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Inflammatory caspase regulation: Maintaining balance between inflammation and cell death in health and disease

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Abstract

Members of the mammalian inflammatory caspase family, including caspase-1, caspase-4, caspase-5, caspase-11, and caspase-12 are key regulators of the innate immune response. Most studies to date have focused on the role of caspase-1 in the maturation of the pro-inflammatory cytokine interleukin-1β and its upstream regulation by the inflammasome signaling complexes. However, an emerging body of research has supported a role for caspase-4, caspase-5, and caspase-11 in both regulating caspase-1 activation and inducing the inflammatory form of cell death called pyroptosis. This non-canonical inflammatory caspase pathway appears essential for the regulation of cytokine processing and, in turn, may provide important and, to date, understudied targets for the treatment of auto-inflammatory disorders where the inflammasome pathway is dysregulated. Here, we will discuss the mechanisms of inflammasome and inflammatory caspase activation and how these pathways intersect to promote pathogen clearance.

Keywords

Inflammasome; caspase-1; Interleukin-1β; NLRP3; ASC

Introduction

The innate immune system serves to sense microbial, host-derived, and foreign danger signals. It employs pattern recognition receptors that respond to pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) released by cells in conditions of cellular damage or stress. Pattern recognition receptors are expressed by cells that make contact with invading microbes, including macrophages, monocytes, dendritic cells, neutrophils, endothelial cells, and cells of the adaptive immune system.

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Three types of pattern recognition receptors exist: Toll like receptors (TLR) that are expressed at the cell surface, intracellular NOD (nucleotide binding oligomerization domain) receptors, and receptors that provide the scaffolds for inflammasome assembly. Engagement of receptors in the first two groups primarily results in the activation of the transcription factor NFκB in response to extracellular or intracellular proinflammatory signals, respectively. The third group initiates the assembly of inflammasomes, cytosolic multi-protein signaling complexes that are essential for the maturation and release of certain cytokines during the innate immune response. A number of distinct inflammasomes exist but they all converge on the activation of caspase-1, a protease required to ensure correct regulation of inflammatory signaling.

Caspase-1 and its role in cytokine maturation

Caspase-1 was the first caspase identified and belongs to the subgroup of caspases termed inflammatory caspases that also includes caspase-4, caspase-5, caspase-11, and caspase-12 [1]. It was originally named interleukin (IL)-1β-converting enzyme (ICE), and was discovered as a protease primarily synthesized in the monocytic cell lineage [2]. Caspase-1 is an endopeptidase with a catalytically active cysteine residue responsible for the nucleophilic attack and cleavage of target proteins after an aspartic acid residue.

Caspase-1 is synthesized as an inactive zymogen (pro-caspase-1) that requires activation [3]. The prodomain of caspase-1 contains a conserved protein-protein interaction motif known as a CARD (caspase recruitment domain) that is essential for the recruitment of caspase-1 to inflammasomes [4]. Recruitment to inflammasomes induces oligomerization, which is sufficient to activate caspase-1 [5]. Three dimensional structures have revealed that the active enzyme is a homodimer of the catalytic domains [6]. Each catalytic domain is comprised of a p20 and a p10 subunit, generated as a result of auto-processing of the enzyme dimer (Figure 1). The p20 subunit contains the catalytic cysteine residue that is conserved among all caspase family members. Based on the structural similarity between caspase-1 and the apoptotic initiator caspases, caspase-2, −8, and −9, dimerization is considered to be essential for the activation of caspase-1, while auto-processing likely serves to stabilize the active enzyme [7, 8].

The main substrates for caspase-1 are the proinflammatory cytokines, IL-1β and IL-18 [2, 9]. These two cytokines share structural similarities, but IL-18 and IL-1β display different biological activities that are mediated through specific receptors [10]. IL-1β is an endogenous pyrogen that triggers fever, leukocyte tissue migration, and expression of other cytokines and chemokines [11]. It is produced as an inactive cytoplasmic precursor (proIL-1β, p35), which must be cleaved at Asp116 to generate the mature active form (p17) that is subsequently released from the cell [10]. IL-18 was first described in 1989 as an endotoxin-induced factor that stimulates the production of interferon(IFN)-γ in splenocytes [12]. It was first cloned in 1995 and was then shown to have an IL-1 signature sequence [13]. Its functions include the induction of other pro-inflammatory cytokines, upregulation of adhesion molecules, and activation of natural killer cell activity [14]. Like IL-1β, it is synthesized as an inactive precursor protein (proIL-18, p24) that is processed by caspase-1 at

Asp36 to produce the mature 18 kDa peptide that is readily released from the cell [9, 15] (Figure 1, 2).

It is generally established that caspase-1 does not play a central role in apoptosis because the *Casp1* knockout mouse does not display a phenotype consistent with disruption of a cell death pathway, unlike the gross abnormalities resulting from loss of *Casp3, 8, or 9* (increased brain size, embryonic lethality, etc. [16]). In contrast, mice with targeted disruption of *Casp1* have no apparent anatomical or developmental abnormalities, with normal counts of erythrocytes, leukocytes, and platelets in the peripheral blood. The mice showed no apparent defect in apoptosis and *Casp1*-deficient macrophages and thymocytes preserved their capacity to undergo apoptosis in response to multiple stimuli [17]. However, these mice have an acute defect in their capability to convert proIL-1β to its mature form and are resistant to lethal doses of endotoxin/lipopolysaccharide (LPS) [17]. These features of the knockout mouse indicate a more prominent role for caspase-1 in inflammation and associated processes than in apoptotic cell death.

There are some circumstances where caspase-1 may induce cell death. Caspase-1 has been shown to cleave the pro-apoptotic executioner caspase, caspase-7, which appears to be required for LPS-induced lymphocyte apoptosis [18]. In addition, caspase-1 has been shown to induce a form of cell death known as pyroptosis [19]. This type of cell death is morphologically distinct from apoptosis, which manifests as cell shrinkage, membrane blebbing and DNA fragmentation, resulting in cells being packaged into apoptotic bodies and phagocytized without causing inflammation. Pyroptosis is initiated in response to microbial pathogens and is characterized by cell swelling, membrane rupture, and release of proinflammatory cellular contents [20]. It is characterized by the formation of plasma membrane pores between 1.1 and 2.4 nm in diameter, large enough to allow the influx of extracellular calcium ions required for lysosome exocytosis [21]. These pores dissipate cellular ionic gradients, inducing a net increased osmotic pressure, water influx, and cell swelling that eventually results in osmotic lysis and release of inflammatory intracellular contents [21]. Thus, cells undergoing pyroptosis display a measurable increase in size [21, 22].

The mechanism by which mature IL-1β is released from the cell is unclear. This was originally thought to be an active secretion event, but IL-1β release does not depend on the conventional ER-Golgi secretion machinery [23]. More recently, it has been proposed that IL-1β release is a byproduct of pyroptotic cell death [24, 25]. However, IL-1β release from living cells has been reported [26, 27] and, therefore, it is possible to uncouple IL-1β release from lytic cell death. Pyroptosis is often thought to be a caspase-1-dependent type of cell death [20, 28], but caspase-1-independent pyroptosis has been observed (see next section). Emerging evidence suggests that this type of cell death is equally dependent on additional members of the inflammatory caspase family.

Caspases-4, −5, −11 and their role in inducing pyroptosis

The inflammatory caspases, including caspase-1, caspase-4, caspase-5, caspase-11, and caspase-12, are encoded by four genes in humans: *CASP1, CASP4, CASP5*, and *CASP12*;

and three genes in mouse: *Casp1*, *Casp11* and *Casp12*. Caspase-1, −4, −5, and −12 are clustered on human chromosome 11q22 and arose by tandem gene duplication. Like caspase-1, each of these proteins encodes a CARD in their prodomain (Figure 1). Sequence analysis of the human inflammatory caspases shows that caspase-1 and caspase-4 share 55% identity, while pro-caspase-4 and −5 share an amino acid sequence identity of 77% [1]. Even though human and mouse caspase-1 are likely orthologs, it is still unclear if human caspase-4, caspase-5, or both, are duplicated counterparts of murine caspase-11. Comparison of the amino acid sequences of human and murine caspases reveals that procaspase-4 and −5 are 59 and 54% identical to procaspase-11, respectively, and 48 and 45% identical to procaspase-12, respectively [1]. Caspase-4 and caspase-11 mRNA have similar tissue distribution patterns [29], but caspase-5 and caspase-11 are both LPS- or IFN-γ-inducible [30]. Despite the similarities between caspase-11 and caspase-5, most publications consider caspase-4 to be the functional homolog of caspase-11. Because caspase-4 and −5 are not expressed in mice, many of the conclusions regarding their functions have been based on research on their closest murine homolog, caspase-11.

Caspase-11 is a murine caspase that has much in common with caspase-1. The phenotype of the *Casp-11* knockout mouse is similar to that of *Casp-1* displaying resistance to endotoxic shock and defects in IL-1β processing [31]. However, caspase-11 did not directly cleave pro IL-1β. Consequently, caspase-11 was initially described as an upstream regulator of caspase-1 activation. It was not until a number of years later, when it was discovered that the published *Casp1* mouse model was also deficient in caspase-11 [32], that it became clear that these two caspases have distinct as well as overlapping functions. The $Casp1^{-/-}$ mouse was generated using strain 129 embryonic stem cells, which has an incidental deletion in the *Casp11* locus. Because *Casp11* is only 1500 base pairs away from *Casp1*, multiple generations of backcrossing to C57BL/6 mice could not segregate the two mutant genes. $Casp11^{-/-}$ and $Casp1^{-/-}/11^{-/-}$ mice were equally resistant to LPS-induced septic shock. However, when caspase-11 expression was reconstituted in $Casp1^{-/-}/Casp11^{-/-}$ mice using a BAC-derived transgene, essentially creating a true caspase-1 knockout, the mice were no longer resistant to LPS challenge [32]. Therefore, sensitivity to LPS is conferred by caspase-11 rather than by caspase-1. Mice lacking both IL-1β and IL-18 do not phenocopy the LPS resistance of the *Casp11* knockout mouse [33]. Thus, the LPS-induced lethality is not considered to be a result of elevated levels of these pro-inflammatory cytokines in the blood. Rather, it is thought that this form of septic shock is actually a direct result of caspase-11-induced tissue damage. While this idea has not been directly tested, it is supported by the fact that caspase-11 appears to be a major driver of pyroptosis in response to certain inflammatory stimuli.

Both caspase-1 and caspase-11 can induce pyroptosis, but the stimuli that engage each of these caspases to do so differ. Caspase-1-dependent cell death was induced by stimuli, such as ATP, that engage known inflammasomes and this was accompanied by IL-1β release. These effects were not dependent on caspase-11. In contrast, IL-1β release in LPS-primed macrophages in response to cholera toxin B (CTB), required both caspase-1 and caspase-11. However, CTBinduced cell death was blocked in the absence of caspase-11. These results suggest that caspase-11 regulates caspase-1 activation and the resulting processing of IL-1β/IL-18, but the role of caspase-11 in death signaling appears to be independent of known

inflammasome components [32]. This pathway has been termed the non-canonical inflammasome pathway.

While CTB was originally considered a specific inducer of caspase-11, a follow up study showed that CTB was functioning to deliver LPS into the macrophages. Dixit and colleagues observed that CTB only induced caspase-11 activation when macrophages were primed with a specific *E.coli* serotype of LPS, O111:B4 [34]. They went on to show that CTB was dispensable for caspase-11 activation, but rather bound to this specific type of LPS and promoted endocytosis of the complex into the cell. Because the activation of caspase-11 was shown to be TLR4-independent, this appears to be a response to intracellular LPS, specifically the lipid A moiety of LPS. Intracellular LPS-induced pyroptosis in human monocytes is similarly dependent on caspase-4, the human homolog of caspase-11 [35]. It has been proposed that LPS directly activates caspase-4, caspase-5, and caspase-11 by binding to the CARD of the caspase and inducing oligomerization [35] (Figure 2). Hence, caspase-4, caspase-5, and caspase-11 appear to be intracellular receptors for LPS, triggering pyroptosis and caspase-1 activation in response to invasive bacteria. Indeed, studies have shown that in the absence of caspase-1, caspase-11 promotes more severe disease in mice infected with *Salmonella typhimurium*. Infected *Casp11*$^{-/-}$ mice had a higher bacterial load than *Casp1*$^{-/-}$/*Casp11*$^{-/-}$ mice [36]. This is thought to result from excess pyroptosis, releasing bacteria that are not effectively cleared by neutrophils due to the absence of caspase-1.

Inflammatory caspase-induced pyroptosis is dependent on a substrate called gasdermin D (GSDMD) that is cleaved by caspase-1, caspase-4, caspase-5, and caspase-11 [37, 38] (Figure 2). GSDMD belongs to the family of gasdermins (GSDMs), which are pore-forming proteins expressed in a variety of cell types and tissues [39]. After cleavage, the N-terminal fragment of GSDMD travels to the plasma membrane to bind to acidic lipids on the inner leaflet, which results in a conformational change that allows GSDMD to form ring shaped structures inserted in the plasma membrane [40, 41]. Based on the solved structure of the GSDMA3 pore (a related member of the family), the pore is estimated to have an inner diameter of 180Å [42]. It has been shown that GSDMD is required for IL-1β release even if cell lysis is prevented [26], which suggests that the GSDMD pore allows IL-1β efflux in addition to the ion influx that causes cell lysis. IL-1β release from living cells has been reported in response to induced caspase-1 activation and in hyperactivated macrophages [26, 27]. It is likely that the extent of GSDMD pore formation determines if pyroptosis occurs but the exact stimuli and physiological conditions that result in IL-1β release without pyroptosis as well as the impact of such an event on the immune response have not been fully elucidated.

Caspase-12 and its role in sepsis

Initial studies in caspase-12-deficient mice suggested that caspase-12 was an ER stress-sensing protease that mediated an ER-specific apoptosis pathway [43]. These studies were later challenged and indicated that caspase-12 played no role in the mitochondrial pathway of cell death [44, 45]. Later studies showed that *Casp12*$^{-/-}$ mice display marked resistance to septic shock suggesting that caspase-12 may function to inhibit caspase-1 [46]. In humans,

caspase-12 is expressed predominantly as a truncated version containing only the N-terminal CARD domain (caspase-12S). Only approximately 20% of people of African descent express the full-length molecule (caspase-12L), which is linked to hypo-responsiveness to LPS-induced production of cytokines such as IL-1β and increased severity of sepsis [47]. Thus, the evolutionary loss of the catalytic domains of caspase-12 may have conferred a selective advantage by increasing resistance to sepsis in human populations.

Inflammasomes: the caspase-1 signaling platforms

The inflammasome is a large intracellular signaling platform composed of a NOD-like receptor (NLR), an adaptor protein (ASC [apoptosis-associated speck-like protein containing a CARD]), and the protease (caspase-1) [4]. The central scaffold NLR proteins of inflammasomes are innate cytosolic receptors that recognize diverse PAMPs and DAMPs. These NLR monomers remain in an inactive conformation until an external or internal signal triggers their conformational change and assembly. NLRs characteristically possess three main domains: the leucine-rich repeat (LRR) domain, which is a region involved in ligand sensing; a central nucleotide-binding domain (NACHT), which drives oligomerization, and a domain involved in recruiting the caspase. The latter domain can be a pyrin domain (PYD), which forms a complex with ASC that, in turn, recruits caspase-1, or a CARD that directly recruits caspase-1 (Figure 1). The CARD and PYD are specific conserved protein interaction domains that mediate these protein-protein interactions. They are characterized by 6 antiparallel α-helices with a hydrophobic core and an outer surface composed of charged residues. There are variations in the length and orientation of these α-helices, and the specificity of protein-protein interactions largely depends on the charged and hydrophobic pockets on the surface [48]. The NLR molecules are thus named NLR with the suffix P or C in reference to the N terminal moiety, PYD or CARD respectively, followed by a number denoting the order in which the NLRs were discovered [49].

A number of distinct inflammasomes exist, the most-well studied being the NLRP1, NLRP3, NLRC4, and AIM2 (absent in melanoma 2) inflammasomes. They each respond to specific stimuli. For example, ATP engages the NLRP3 inflammasome; flagellin triggers the NLRC4-dependent inflammasome; and poly(dA:dT) or double-stranded DNA (dsDNA) activates the AIM2-dependent inflammasome. Common to most of the characterized inflammasomes is the adaptor protein ASC. ASC is required for NLRP3, and AIM2 activation of caspase-1. Like *Casp1*$^{-/-}$ cells, *Asc*-deficient cells display inefficient cytokine processing, and therefore lower levels of mature IL-1β and IL-18 release in response to a range of stimuli [50]. In response to most inflammasome activating stimuli, endogenous ASC assembles in the cytoplasm to form a single speck with a diameter of over 2 μm [51–53]. This ASC speck is often interpreted as representing the platform for recruitment and activation of caspase-1 [54, 55]. *In vitro* reconstitution of the ternary inflammasome suggests caspase-1 is over-stoichiometric to ASC, by approximately 3.5-fold [52].

Cryo-EM structures of the AIM2 and NLRP3 inflammasomes show that AIM2 and NLRP3 are able to induce full length ASC to convert to a self-perpetuating prion form [52, 56]. This prion-like polymerization of ASC provides a mechanism of response to a range of noxious agents. NLRP3 or AIM2 activation induces a conformational change that promotes the

oligomerization of their individual PYDs. This is followed by the recruitment of multiple ASC proteins through PYD-PYD interactions resulting in prion nucleation, a process otherwise prevented from occurring spontaneously due to a high-energy barrier. These ASC prions guide other ASC molecules resulting in the formation of large polymers or filaments. Finally, the ASC filaments recruit multiple caspase-1 molecules through CARD-CARD interactions, bringing them into close proximity to induce their dimerization and activation. Further amplifying the signal, the ASC-CARD and caspase-1-CARD can each self-assemble into filaments [57, 58]. Nucleation of ASC prions is tightly regulated by heterotypic interactions with upstream protein sensors. The tight regulation of nucleation followed by efficient polymerization produces a highly sensitive and robust response to harmful signals.

The NLRP3 Inflammasome

Although it was not the first inflammasome discovered, the NLRP3 (NLR family pyrin-domain containing 3) inflammasome (also known as cryopyrin, NALP3, PYPAF1, or CIAS1) is the one that is best characterized. This is because a large number of mechanisms have been shown to play a role in the activation of the NLRP3 inflammasome, providing it a central role in anti-microbial immunity and sterile inflammation. Upon activation, NLRP3 nucleates ASC helical clusters through PYD-PYD interactions. The oligomerized ASC CARDs then form the platform for caspase-1 CARD to nucleate into filaments, which in turn activates caspase-1 (Figure 2) [59]. Pore formation is a common step shared by a number of NLRP3 activating stimuli. Consequently, NLRP3 inflammasome activation has been observed in response to many bacterial pore-forming toxins including: the marine toxin, maitotoxin, listeriolysin O from *Listeria monocytogenes*, aerolysin from *Aeromonas hydrophila* and *Staphylococcus aureus* hemolysins [60, 61]. NLRP3 is also activated by a range of DAMPs including uric acid crystals, extracellular ATP, silica, aluminium adjuvants, and asbestos [62–64].

One event that is generally required, but not sufficient, for NLRP3 inflammasome activation is the efflux of intracellular potassium [65]. Thus, the bacterial potassium ionophore, nigericin, is a potent inducer of the NLRP3 inflammasome [65, 66]. ATP also activates caspase-1 in an NLRP3-dependent fashion that requires K+ efflux [61, 67]. It has been proposed that ATP binds to the P2X7 receptor to recruit the channel pannexin-1, leading to the formation of a membrane channel mediating K+ efflux [66, 68]. However, a more recent study has identified TWIK2 as an ATP-responsive K+ efflux channel. Using gene expression analysis and targeted gene depletion, it was established that TWIK2 is required for the regulation of the ATP-induced NLRP3 inflammasome activation and sepsis-induced inflammatory lung injury in mice [69]. How K+ efflux induces NLRP3 activation is unclear. It has been shown that K+ efflux promotes the binding of the kinase NEK7 to NLRP3 [70, 71]. This interaction appears to be essential for NLRP3 inflammasome assembly and it is possible that binding of NEK7 to the LRRs of NLRP3 induces a conformational change allowing oligomerization of NLRP3.

The requirement of generation of reactive oxygen species (ROS) for NLRP3 activation is subject to some debate. Most stimuli that activate the NLRP3 inflammasome increase mitochondrial ROS (mtROS) and the use of ROS scavengers or inhibitors is known to block

NLRP3-dependent caspase-1 activation [62]. One study showed that mtROS generation induced by treatment with the complex I inhibitor rotenone was sufficient to activate NLRP3 [72]. However, studies using cells from patients with mutations in subunits of NADPH-oxidase (NOX), which are essential for the generation of mtROS, have no defects in NLRP3 signaling [73–75]. Unique among the inflammasome receptors, NLRP3 requires a priming step for activation [76, 77]. In experimental practice, this is often in the form of LPS treatment, which is needed to induce NLRP3 expression. Inhibition of ROS inhibits this priming step [78]. Therefore, while mitochondrial ROS generation may be required to induce sufficient NLRP3 expression to allow the inflammasome to assemble, it does not appear to be a direct activator of NLRP3 and a second signal is required. This second signal may be oxidized mitochondrial DNA (mtDNA) that has been shown to bind and activate the NLRP3 inflammasome [79, 80]. The production of oxidized mtDNA results from TLR-dependent CMPK2 expression which is required for *de novo* mtDNA synthesis. mtDNA is highly susceptible to oxidization and fragmentation and the release of the mtDNA fragments from mitochondria lead to NPRP3 activation [79]. Thus, it appears that mtROS production and mitochondrial damage play an important, if indirect role in the assembly of the NLRP3 inflammasome providing the priming signal for NLRP3 expression and for production of the NLRP3 intracellular ligand.

The NLRC4 inflammasome

NLRC4 (also known as IPAF, CARD12, CLR2.1, or CLAN) is also capable of initiating caspase-1 activation and IL-1β processing. Flagellin is the canonical stimulus for the NLRC4-dependent inflammasome, but the NLRC4 inflammasome can also be activated independently of flagellin [81]. For example, the non-flagellated bacterium *S. flexneri* has been shown to activate caspase-1 in an NLRC4-dependent manner [82]. NLRC4 lacks a PYD but contains a CARD and is thus able to directly interact with and activate caspase-1, independently of ASC [83] (Figure 1). Therefore, the NLRC4 inflammasome can induce caspase-1 activity in cells that are deficient in *Asc* [55]. Nevertheless, it has been shown that ASC greatly enhances the efficiency of NLRC4-mediated pro-IL-1β and pro-IL-18 maturation [55, 84]. Activation of the NLRC4 inflammasome by flagellated bacteria such as *S. typhimurium* induces pyroptosis. This type of NLRC4-dependent cell death is induced by *S.typhimurium* in logarithmic phase and requires the type III secretion system (T3SS) encoded by Salmonella pathogenicity island 1 (SPI-1), which causes the bacteria to secrete flagellin [84]. Cell death through this mechanism was independent of ASC and caspase-1 [55]. This suggests that while NLRC4 can recruit ASC and caspase-1 to induce cytokine processing, it can also form as separate complex independent of caspase-1 that induces cell death. We previously demonstrated that caspase-4 or capase-5 dimerization is induced upon NLRC4 overexpression [53]. Thus, it is possible that pyroptosis induced by this logarithmic phase *S.typhimurium* assembles an NLRC4 inflammasome that recruits and activates caspase-4 or caspase-5 to induce pyroptosis. Evidence also suggests that triggers for NLRC4 can independently induce pyroptosis. When cells are infected with *S. typhimurium* in stationary phase, such that the bacteria can invade the cell, it induces a slower form of lytic cell death. Intracellular *S. typhimurium* engaged both the NLRC4 and NLRP3 inflammasomes to induce caspase-1 activation and cytokine processing [54], but cell death

induced in this context was only partially dependent on NLRC4 and independently required caspase-11 [36].

NLRC4 does not sense bacterial ligands directly, but instead does so via NLR apoptosis-inhibitory proteins (NAIPs). NAIPs are a family of NLR proteins found in the cytosol that directly recognize pathogenic ligands and trigger assembly of the NLRC4 inflammasome in a ligand specific fashion. The NAIPs are homologues of NLRC4, containing a BIR (baculovirus inverted repeat) domain in place of the CARD (Figure 1). Mice express up to 7 NAIPs, all of them found within the same genomic locus, with *Naip1, Naip2, Naip5 and Naip6* expressed in the commonly used C57BL/6 strain. Humans express a single *NAIP* gene. In mice, NAIP5 was shown to be required for NLRC4 activation by the C-terminus of flagellin [85], while NAIP2 was required for the NLRC4 response to the inner rod protein TTSS, such as PrgJ in *Salmonella enteric*a or BsaK in *B. thailandensis* [86, 87]. The LRRs of NAIP5 or NAIP2 protein bind to flagellin or the TTSS rod protein respectively, allowing it to assume an open confirmation, which sequentially recruits NLRC4 monomers, similarly forcing each one in turn to overcome its auto-inhibited confirmation [88, 89]. This active conformation propagates to 8–10 more NLRC4 molecules creating a wheel like structure that provides the platform for caspase-1 CARD recruitment.

The NLRC4 inflammasome can also recruit the pro-apoptotic initiator, caspase-8, in an ASC-dependent fashion, but independent of caspase-1 and caspase-11 [90]. This appears to result in activation of caspase-8, which contributes to the regulation of pro-IL-1β expression but not IL-1β processing or cell death. It seems, therefore, that caspase-8 serves as a checkpoint to modulate the amount of pro-IL-1β available for caspase-1-dependent maturation. This NLRC4-ASC-caspase-8 complex was shown to be important in the inflammatory response of intestinal epithelial cells (IECs) to *Salmonella* [91]. Caspase-8 was required for the non-lytic expulsion of IECs and release of IL-18, which could compensate for the loss of caspase-1. In macrophages, inhibition of caspase-1 or GSDMD, favors the formation of the NLRC4-ASC-caspase-8 complex [92] and *Casp8* deficiency in $Casp1^{-/-}Casp11^{-/-}$ macrophages conferred resistance to NLRC4-mediated cell death [93]. In cells that either lacked caspase-1 expression or displayed low caspase-1 activity, the NLRC4/ASC/caspase-8 complex led to induction of apoptosis, an event that could be inhibited by TLR-mediated upregulation of the caspase-8 inhibitor cFLIP [93, 94]. Similar observations have been made for the AIM2, NLRP1B, and NLRP3 inflammasomes, suggesting that caspase-8 recruitment is a more general cell death response of inflammasomes when the caspase-1 pathway is blocked [94–96]. However, the significance of this for controlling inflammation or clearance of pathogens is unclear.

NLRP1 inflammasome

NLRP1 (NLR family Pyrin domain containing 1 [also known as NALP1, DEFCAP, NAC, CARD7 and CLR17.1]) was initially characterized as a member of the CED-4 family of mammalian apoptotic proteins, based on its structural similarity with APAF1 (apoptotic peptidase activating factor 1). Human NLRP1 contains an N-terminal PYD, followed by five tandem LRRs, a centrally located NACHT domain, and a C-terminal CARD (Figure 1) [97, 98].

The NLRP1 inflammasome was the first inflammasome identified and was originally reported to assemble in response to LPS [4]. Later, it was found that the activating component was actually a common contaminant of LPS preparations, the peptidoglycan component muramyl dipeptide (MDP) [99]. Removal of the LRR domain activates the NLRP1 inflammasome indicating that this domain has an auto-inhibitory function [4]. Therefore, a two-step activation mechanism has been proposed where first, MDP binds to the LRR inducing a conformational change in NLRP1, and second, NTPs bind to the NACHT domain inducing oligomerization to create a platform for caspase activation [99]. ASC is not required for NLRP1-mediated caspase-1 activation, but it does increase caspase-1 activity in a concentration-dependent manner. This improved efficiency is apparently dependent on ASC interacting with the PYD, allowing each molecule of NALP1 to recruit two procaspase-1 molecules [99]. In addition to its recruitment of caspase-1, NLRP1 has also been shown to bind caspase-5, mediated by the C-terminal CARD [4]. However, the functional significance of this interaction remains unclear.

In mice, the dominant form of NLRP1 expressed is *Nalp1b* which lacks the N-terminal PYD and therefore activates caspase-1 by a direct binding mechanism via the CARD (Figure 1). This isoform of NLRP1 is activated by the lethal factor (LF) component of *B. anthracis* lethal toxin (LT) [100]. LF cleaves a less than 10 kDa fragment off the N-terminal end of NLRP1B, a cleavage event that appears essential for NLRP1B inflammasome assembly [101]. Activation of NALP1B protein by anthrax LT in the absence of ASC induces caspase-1 activation, IL-1β release, and cell death, but not caspase-1 processing [102]. Thus, autocleavage of caspase-1 is not essential for activation by the NLRP1B inflammasome.

AIM2 inflammasome

AIM2 (also known as PYHIN4) is an interferon-inducible gene that was identified during a screening for tumor suppressor genes associated with melanoma [103]. AIM2 is a member of the HIN-200 family of IFN-inducible proteins and is the only one capable of activating caspase-1. It is a cytoplasmic DNA sensor with a high affinity for dsDNA. DNA sensing is mediated by the *C*-terminal HIN-200 domain for oligonucleotide/oligosaccharide-binding [104]. AIM2 recruits ASC and caspase-1 via its N-terminal PYD to facilitate DNA-mediated IL-1β processing and pyroptosis [105]. Intramolecular interaction between the HIN-200 domain and the PYD maintains the receptor in an auto-inhibited state in the absence of ligand binding [106]. Crystal structures of the PYD and HIN-200 domain demonstrate a strong preference for the two domains to interact through their respective charged surfaces. This auto-inhibition serves to ensure that AIM2 interacts with the downstream adapter ASC only upon activation by the dsDNA ligand [107].

Initial studies showed that silencing of AIM2 in human or mouse macrophages led to decreased inflammasome activation, caspase-1 activation, and cell death induced by vaccinia virus, cytoplasmic DNA, or poly (dA:dT) [105, 108]. This was confirmed in the *Aim2*$^{-/-}$ mice as the mice had impaired IL-1β release in response to synthetic DNA but not to activators of other inflammasomes [109–111]. Thus, the AIM2 inflammasome is essential for the inflammatory response to DNA viruses [109, 110]. The *Aim2*$^{-/-}$ mice also have impaired inflammation and survival in response to certain bacteria such as *Francisella*

tularensis, the virulence of which is dependent on its ability to replicate in the host cell [109–111]. AIM2 is activated by other bacteria such as *L. monocytogenes* and *F. novicida* that release their DNA in the host cytosol after lysis of the bacteria within the host cell [112–117]. AIM2 is also activated by DNA released from necrotic cells. For example, in a murine model of chronic kidney injury, *Aim2* deficiency diminished renal injury, fibrosis, and inflammation due to impaired macrophage uptake of DNA from necrotic cells [118].

In addition to activating the AIM2 inflammasome, cytosolic DNA can engage the cGAS/STING pathway to produce an interferon response. Cleavage of GSDMD downstream of the AIM2 inflammasome has been shown to induce K+ efflux that inhibits the cGAS/STING pathway [119]. This may be a means to mitigate damage resulting from sustained IFN signaling. Similarly, the cGAS/STING pathway itself can induce K+ efflux downstream of lysosomal damage that activates the NLRP3 inflammasome pathway [120]. Therefore, there is considerable crosstalk and cross-regulation between different inflammasomes and different inflammatory pathways.

Additional Inflammasomes

Other inflammasomes exist, including IFI-6, NLRP6, NLRP7, NLRP12, and NLRC5, but are less well characterized. While these atypical inflammasomes all have been documented to include ASC and caspase-1, the NLR components of each have more restrictive or additional, more dominant, roles. IFI-6 (interferon-inducible protein 16) is similar to AIM2 but is predominantly expressed in the nucleus to respond to DNA from viruses that enter the nucleus [121]. NLRP6 and NLRP12 have both been shown to dampen the immune response by suppressing NFκB signaling [122–124]. However, in the context of inflammasome activation these proteins have both been reported to have proinflammatory roles. NLRP6 is a key regulator of intestinal homeostasis [125] and has been shown to respond to lipoteichoic acid to recruit ASC and both caspase-1 and capsase-11 [126]. NLRP12 activates caspase-1 and IL-18 in response to *Yersinia Pestis*, the causative agent of plague, but the precise ligand for NLRP12 is unknown [127]. NLRP7 is expressed in oocytes and is important for embryonic development [128]. Finally, NLRC5 can interact with NLRP3, potentially enhancing the function of the NLRP3 inflammasome [129].

Genetic alteration of inflammasome pathways in auto-inflammatory diseases

Correct regulation of the inflammasome pathways has been implicated in the prevention of multiple disease states including sepsis, cardiovascular disease, and neurodegeneration [130–132]. The essential nature of inflammasomes is particularly demonstrated in a rare collection of monogenic human auto-inflammatory disorders that have been associated with mutations in the scaffold proteins of inflammasomes [55] (Table 1). The most well-known of these disorders, the cryopyrin-associated periodic syndromes (CAPS), are the result of mutations in *NLRP3*, which result in a constitutively active protein and lead to increased activation of the NLRP3 inflammasome and resultant increased secretion of IL-1β [133]. The clinical phenotypes of patients with CAPS vary in organ involvement and severity but can span from recurrent fevers and inflammatory skin rashes to hearing loss and devastating

neuro-inflammation [134–136]. Fortunately, therapeutic blockade of the exacerbated IL-1β production has proven to be highly successful in abrogating disease activity in CAPS [137, 138]. Human disease is also caused by gain-of-function mutations in NLRC4, which seem to similarly release the protein from its baseline state of auto-inhibition and lead to high serum levels of both IL-1β and IL-18 [139]. As in CAPS, patients with NLRC4 inflammasomopathies present with a varied spectrum of inflammatory findings from recurrent skin rashes across the clinical continuum to life-threatening neonatal entercolitis [140]. Some patients with NLRC4 mutations appear to partially respond to IL-1 blockade [140], but elevated free IL-18 levels seem to uniquely distinguish this disorder from CAPS [141], and targeted therapeutics are being pursued (clinicaltrials.gov NCT03113760). Variants in and around *NLRP1* have also been described in association with human disease [142–144] and in some cases enhanced NLRP1 inflammasome activation from these mutations has been confirmed and results in elevated IL-1β and IL-18 [142, 144]. The clinical phenotype associated with NLRP1 mutations appears to be predominantly cutaneous disease, spanning from vitiligo to dyskeratosis [142–144]. *NLRP1* mutations only appear to be additionally associated with auto-inflammatory features, such as fever, in a subset of patients, one of whom was successfully treated with IL-1 blockade [144]. Human mutations in AIM2 as a cause of monogenic auto-inflammation have not been reported, perhaps due to the dual role of AIM2 as a tumor suppressor [103]. The finding that gain-of-function mutations in critical inflammasome proteins leads to human auto-inflammation underscores the importance of regulating inflammatory caspase activation. Further understanding of the mechanisms behind inflammasome activation will expand the therapeutic targets available for controlling human inflammatory disease [145, 146].

Closing Remarks

IL-1β targeted therapy has shown great success as a therapeutic intervention for a number of auto-inflammatory conditions. However, it is not effective for every patient and for every disease. Over the last two decades, research into the role of inflammasomes in the regulation of capsase-1 activation and the consequent inflammatory cytokine signaling has provided insight into the crucial role of these complexes both in protecting from infection and injury, and in preventing auto-inflammation. Recent discoveries regarding the crucial inflammatory roles of caspase-4, −5, −11 and GSDMD has renewed the focus on these important pathways. The non-canonical inflammasome pathway that leads to caspase-4, −5, and −11 activation and the inflammasome-dependent caspase-1 pathway appear to be both mechanistically divergent and interdependent. Thus, it is critical to continue to clarify the mechanisms of these two pathways and the cross-talk between them. Further understanding of these complex pathways will illuminate the crucial role of inflammatory caspases in regulation of inflammation, and will no doubt provide novel druggable targets so the therapeutic potential of these pathways can soon be fully realized.

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Abbreviations

AIM2	absent in melanoma 2
APAF1	apoptotic peptidase activating factor 1
ASC	apoptosis-associated speck-like protein containing a CARD
BIR	baculovirus inverted repeat
CAPS	cryopyrin-associated periodic syndromes
CARD	caspase recruitment domain
CTB	cholera toxin B
DAMP	damage-associated molecular patterns
dsDNA	double-stranded DNA
GSDMD	gasdermin D
ICE	interleukin (IL)-1β-converting enzyme
IEC	intestinal epithelial cell
IFI-6	interferon-inducible protein 16
IFN	interferon
LPS	lipopolysaccharide
LRR	leucine-rich repeat
MDP	muramyl dipeptide
mtROS	mitochondrial ROS
NAIP	NLR apoptosis-inhibitory protein
NLR	NOD-like receptor
NLRC	NLR family CARD containing
NLRP	NLR family Pyrin domain containing
NOD	nucleotide binding oligomerization domain
NOX	NADPH-oxidase
PAMP	pathogen-associated molecular pattern
PYD	pyrin domain
ROS	reactive oxygen species
TLR	toll like receptor

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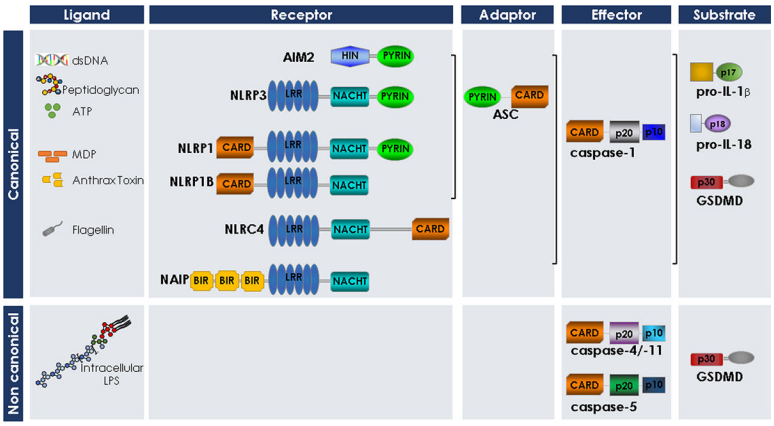

Figure 1:

Domain organization of the inflammasome components, the inflammatory caspases and the inflammatory caspase substrates described in this review.

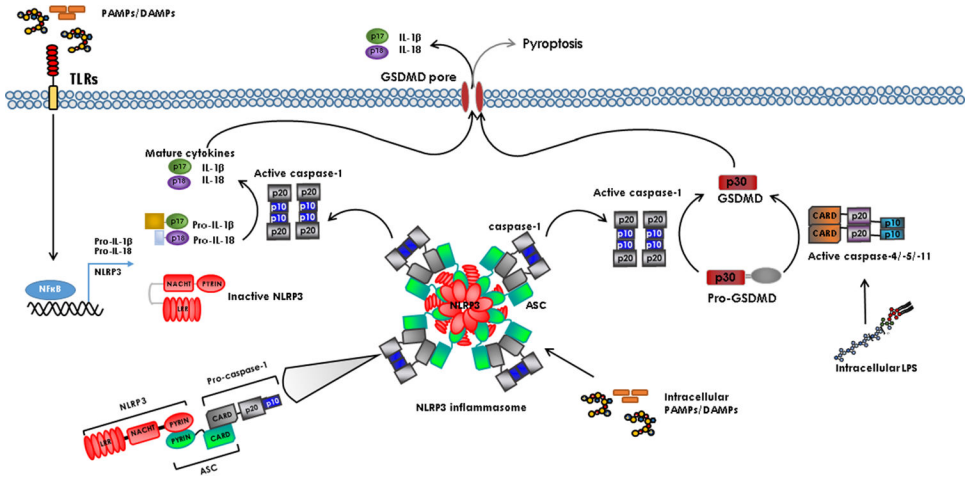

Figure 2:

Model for inflammatory caspase activation. PAMPs and DAMPs activate TLRs on the plasma membrane, which induces expression of pro-IL-18, pro-IL-1β, and certain upstream inflammasome components including NLRP3. PAMPs and DAMPs trigger inflammasome assembly by inducing a conformational change in the NLR protein (NLRP3 is shown as an example) followed by oligomerization. NLRP3 recruits ASC bringing several caspase-1 molecules into proximity facilitating dimerization and activation. Once activated, caspase-1 cleaves IL-1β and IL-18 that are released from the cell through the GSDMD pore. Caspase-4/−5/−11 are activated directly by intracellular LPS to cleave GSDMD.

Table 1.

Conditions involving inflammatory caspases and inflammasome components

Condition/Disease	Inflammasome involved	Characteristics	Citations
Vitiligo	NLRP1	Loss of pigment-forming melanocytes; patches of white skin	[143, 147]
Addison disease	NLRP1	Adrenocortical insufficiency. Requires lifelong glucocorticoid and mineralocorticoid replacement therapy	[148, 149]
Systemic lupus erythematosus	NLRP1	Immune response against double-stranded DNA; cell death; organ failure.	[150]
NLRP1-associated auto-inflammation with arthritis and dyskeratosis (NAIAD)	NLRP1	Dermatological anomalies; recurrent fever; chronic synovial inflammation of multiple joints	[144]
Kawasaki disease	NLRP1	Acute febrile illness of childhood. Systemic vasculitis with infiltration of lymphocytes, macrophages and neutrophils in the vascular walls	[151]
Celiac disease	NLRP1 and NLRP3	Abnormal immune response to gluten; gastrointestinal problems; failure to grow normally	[152]
Muckle-Wells syndrome (MWS)	NLRP3	Frequent nonspecific limb pain, acute febrile inflammatory episodes; abdominal pain, joint inflammation, myalgia, urticaria, and conjunctivitis.	[134, 136]
Familial cold urticaria (FCU/FACS)	NLRP3	Hypersensitivity to cold air, skin lesions, urticarial lesions, petechiae, joint pain, conjunctivitis, chills, nausea, fever.	[136]
Chronic infantile neurological cutaneous and articular syndrome (CINCA, NOMID)	NLRP3	Onset very early in life; severe dermatologic, rheumatologic, and neurologic manifestations; multisystem inflammation.	[135]
NLRC4 macrophage activation syndrome (NLRC4-MAS)	NLRC4	Human NLRC4 gain-of-function mutations (H443P, T337A and V341A)	[139]
Syndrome of enterocolitis and auto-Inflammation associated with mutation in NLRC4 (SCAN4)	NLRC4	Gain-of-function mutations (H443P, T337A and V341A) of the human NLRC4	[153]
Inflammation in Hepatitis B	AIM2	Increased inflammation in chronic hepatitis B patients	[154]