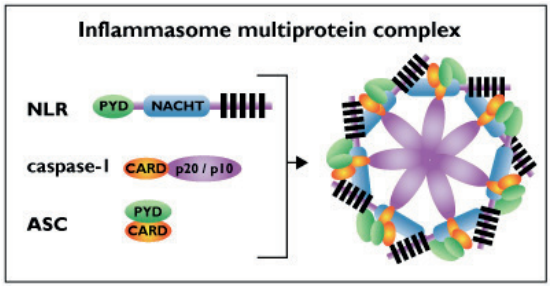


The requirement for a second signal for IL-1β maturation might constitute a fail-safe mechanism to ensure that induction of potent inflammatory responses occurs only in the presence of a bona fide stimulus, such as pathogen infection and/or tissue injury.

NLRP1 INFLAMMASOME

NLRP1 assembles a multimolecular complex inflammsome with caspase-1, caspase-5, ASC, and a triphosphate ribonucleotide [1,2,10].

NLRP1 directly binds to ASC, via its pyrin (PYD) domain and directly to caspase-1 via its CARD domain. Activity of the NLRP1 inflammasome is induced by muramyl dipeptide (MDP) and anthrax lethal toxin (mouse NLRP1b) [3]. Studies have indicated that NOD2 is needed for in vitro sensing of both MDP and anthrax lethal toxin.

Activation of the NLRP1 inflammasome is tightly linked to the apoptotic pathway. The anti-apoptotic proteins Bcl-2 and Bcl-X(L) bind NLRP1 in resting conditions, suppressing caspase-1 activation and IL-1β secretion.

Several NLRP1 gene variations have been associated with an increased risk of autoimmune disorders and vitiligo, an autoimmune condition that results in patchy changes in skin pigmentation. However, the precise role of the NLRP1 inflammasome in immune responses remains poorly understood.

NLRC4 INFLAMMASOME

NLRC4 (also known as IPAF) is the only member of the NLRC family currently known to assemble an inflammasome [2,4,5].

NLRC4 associates with pro–caspase-1 with its CARD domain without the need of an adaptor protein, and interaction with ASC is required for robust IL-1β secretion.

Oligomerization of NLRC4 is triggered by cytosolic flagellin from a variety of bacteria such as Salmonella typhimurium, Legionella pneumophila, Shigella flexneri, and Pseudomonas aeruginosa or other stimuli possibly delivered by a bacterial secretion system (type III or type IV).
NAIP5, another member of the NLR family, appears to be involved in the recognition of the ligand under certain circumstances [11].

Flagellin is an interesting ligand triggering both TLR5 and the NLRC4 inflammasome [12]. As such, flagellin is likely to independently signal the production of cytokines and drive their maturation via caspase-1.

NLRP3 INFLAMMASOME

Among the inflammasomes, NLRP3 inflammasome is the most studied.

Its activation in macrophages can be achieved with a plethora of PAMPs, such as liposaccharide, peptidoglycan, and bacterial nucleic acids, provided the cells are exposed to ATP.
Indeed, in the absence of ATP, macrophages stimulated with LPS produce large quantities of pro-IL-1β, but release little mature cytokine to the medium. ATP and certain bacterial toxins, such as nigericin and maitotoxin, cause a change in the intracellular ion composition leading to the activation of the NLRP3 inflammasome. The effect of ATP is mediated by the purinergic P2X7 receptor together with pannexin, which causes a rapid potassium efflux from the cytosol upon activation [13].

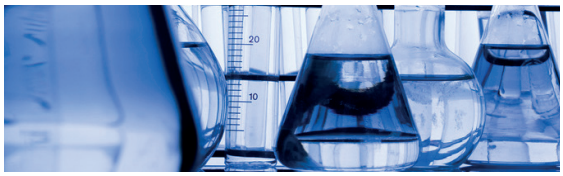
Crystals of monosodium urate (MSU) and calcium phosphate dihydrate (CPPD) are known to activate caspase-1 in a NLRP3-dependent manner [14]. Deposition of MSU and CPPD crystals in joints is responsible for the inflammatory conditions gout and pseudogout, respectively, implicating NLRP3 in their etiology. Uric acid in addition is released into the extracellular milieu by necrotic cells, suggesting an important role of NLRP3 in the detection of endogenous 'danger' signal.

Crystalline silica and asbestos are known to activate the NLRP3 inflammasome, implicating its role in the pathogenesis of silicosis and asbestosis [15-17].

Aluminium salt (alum) can also activate the NLRP3 inflammasome, albeit in the presence of PAMPs such as LPS [17-19].

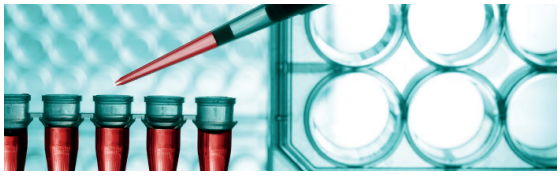
Phagocytosis of crystals leads to lysosomal swelling and damage. The lysosomal perturbation together with the release of cathepsin B, a lysosomal cysteine protease, result in the activation of the NLRP3 inflammasome [17].

INVIVOGEN'S CATEGORIES



IL-1β/IL-18 Sensor cells

Inflammasome Test Cells



NLRC4 Reporter Assay

Inflammasome Inducers

Inflammasome Inhibitors

Inflammasome Primers

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