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The inflammasomes: mechanisms of activation and function

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Summary

In response to injurious or infectious agents caspase-1 activating multiprotein complexes, termed inflammasomes, assemble in the cytoplasm of cells. Activated caspase-1 cleaves the pro-forms of the interleukin-1 cytokine family members leading to their activation and secretion. The IL-1 family cytokines have multiple pro-inflammatory activities implicating them in the pathogenesis of many inflammatory diseases. While defined ligands have been identified for the NLRP1, IPAF and AIM2 inflammasomes, little is known about the activation mechanisms of the NLRP3 inflammasome. Numerous different molecular entities, such as various crystals, pore-forming toxins or extracellular ATP can trigger the NLRP3 inflammasome. Recent work proposes that NLRP3 is activated indirectly by host factors that are generated in response to NLRP3 triggers.

Introduction

In the last decade many molecular mechanisms that operate to activate cells in response to infection and tissue damage have been discovered. Innate immune cells and other host cells express a group of transmembrane and cytosolic signaling receptors, which are triggered by molecules uniquely found in microbes or by host molecules that appear in non-physiological locations or that are chemically altered during tissue damage. Most of the innate immune signaling receptors, such as members of the Toll-like receptor (TLR) or the Rig-I like helicase families, activate distinct transcriptional programs leading to inflammation, anti-viral responses and the induction of adaptive immunity [1]. The members of the nucleotide-binding domain leucine-rich repeat containing (NLR) and the pyrin domain and HIN200 domain containing (PYHIN) protein families can form so-called inflammasomes, which initiate the cleavage and release of interleukin-1 family cytokines [2].

While most of the hitherto recognized inflammasomes form in response to a certain molecular trigger, the NLRP3 inflammasome can be activated by a wide variety of molecular substances of dissimilar physico-chemical nature. Here, the recent progress in our - still incomplete - understanding of the mechanisms leading to inflammasome activation is reviewed.

Dual control of the IL-1b cytokine family activation

Many cells can produce and secrete cytokines in response to their activation by cellular stimuli. Most cytokines are transcriptionally regulated and, upon induction, are released into the

environment through the secretory pathway. The IL-1b cytokine family members are also under transcriptional control, however, these cytokines differ from other cytokines in that they lack a leader sequence and they are expressed as biologically inactive pro-forms in the cytoplasm of cells. These cytokine pro-forms are the substrates of the cysteine protease caspase-1, which mediates the cleavage and release of the mature, biologically active cytokine forms. Caspase-1 itself is present as an inactive pro-form in the cytoplasm and it is activated by proteolytic self-processing [3]. Several multimolecular proteins complexes, referred to as inflammasomes, have been identified as caspase-1 activators [2]. These molecules control the second, required step of IL-1b cytokine activation.

NLR and PYHIN family proteins can form inflammasomes

The NLR proteins are commonly organized into three domains, a C-terminal leucine-rich repeat (LRR) domain, an intermediate nucleotide binding and oligomerization domain (NOD, also called NACHT domain) and a N-terminal pyrin (PYD), caspase activation and recruitment domain (CARD) or a baculovirus inhibitor of apoptosis repeat domain (BIR). The LRR domains of these proteins are hypothesized to interact with putative ligands and play a role in auto-regulation of these proteins. The NACHT domain can bind to ribonucleotides, which regulates the self-oligomerization and inflammasome assembly [4]. The N-terminal domains, which mediate protein-protein interactions with downstream signaling intermediates, are also used to subcategorize the NLR proteins. A group of 14 NLRP proteins in humans carry a PYD domain. NOD1 (NLRC1), NOD2 (NLRC2) and NLRC4 (also called IPAF) instead express an N-terminal CARD domain while NAIP5 has a BIR domain at the N-terminus [5].

Up until now, the three NLR proteins NLRP1, NLRP3 and NLRC4 have been identified to form inflammasomes. NLRP1, which is the only NLRP protein that has an additional C-terminal CARD domain, was initially identified to form an intracellular multimolecular complex with the adapter protein apoptosis-associated speck like protein (ASC) and the proteins CARDINAL and caspase-5 [6]. In analogy to the formation of the apoptosis regulating multimolecular apaptosome complex, the caspase-1 activating multi-protein complex was coined inflammasome [6]. The bacterial peptidoglycan derivative muramyl dipeptide (MDP) can trigger the NRLP1 inflammasome assembly in vitro [7] and one of the three mouse NLRP1 genes (*Nlrp1b*) senses the lethal toxin expressed by *Bacillus anthracis* [8].

The NLRC4 inflammasome is activated by the bacterial flagellar protein flagellin, which also activates the transmembrane Toll-like receptor 5. Depending on the recognized bacterial species, the NLRC4 inflammasome could also recruit NAIP5. Since NLRC4 lacks a PYD, it could activate pro-caspase-1 directly, however, ASC is still required for full activation of pro-IL-1b (reviewed in[9]).

The NLRP3 inflammasome also activates caspase-1 via its interaction with ASC. A large number of NLRP3 inflammasome triggers with different physical properties and chemical compositions have been described. These include microbial stimuli (viruses, bacteria, protozoans and funguses) [10–16], crystalline or aggregated substances (asbestos, silica, uric acid, Abeta peptides, etc) [17–20], pore-forming toxins, as well as extracellular ATP or necrotic cell components [21,22]. In addition, low intracellular potassium appears to be a further requirement for NLRP3 activation [23]. Conceivably, direct recognition of such a large array of substances is improbable. The likely indirect mechanisms involved in NLRP3 inflammasome activation are further discussed below.

Double stranded DNA of synthetic, mammalian or microbial origin that is present in the cytosol is recognized by another inflammasome. The cytosolic PYHIN protein family member absent in melanoma-2 (AIM2) interacts with DNA through the C-terminal HIN200 domain and recruits ASC via its PYD to form a caspase-1 activating inflammasome [24–27]. The other

human family members (IFI16, IFIX and MNDA) also contain HIN200 and PYD domains. However, these proteins are expressed mostly in the nucleus and an immunological function has not yet been ascribed to these family members. AIM2 likely plays an essential role in the control of certain viral and bacterial infections and since the PYHIN locus is associated with lupus erythematosus susceptibility it is possible that AIM2 could contribute to autoimmune disease (Fig. 1).

At least two signals are required for NLRP3 inflammasome activation

Cells that are activated to assemble the NLRP3 inflammasome produce copious amounts of pro-inflammatory cytokines and also secrete other leaderless proteins involved in inflammation and the ensuing tissue repair [28]. Concomitantly, a special form of cell death, termed pyroptosis, is induced leading to the destruction of the activated cell and spillage of cellular contents [29]. Hence, NLRP3 inflammasome activation generates a drastic immune response with far-reaching consequences for the activated cells and the surrounding tissues. First, the generated biologically active IL-1 cytokine family members act on surface receptors that share their intracellular signaling domains with that of TLRs (Toll/Interleukin-1 receptor, TIR) [1]. As a result, a highly proinflammatory gene program downstream of the adaptor molecule MyD88 is induced leading to the generation of additional inflammatory mediators. This activity of IL-1b has long been described with its dub name ‘endogenous pyrogen’ [30]. Secondly, after inflammasome activation, a swift influx of circulating immune cells into the endangered tissue is provoked, and their actions could lead to collateral tissue damage. In fact, the neutrophil influx into tissues after application of NLRP3 stimuli has frequently been used as an in vivo read-out for the function of NRLP3 inflammasome proteins [18,20]. It is therefore not too surprising that the commitment of a cell to assemble the NLRP3 inflammasome is tightly controlled. One common theme in immunity is that important decisions, for example the induction of adaptive immunity, rely on two (or more) signals that frequently are further controlled by subtle thresholds for full cell activation. Similarly, recent reports suggest that cells - at least in vitro - require two (and potentially more) signals for full NLRP3 inflammasome activation [31,32]. The most upstream events in NLRP3 inflammasome activation, *i.e.*, ASC speck formation or cleavage of caspase-1, only proceeded if cells had received a priming signal from a transcriptionally active TLR, NLR or cytokine receptor prior to activation of NLRP3 with pore-forming toxins, ATP or various crystals [32]. The limiting factor for NLRP3 activation appeared to be the expression level of NLRP3 itself, since heterologous expression of NLRP3 was sufficient to overcome the necessity of priming by transcriptionally active signaling receptors [32]. Hence, NLRP3 inflammasome activation is tightly controlled by signals downstream of pattern recognition or cytokine receptors [33].

Possible mechanisms of NLRP3 activation and parallels to plant immunity

The exact sequence of molecular events leading to NLRP3 inflammasome activation is currently not well understood. Recently, two - potentially interconnected - pathways upstream of NLRP3 activation have been proposed to operate. According to one hypothesis, NLRP3 activators lead to the production of reactive oxygen species (ROS), which could be sensed directly or indirectly by NLRP3 [14,17,34]. Support for this hypothesis comes from experiments demonstrating that ROS scavengers, such as N-acetyl cysteine or RNAi-mediated knock-down of the P22(phox) subunit of the NADPH oxidase, which is critically involved in ROS production, attenuated caspase-1 activation [17]. It would be conceivable that NLRP3 could be modified directly under increased ROS stress. Alternatively, it seems possible that NLRP3 could bind to an ROS-modified or –induced intermediate molecule leading to its activation. This type of indirect activation mechanism could explain how different chemical or physical entities could activate one common downstream pathway. However, some signals that are known to activate ROS production, such as several TLR ligands alone, appear to be

insufficient for NLRP3 inflammasome activation suggesting that other, ROS-independent triggers may additionally be required for full NLRP3 activation [1]. Moreover, increased ROS can also reversibly inactivate caspase-1 by oxidation and glutathionylation, indicating that increased ROS can also downregulate caspase-1 activity [35]. These data suggest that ROS-mediated NLRP3 activation would likely be tightly controlled.

A second hypothesis places NLRP3 downstream of or within a proteolytic cascade. This theory is based on the observations that NLRP3 inflammasome activators can inflict lysosomal damage leading to the release of lysosomal proteases into the cytosol and that even physical or pharmacological disruption of lysosomes in the absence of any crystalline materials can mediate NLRP3 inflammasome activation [19,20]. Further support for the involvement of lysosomal damage upstream of NLRP3 stems from experiments that show that proton pump inhibitors, which prevent lysosomal acidification and therefore inhibit the activation of acid-dependent lysosomal proteases, could almost completely abrogate NLRP3 inflammasome activation by crystals. Indeed, inhibition or lack of the single lysosomal protease cathepsin B led to a substantial, albeit incomplete inhibition of NLRP3 activation [20]. Thus, so far, clear genetic evidence for an essential role of cathepsins upstream of NLRP3 is lacking due to functional redundancy of cathepsins and the lethality of double mutants. It is likely that the activation of NLRP3 is more complex and requires a combination of factors, such as ROS activity and protease activity (Fig. 2).

There are similarities between this latter model and the presumed mode of activation of some of the NLR orthologue proteins acting in plant immune resistance. Similar to vertebrate cells plant cells express surface receptors that recognize pathogenic microbes by virtue of so-called pathogen-associated molecular patterns (PAMPs). Many plant pathogens, in turn, deliver avirulence (avr) effector proteins into the cytoplasm, most of which have proteolytic activity that can modify the signaling response of the activated transmembrane signaling proteins [36]. However, in an evolutionary arms race plants have evolved a large number of cytoplasmic immune signaling receptors, some of which have the ability to sense the enzymatic activity of pathogen-derived avr proteins and, in response, mount an effector-triggered immune response (ETI) [37]. The largest class of these cytosolic resistance or R protein signaling receptors is represented by a family of proteins (NB-LRRs) with structural similarity to members of the mammalian NLR protein family. Plant NB-LRRs do not directly interact with their corresponding effector proteins; they rather indirectly detect the activity of avr proteins by interacting with the modified host avr target proteins. For example, NB-LRRs are activated upon phosphorylation or cleavage of their host molecule binding partner (reviewed in[37]). This kind of mechanism led to the proposal of a guard model for plant–pathogen interactions in which it is suggested that NB-LRRs detect molecular changes of a limited number of key avr virulence targets and do not directly detect the large range of bacterial avr proteins themselves [38]. It is possible that a similar mechanism could be operative in mammalian innate immune sensing by NLRs. However, a ‘guardee’ for NLRP3 has yet to be described and it is not known whether plants NB-LRRs can be activated in a similar manner after non-infectious insults. It appears possible that NLRP3 senses the appearance of a proteolytic fragment that is generated by protease activity in the cytosol or, alternatively, that an NLRP3 inhibiting protein becomes processed leading to deinhibition and subsequent NLRP3 activation (Fig. 2).

Conclusion and future direction

In recent years it became increasingly evident that in addition to their fundamental for the development of auto-inflammatory diseases [39], inflammasomes are also critical for infection control, the recognition of tissue damage and for the development of immune pathologies in general. Recent evidence furthermore suggests a role of NLRP3 in tumor surveillance [40]. Not surprisingly, the NLRP3 inflammasome represents an attractive drug target. While much

progress towards the understanding of NLRP3 activation and its role in immunity has been made, the precise molecular details leading to the NLRP3 inflammasome assembly remain to be determined. This fragmentary understanding of NLRP3 activation represents a major hurdle for the identification and development of specific pharmacologic inhibitors of the NLRP3 inflammasome. Currently, we are left with therapeutic approaches directed against the outcome of NLRP3 activation, namely anti-IL-1b strategies. Anti-IL-1b therapies, fortuitously, have proven to be successful for the treatment of disabling auto-inflammatory diseases and also show promising results in the control of crystal-induced inflammatory diseases [39]. As we learn more about the upstream mechanisms of NLRP3 activation and more reporter systems become available the probability to identify specific inhibitors of this important innate immune pathway will certainly increase in the coming years.

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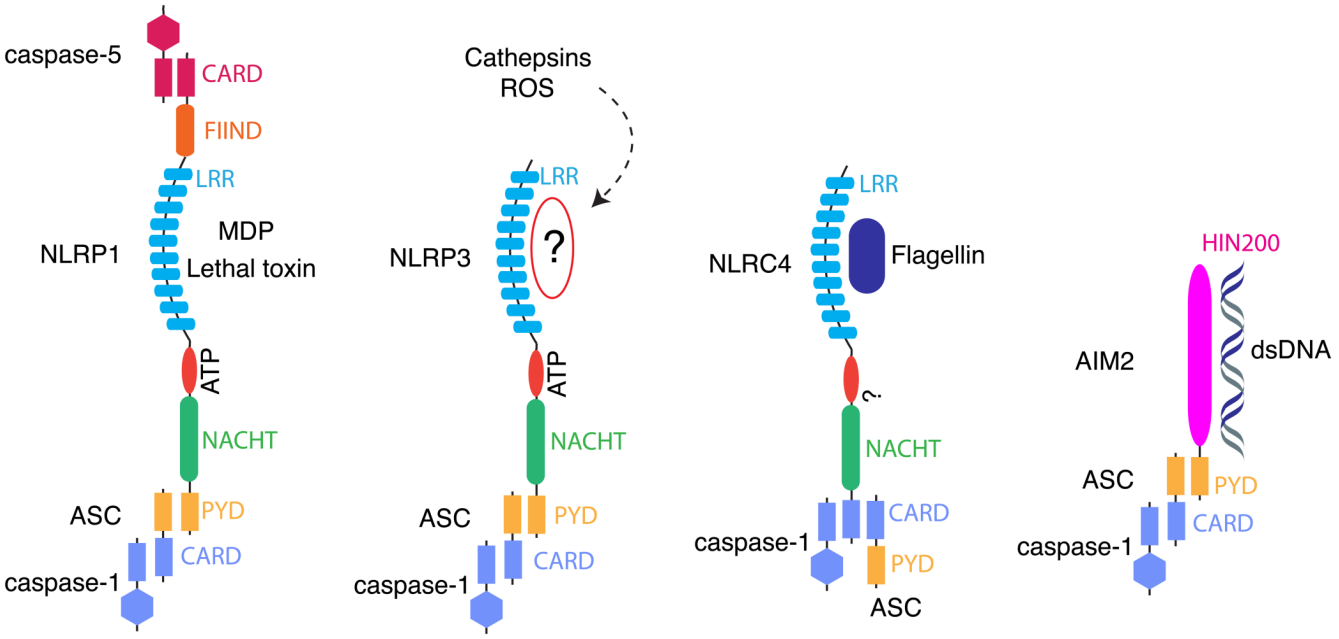

Figure 1. Schematic of characterized inflammasomes

The NLRP1 inflammasome consists of a NACHT and LRR domains and can bind to caspase-5 via the C-terminal CARD domain and to the adapter molecule ASC via the N-terminal PYD domain. ASC interacts with caspase-1 via its CARD domain. Muramyl dipeptide (MDP) and lethal factor of *Bacillus anthracis* are presumed to interact with the LRRs of NLRP1. NLRP3 has LRRs possibly interacting with an intermediate molecule that is generated by cathepsin and/or ROS activity. The NACHT domain can associate with ATP and NLRP3 binds to ASC via its N-terminal PYD domain. ASC, in turn, associates with caspase-1. The NLRC4 inflammasome consists of LRR domains that could interact with bacterial flagellin and a NACHT domain followed by an N-terminal CARD domain. The CARD domain can either directly interact with caspase-1 or via the CARD domain of ASC. The AIM2 inflammasome can directly interact with double-stranded DNA through its C-terminal HIN200 domain. AIM2 activates caspase-1 via ASC at the N-terminus of the protein.

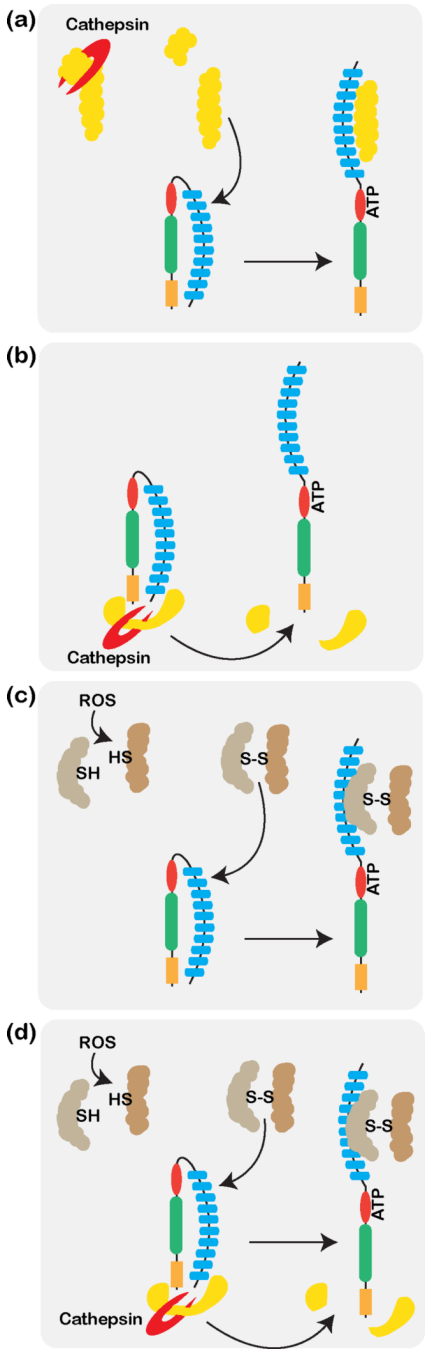

Figure 2. Possible scenarios leading to NLRP3 inflammasome activation

A. A protease acts on a cytoplasmic protein and the cleavage product binds to and activates NLRP3. B. NLRP3 is auto-inhibited by binding to a protease sensitive protein. After cleavage of the NLRP3 interacting protein, NLRP3 becomes deinhibited and activated. C. Reactive oxygen species act on a substrate in the cytoplasm of cells, which becomes modified and acts as an activator of the NLRP3 inflammasome. D. A combination of an ROS-mediated activator and protease cleaved inhibitor could act to activate the NLRP3 inflammasome.