Review

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Mechanisms of inflammasome activation: recent advances and novel insights

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Inflammasomes are cytosolic multiprotein platforms assembled in response to invading pathogens and other danger signals. Typically inflammasome complexes contain a sensor protein, an adaptor protein, and a zymogen – procaspase-1. Formation of inflammasome assembly results in processing of inactive procaspase-1 into an active cysteine-protease enzyme, caspase-1, which subsequently activates the proinflammatory cytokines, interleukins IL-1β and IL-18, and induces pyroptosis, a highly-pyrogenic inflammatory form of cell death. Studies over the past year have unveiled exciting new players and regulatory pathways that are involved in traditional inflammasome signaling, some of them even challenging the existing dogma. This review outlines these new insights in inflammasome research and discusses areas that warrant further exploration.

Introduction

Inflammasomes play a central role in maintaining the sanctity of the cytosol. These multimeric complexes comprise a sensor protein belonging to the AIM2 (absent in melanoma 2)-like receptor, ALR, or the NLR [nucleotide-binding domain (NBD) and leucine-rich-repeat-(LRR)-containing) family, an adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and an inactive zymogen, procaspase-1 [1,2]. Formation of inflammasomes in response to microbial or danger signals leads to cleavage of procaspase-1 into active caspase-1 enzyme, which further cleaves proforms of the inflammatory cytokines, IL-1β and IL-18, into their active forms. Inflammasome activation also results in pyroptosis, an inflammatory form of cell death [2,3].

Inflammasomes are essential components of host defense and they guard the host robustly from the assault of microbial pathogens and endogenous danger signals. Despite their cytosolic location, they are capable of launching an effective immune response against extracellular, vacuolar, and intracellular bacteria, fungi, and viruses. Inflammasomes also sense crystalline substances such as silica and alum, and endogenous danger signals such as ATP, and mount appropriate immune responses [2,4]. Although optimal inflammasome activation is highly beneficial to the well-being of the host, dysregulation of inflammasome activation can lead to exacerbation of symptoms in infectious diseases and to the development of autoimmune and inflammatory disorders [5]. Inflammasome research has witnessed outstanding advancements; this review aims to summarize and update the reader on the key findings from the past few years.

Molecular mechanisms of inflammasome activation

With few exceptions, members of the NLR family typically have a tripartite structure with a C-terminal LRR domain, a central NACHT domain, and an N-terminal caspase recruitment and activation (CARD) or pyrin (PYD) domain [6]. By contrast, members of the ALR family have a PYD and up to two HIN-200 domains [7]. The HIN-200 domains directly bind to dsDNA, leading to the activation of ALRs [2]. Despite the NLRs being categorized as PRRs, no direct interaction between NLRs and their activating stimuli has been formally demonstrated. Once activated, the NLRs and ALRs typically oligomerize through their NACHT and HIN-200 domains, respectively, resulting in recruitment of the adaptor protein, ASC, through interaction between the PYD of ASC and the PYD of the NLR/ALR [8]. Further, ASC recruits procaspase-1 into the complex via its CARD domain.

ASC is believed to function as a molecular platform for protein–protein interactions during inflammasome assembly, and recent studies have shed light on the ultrastructure of these platforms in detail [9,10]. These studies reported that activation of NLRP3 and AIM2 inflammasomes results in the interaction of their PYD with the PYD of ASC, an event that precipitates ASC prion-like nucleation. Subsequently, more ASC molecules are recruited into this structure, and the ASC prion self-perpetuates, leading to the generation of large stable filaments, which are necessary and sufficient for inflammasome activation. Importantly, this ASC prion-like structure provides a platform for caspase-1 activation and subsequent cytokine processing. Together, these two landmark studies have revealed the existence of an assembly

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mechanism for ASC-dependent activation that unifies our understanding of the activation mechanisms of the NLR and ALR inflammasomes. Furthermore, recent studies have demonstrated that ASC prions also function as a cell-to-cell communication signal [11,12]. Following inflammasome-induced cell death, ASC oligomers accumulate in the extracellular space and continue to process extracellular IL-1β. Ingestion of ASC specks by macrophages results in lysosomal damage and IL-1β production, indicating their ability to act as a danger signal. Together, these studies point at a mechanism whereby inflammasome triggers of minimal intensity can induce an immensely amplified response; the trigger activates relatively few sensor molecules, however, this is sufficient for polymerization of a large number of ASC-caspase-1 prions, which then, through self-perpetuation and cell-to-cell propagation lead to a highly magnified, inflammasome response [13].

Canonical inflammasomes: NLR and ALR inflammasomes

NLRs such as NLRP1b, NLRP3, and NLRC4, as well as the ALR, AIM2, constitute the best-characterized inflammasomes (Figure 1) [2]. Among these, NLRP3 is still the most intensively investigated NLR, and it is activated by a vast array of microbe- and host-derived triggers. Conversely, NLRP1b is activated by anthrax lethal toxin and NLRC4 by bacterial type III secretion system (T3SS) components and flagellin. By contrast, AIM2 is activated by bacterial or viral double-stranded (ds)DNA in the cytosol. Interestingly, recent studies have identified novel pathways and triggers associated with these inflammasomes, as well as novel inflammasomes formed by sensors such as a non-NLR protein, pyrin, and NLRs such as NLRP6 and NLRP12 that have significant roles in microbial infections (Figure 2). These advances are described in detail below.

The NLRP1b inflammasome

NLRP1b, the first inflammasome to be characterized, is activated in a physiologically relevant manner only by a single signal, the anthrax lethal toxin (LeTx). LeTx is composed of protective antigen (PA) and lethal factor (LF). LF, a putative metalloprotease, has a zinc metalloprotease-like consensus sequence that is responsible for NLRP1b activation [14]. The presence of LeTx in the cytosol leads to the assembly of NLRP1b inflammasome, which is essential for defense against *B. anthracis* spores in mice [15,16]. LeTx cleaves NLRP1b close to its N terminus, which is essential and sufficient for NLRP1b activation [17].

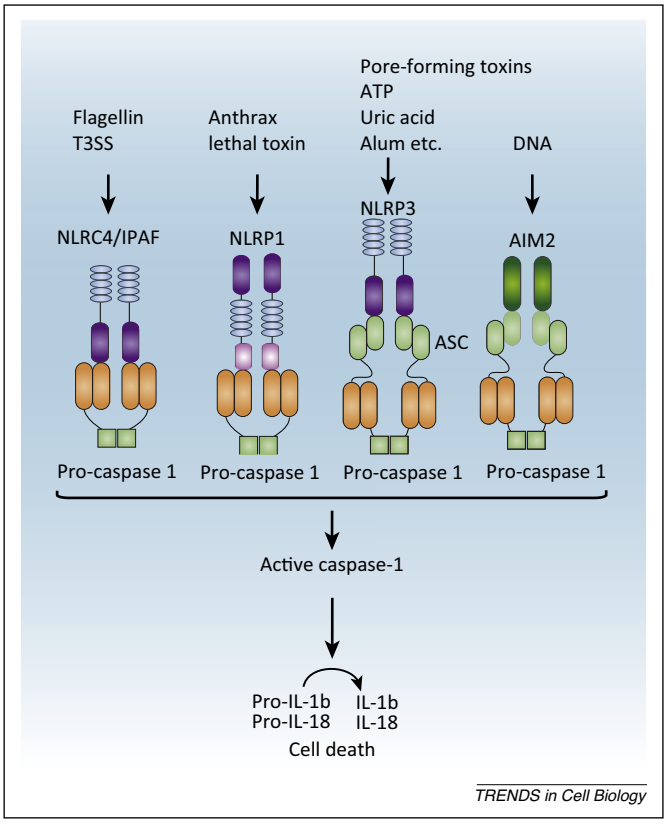

Figure 1. Canonical inflammasomes. Canonical inflammasomes contain sensors belonging to the NLR or ALR family. NLRC4 is activated by bacterial flagellin and T3SS components, NLRP1b is activated by anthrax lethal toxin, and AIM2 is activated by cytosolic dsDNA. NLRP3 is activated by a wide variety of signals including pore-forming cytotoxins, ATP, uric acid, and alum. Once activated the receptors form an inflammasome complex with or without the adaptor, ASC, and recruit procaspase-1, which is subsequently cleaved into active caspase-1. Caspase-1 cleaves pro-forms of IL-1β and IL-18 into their active forms as well as induces cell death. Abbreviations: AIM2, absent in melanoma 2; ALR, AIM2-like receptor; ASC, apoptosis-associated speck-like protein containing a CARD; IL, interleukin; NLR, nucleotide-binding domain (NBD) and leucine-rich-repeat-(LRR)-containing family; T3SS, type III secretion system.

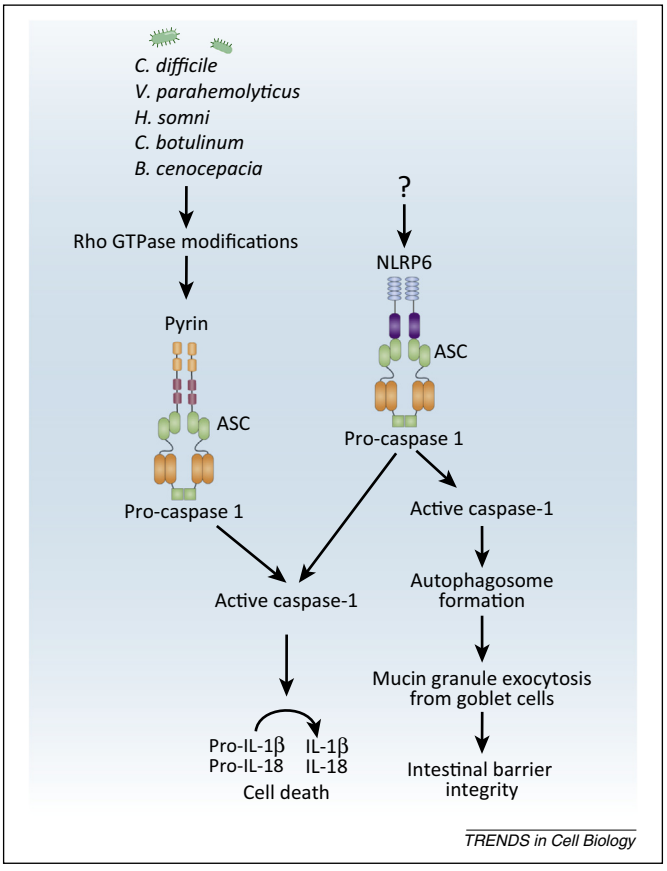

Figure 2. Pyrin and NLRP6: newly characterized inflammasomes with atypical activators and downstream effects. Unlike classical inflammasomes, pyrin senses pathogen-induced alterations in cellular machinery such as modifications in Rho GTPases. The activator of NLRP6 is not yet identified. In addition to inducing caspase-1 activation and subsequent IL-1 cytokine production, NLRP6 inflammasome sustains intestinal homeostasis. NLRP6 regulates autophagosome formation, which is essential for mucin granule exocytosis from goblet cells and for the maintenance of intestinal barrier integrity.