Inflammasome Structures and Mechanisms of Action

Subjects: Immunology

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Inflammasome complexes and their integral receptor proteins have essential roles in regulating the innate immune response and inflammation at the post-translational level. Yet despite their protective role, aberrant activation of inflammasome proteins and gain of function mutations in inflammasome component genes seem to contribute to the development and progression of human autoimmune and autoinflammatory diseases.

inflammasome interleukin 1 pyroptosis

1. NLRP1

NLRP1 was the first NLR shown to form a cytosolic inflammasome complex that specifically recruits and activates a downstream caspase-1 [1]. The human NLRP1 (hNLRP1) is encoded by a single gene, differently from its murine counterpart, which instead is encoded by three paralogues (*NLRP1a*, *NLRP1b*, and *NLRP1c*), with the latter considered a pseudogene [2]. In addition, the expression and activation of mouse NLRP1 has been mostly studied in myeloid lineage cells, such as macrophages, whereas human NLRP1 is found to be primarily expressed at the epithelial barrier, including in keratinocytes and bronchial epithelial cells [3].

hNLRP1 is the only NLR known to undergo constitutive post-translational autoproteolysis, at position Ser1213 between the subdomains ZU5 and UPA in the FIIND [4], that results in the C-terminal (NLRP1^{CT}) and N-terminal (NLRP1^{NT}) portions remaining noncovalently linked. Although only a fraction of the total NLRP1 protein undergoes autoproteolysis [5], this event is essential for subsequent NLRP1 activation as the released NLRP1^{CT} self-oligomerizes and assembles the inflammasome [4][6]. Besides FIIND autocleavage, hNLRP1 also undergoes N-terminal cleavage between the PYD and NACHT domains. Interestingly, while the N-terminal PYD is fundamental for hNLRP1 activity, it is not present in the mouse NLRP1 homolog [5]. Due to these differences between mice and humans, the results of mouse studies could only partially contribute to understanding the role of hNLRP1.

The hNLRP1 CARD motif can recruit caspase-1 directly, but the interaction can also be stabilized by the PYD-CARD adaptor protein ASC. Indeed, ASC is necessary for caspase-1 auto-processing caused by hNLRP1, but not for pyroptosis or IL-1 secretion [7]. An auto-inhibitory role has also recently been attributed to the region between the PYD and NACHT domains called Linker1; at steady state, the interaction between Linker1 and the FIIND silences hNLRP1 activation in auto-inhibitory complexes (**Figure 1**) [8]. Another mechanism of autoinhibition relies on dipeptidyl peptidases (DPP) 8 and 9. Because the CARD-containing NLRP1^{CT} can activate caspase-1, CARD-

containing NLRP1^{CT} is sequestered in a ternary complex made up of full-length NLRP1 and DPP8 and/or DPP9 (**Figure 1**) [9][10].
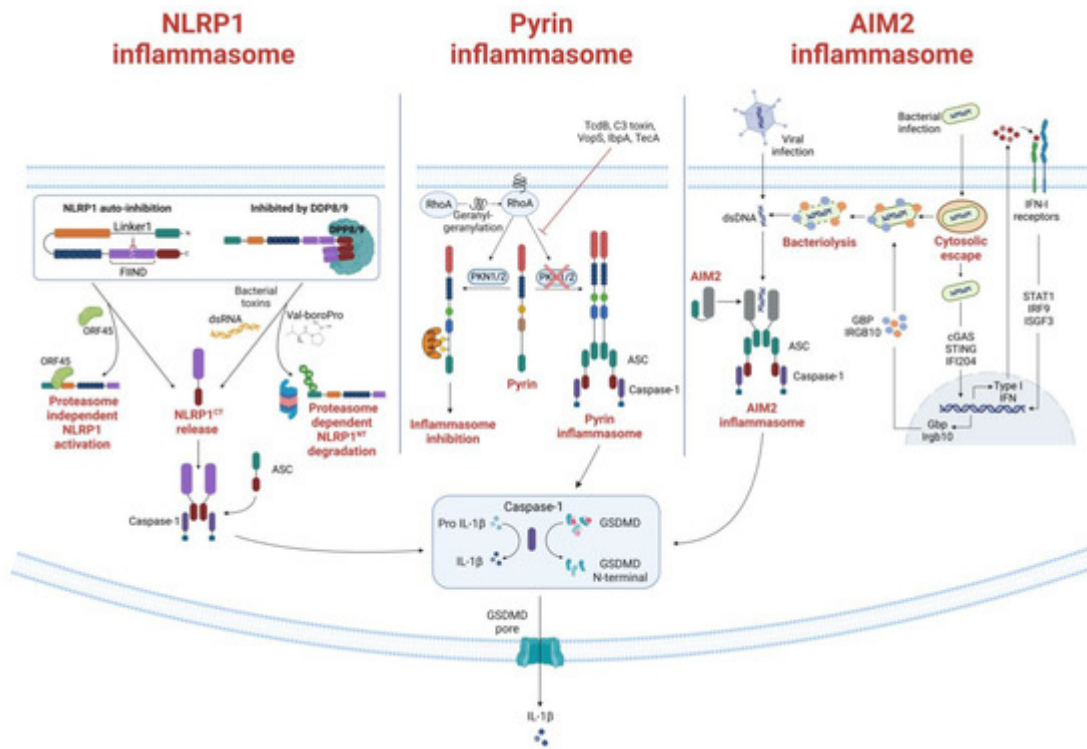

Figure 1. Formation and activation of Pyrin, NLRP1 and AIM2 inflammasomes. (**Left**) NLRP1 inflammasome formation. Under homeostatic conditions, NLRP1 is inactivated through auto-inhibition or by binding to the inhibitor dipeptidyl peptidases 8 and 9 (DPP8/9). The Kaposi sarcoma-associated herpes virus protein ORF45 is shown to bind to the Linker 1 region, lifting the auto-inhibition and DPP8/9 inhibition of NLRP1 and allowing NLRP1^{CT} to assemble the inflammasome. Another activation mechanism of the NLRP1 is through proteasomal degradation of the NLRP1^{NT}. When bacteria or ubiquitin ligases ubiquitinate NLRP1, NLRP1 is directed to the proteasome, where NLRP1^{NT} is degraded, and NLRP1^{CT} is released for inflammasome assembly. The DPP8/9 inhibitor Val-boroPro can also direct proteasomal degradation of NLRP1 and subsequent release of NLRP1^{CT}. (**Middle**) Pyrin inflammasome activation mechanism. RhoA activity is induced by geranylgeranylation (mevalonate kinase pathway). Pyrin is subsequently phosphorylated by the RhoA effector kinases PKN1 and PKN2, which then bind to the inhibitory protein 14-3-3. When PKN1/2 inhibiting substances are present—i.e., TcdB, C3 toxin, VopS—or when the mevalonate kinase (MVK) pathway is not functioning correctly, PKN1/2 is inactivated and reduced pyrin phosphorylation results in the release of mature IL-1 and IL-18 from the pyrin inflammasome. The creation of the gasdermin D (GSDMD) N-terminal fragment, which forms plasma membrane pores, further promotes the release of IL-1 and IL-18. (**Right**) AIM2 canonical and non-canonical activation. The canonical activation, which does not involve type I interferon (IFN) activation, is induced when dsDNA is directly recognized by AIM2, triggering the inflammasome formation. On the contrary, the non-canonical activation depends on IFN activity. It is principally involved in bacterial infections that escape the vacuoles, releasing a small amount of DNA that activates cyclic-GMP-AMP synthase and IFI204. Secreted IFN exits the cells and binds to IFN receptors, driving the downstream activation and inducing bacteriolysis which releases large quantities of bacterial DNA recognized by the AIM2

inflammasome. The activated AIM2 inflammasome drives the proteolytic maturation of IL-1β and IL-18 and the maturation of GSDMD, which induces pyroptosis.

Current understanding of NLRP1 inflammasome activation is largely limited to the degradation of the NLRP1[NT] by the proteasome [11][12]. Direct activators, such as the *B. anthracis* lethal toxin, can activate NLRP1 by degrading NLRP1[NT] via the ubiquitin ligase UBR2, which liberates NLRP1[CT] for inflammasome assembly [11][12][13]. Indirect activators include the inhibitors of DPP8/9. As previously mentioned, DPP9 forms a ternary complex with full-length NLRP1 and NLRP1[CT] to sequester it and prevent its oligomerization [9][10][14]. The DPP8/9 inhibitor Val-boroPro weakens hNLRP1–DPP9 interaction and indirectly accelerates hNLRP1[NT] degradation, promoting inflammasome activation [9].

The panel of stimuli sensed by NLRP1 is expanding. For example, Bauernfried et al. discovered that NLRP1 binds directly to double-stranded RNA (dsRNA) through its LRR domain [15]. In addition, Yang et al. identified the first viral protein—tegument protein ORF45—that directly binds to and activates the NLRP1 inflammasome in human epithelial or macrophage-like cell lines without the aid of the proteasome [8]. They also showed that ORF45 induces NLRP1 inflammasome activation in human epithelial or macrophage-like cell lines. Mechanistically, ORF45 binding to Linker1 displaces UPA from the Linker1–UPA complex and induces the release of the hNLRP1[CT] for inflammasome assembly. NLRP1 has developed the ability to sense various molecular entities or perturbations. The mechanisms by which NLRP1 senses these various modalities are more intricate than those of a promiscuous receptor, which binds to various ligands through the same ligand-binding domain and molecular mode of action. Overall, it is obvious that NLRP1 has not yet divulged all its secrets and that there is still much research to be done in this new field.

2. NLRP3

While not the first inflammasome to be discovered, NLRP3 is the most well studied due to its critical role for host immune defenses against bacterial, fungal, and viral infections [16]. NLRP3 is mainly expressed by myeloid cells (monocytes, neutrophils, macrophages, dendritic cells) but can also be found at the level of the central nervous system [17], and epithelium. NLRP3 is a tripartite protein that consists of a PYD, a NACHT domain and a LRR domain and can be activated through canonical, non-canonical, and alternative pathways (**Figure 2**). For canonical NLRP3 activation, macrophages must first be exposed to priming stimuli, such as TLR, NLR (e.g., NOD1 and NOD2), or cytokine receptor ligands. These ligands ultimately activate the NF-κB transcription factor, which, in turn, upregulates NLRP3 and pro-IL-1β expression, which are not constitutively expressed in resting macrophages [18][19].
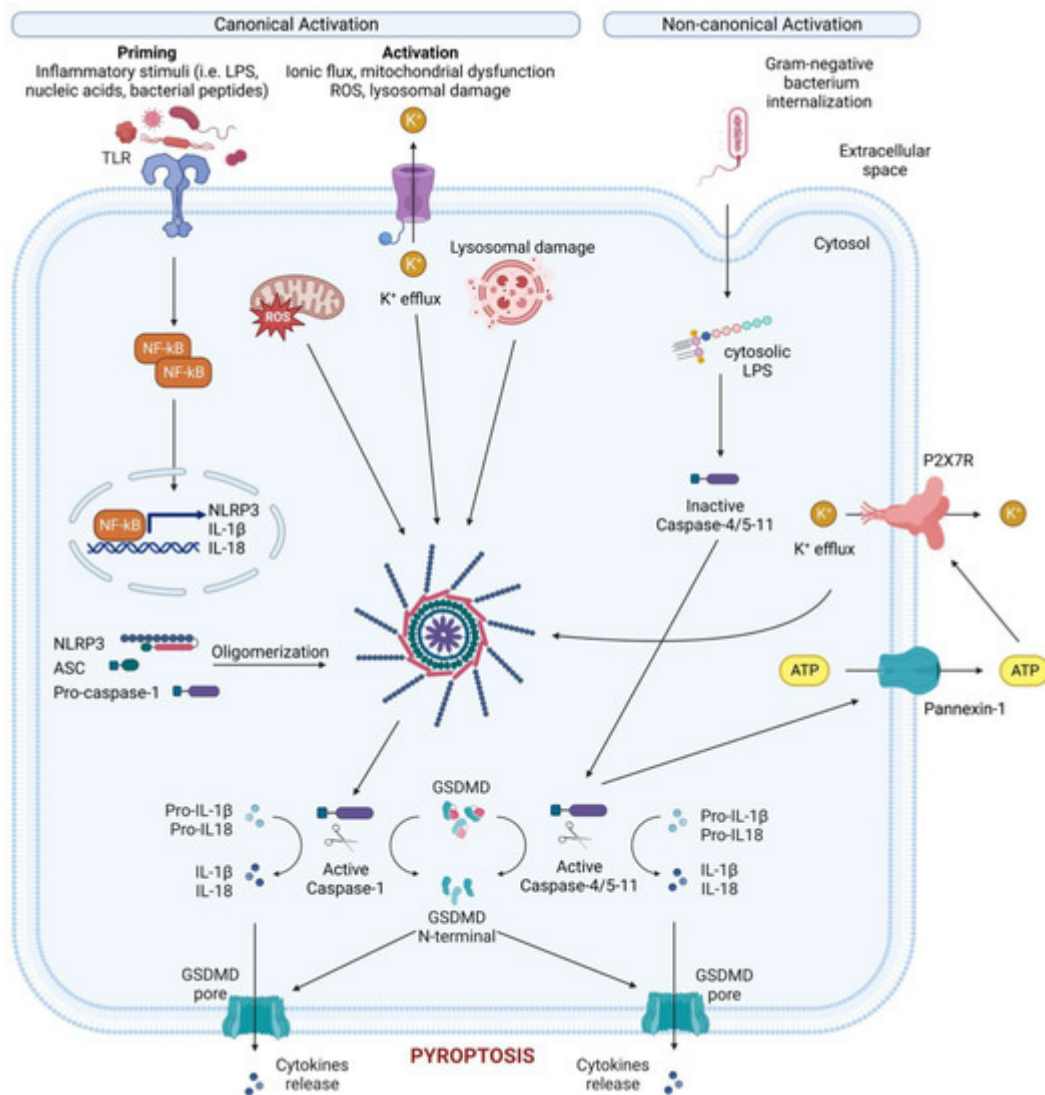
Figure 2. Canonical and non-canonical NLRP3 inflammasome activation. Canonical NLRP3 inflammasome activation requires two steps: the priming step and the activation step. In the priming step, TLR stimulation induces the transcription and expression of NLRP3 and pro-IL-1 through NF-кB. Subsequently, various PAMPs and DAMPs induce the activation step by initiating numerous molecular and cellular events, including K+ efflux, mitochondrial dysfunction, reactive oxygen species (ROS) release, and lysosomal disruption. The NLRP3-dependent self-cleavage and activation of pro-caspase-1 self-cleavage and activation leads to the maturation of the pro-inflammatory cytokine's interleukin 1 (IL-1) and interleukin 18 (IL-18). Additionally, gasdermin D (GSDMD) is cleaved by activated caspase-1, releasing its N-terminal domain, which then integrates into the cell membrane to create pores. These pores allow the release of cellular contents, including IL-1 and IL-18, and trigger pyroptosis, a form of inflammatory cell death. The non-canonical NLRP3 inflammasome is activated by cytosolic LPS, which directly interacts with caspase-4/5 in human (caspase-11 in mice). This interaction results in the autoproteolysis and activation of these caspases. The activated caspases subsequently open the pannexin-1 channel, allowing ATP release from the cell and activating the P2X7R, causing K+ efflux, canonical NLRP3 activation and the maturation of IL-1 and IL-18. In addition, activated caspase-4/5-11 cleaves GSDMD to cause membrane pore formation and pyroptosis, contributing to the release of IL-1 and IL-18.

Following priming, NLRP3 can be activated by diverse stimuli, including ATP, ion flux (in particular, K^+ efflux) [20][21], particulate matter [22][23][24], pathogen-associated RNA [25], and bacterial and fungal toxins and components [26][27]. In addition, mitochondrial dysfunction, the release of reactive oxygen species (ROS), and lysosomal disruption have been proposed to be signals for the assembly and activation of inflammasomes [28]. Given that NLRP3 does not interact directly with any of these agonists and that they are biochemically distinct, it is thought that they all cause a similar cellular signal.

Most NLRP3 stimuli cause macrophages and monocytes to experience K^+ efflux. In fact, IL-1 maturation and release from macrophages and monocytes in response to ATP or nigericin, which are now known to be NLRP3 stimuli, is mediated by cytosolic K^+ depletion [20][29][30][31]. Additionally, K^+ efflux alone was shown to activate NLRP3 in murine macrophages, and high extracellular K^+ blocks NLRP3 inflammasome activation but not NLRC4 or AIM2 inflammasome activation [21][32]. It has, therefore, been assumed that diminished intracellular K^+ levels can trigger NLRP3 inflammasome activation [21]. Recent research, however, has found small chemical compounds— i.e., imiquimod and CL097—that activate NLRP3 independently of K^+ efflux [33]. This finding suggests that either NLRP3 inflammasome activation is caused by an event downstream of K^+ efflux, or that K^+ efflux-independent pathways also exist for NLRP3 inflammasome activation.

During non-canonical NLRP3 activation, cytoplasmic lipopolysaccharide (LPS) directly binds the CARD of caspase-4/5/11 (which induces pyroptosis via GSDMD) and pannexin-1, a membrane channel that releases ATP (**Figure 2**) [34][35][36]. This extracellular ATP activates the purinergic P2X7 receptor (P2X7R) [37], an ATP-gated cation selective receptor that forms a pore in the plasma membrane that mediates K^+ efflux. Besides directly causing pyroptosis, the non-canonical inflammasome also induces the canonical NLRP3 inflammasome to promote IL-1β and IL-18 maturation and release [38].

Unlike both the canonical and non-canonical pathways, the alternative inflammasome pathway does not require K^+ efflux or ASC speck formation, and does not induce pyroptosis [39]. Rather, caspase-1 activation and IL-1 maturation and secretion in human monocytes is induced by LPS stimulation alone [40]. This alternative pathway requires caspase4/5, Syk activity, and Ca^{2+} flux instigated by CD14/TLR4-mediated LPS internalization. In murine dendritic cells, prolonged LPS exposure, in the absence of any other activating signals, resulted in NLRP3-mediated IL-1β processing and secretion independent of P2X7R [41].

NLRP3 inflammasome activation is likely regulated by various post-translational modifications, with ubiquitination and phosphorylation being the most thoroughly studied [42], as well as nitrosylation and sumoylation [43].

Several groups have demonstrated that the mitotic spindle kinase NEK7 is a crucial regulator of NLRP3 inflammasome activation [44][45]. This role of NEK7 is distinct from its function in the cell cycle, as its kinase activity is not required for NLRP3 activation [44]. According to the proposed activation model, NEK7 binding induces conformational changes to NLRP3 whereby exposed PYDs can recruit ASC leading to subsequent caspase-1 activation. Nevertheless, it was recently demonstrated that another kinase called IKKβ, which is activated during priming, causes NLRP3 to be recruited to phosphatidylinositol-4-phosphate (PI4P), an abundant phospholipid on

the trans-Golgi network. When IKKβ recruits NLRP3 to PI4P, NEK7—previously believed to be essential for NLRP3 activation—becomes redundant.

In the past decade, intense efforts have been put into the investigation of the mechanism of NLRP3 inflammasome activation. However, much more work is needed to understand how diverse cell signaling events are integrated to activate the NLRP3 inflammasome.

3. NLRP6

NLRP6 ensures microbial homeostasis, as shown in NLRP6-deficient mice that exhibit decreased IL-18 levels and dysbiosis, altering the composition of the intestinal microbial community. Indeed, NLRP6 is highly expressed in intestinal goblet cells and in lungs, liver, and tubular epithelium of kidneys. Moreover, it seems to have a role in the regulation of homeostasis in the periodontium and gingiva [46]. NLRP6 has an N-terminal PYD, a nucleotide-binding domain, and a C-terminal LRR [46]. Gram-positive, bacteria-derived lipoteichoic acid activates the NLRP6 inflammasome by binding its LRR domain and cleaves caspase-11 through the glycerophosphate repeat of lipoteichoic acid [47]. LPS also directly binds the NLRP6 monomer via its LRR, inducing conformational changes and dimerization, which, together with ASC and caspase-1, form the inflammasome complex responsible for the maturation of the pro-inflammatory cytokines IL-1β and IL-18 [48]. NLRP6 is also involved in the anti-viral response, as seen in NLRP6-deficient mice that are more susceptible to encephalomyelitis virus infections than their wildtype counterparts [49]. This function of NLRP6 is achieved in collaboration with DHX15, which together recognize dsRNA to induce type I interferon (IFN) and IFN-stimulated gene activation via mitochondrial antiviral signaling proteins to counteract viral infections.

4. NLRP7

NLRP7 belongs to the family of signal-transducing ATPases and, to date, it has been described in humans and sheep. It has been reported that human NLRP7 is expressed in B, T, and monocytic cells, as well as in the lung, spleen, thymus, testis, and ovaries [50]. The ability of NLRP7 to form an inflammasome complex remains controversial. A study in human macrophages showed that NLRP7 can form an inflammasome complex in response to bacterial infections [51]. Specifically, mycoplasma and Gram-positive bacterial infections can activate NLRP7, which, in turn, induces IL-1β secretion. To form an inflammasome, NLRP7 requires binding and hydrolysis of ATP in its NACHT domain [52]. Moreover, complex post-translational modifications regulate its activity; namely, NLRP7 is either ubiquitinated to regulate its functions, or deubiquitinated by the STAM-binding protein to prevent its trafficking to lysosomes and its degradation [53]. Some observations also suggest that NLRP7 might have anti-inflammatory activity under certain conditions. NLRP7 can inhibit IL-1β secretion mediated by the NLRP3 inflammasome without affecting NF-κB activation required for the priming [54][55]. These features have led to the hypothesis that the interaction between NLRP7, pro-caspase-1, and pro-IL-1β may inhibit pro-IL-1β maturation. Indeed, peripheral blood mononuclear cells from hydatidiform mole patients with mutations in *NLRP7* exhibit

reduced IL-1β secretion upon LPS treatment compared to healthy individual cells [56]. Whether these mutations are gain- or loss-of-function remains to be elucidated.

Altogether, these observations need to be better characterized to evaluate the involvement of NLRP7 in regulating inflammation. Moreover, the observation of an anti-inflammatory role in non-immune cells represents a good starting point to elucidate the mechanism that leads to NLRP7 inflammasome activation.

5. NLRP10

NLRP10 (also known as NOD8, PAN5, or PYNOD) is the only NLR lacking the characteristic LRR domain involved in protein–protein interactions, suggesting that NLRP10 might have an inflammasome-independent function. NLRP10 is expressed in various human and mouse tissues and cell types, including epithelial cells, keratinocytes, macrophages, DCs, and T cells [57]. However, the expression patterns seem to be cell-type- and context-dependent, and its function may vary depending on the cellular environment and the signaling pathways involved. Although the physiological role of NLRP10 has been largely uncharacterized, data suggest a role in the recognition and response to bacterial pathogens (*Salmonella* and *Mycobacterium tuberculosis*) and parasites (*Leishmania major*) [58][59][60].

Early studies showed that NLRP10 negatively regulates NF-κB activation, cell death, and IL-1β release [61], and inhibits caspase-1-mediated maturation of IL-1β [58]. Conversely, others reported normal canonical activation of NLRP3 and IL-1β production in NLRP10-deficient mouse DCs [59]. These pieces of evidence point to the possibility that NLRP10 may operate variably in different cellular environments. Indeed, Próchnicki et al. and Zheng et al. identified that the phospholipase C activator 3m3-FBS is the first trigger for NLRP10-based inflammasome assembly in colonic epithelial cells and differentiated keratinocytes [62][63]. Mechanistically, 3m3-FBS causes mitochondrial destabilization that recruits NLRP10 to damaged mitochondria, where it assembles, independently of the priming step, to form a canonical inflammasome together with ASC and caspase-1. Further research is needed to fully understand the immune and non-immune functions of NLRP10.

6. NLRP12

NLRP12 was described in 2012 as a negative regulator of the NF-κB in activated B-cell signaling, with a crucial role in controlling inflammation in both hematopoietic and non-hematopoietic compartments [64]. Indeed, we now know it is expressed in bone marrow DCs, neutrophils, macrophages, and granulocytes [65]. NLRP12 negatively regulates the canonical NF-κB signaling pathways by interacting with hyperphosphorylated IRAK1, which inhibits its accumulation. On the other hand, NLRP12 dampens the non-canonical pathway by inducing the degradation of NF-κB-inducing kinase via interaction with TRAF3 [64][66][67]. One of the consequences of suppressing NFκB signaling is that macrophages do not produce the chemoattractant factor CXCL1, negatively impacting neutrophil migration and recruitment to infection sites during microbial infections [68][69][70]. Moreover, NLRP12 negatively

regulates T-cell responses, as shown by the higher production of IFN-γ, IL-17, and Th2-associated cytokines in NLRP12-deficient compared to wildtype T cells [71][72].

Besides negatively regulating immune signaling, NLRP12 has been studied as an inflammasome component. For example, during *Yersinia pestis* infection, NLRP12 activation induces the caspase-1, IL-1β, IL-18 cascade [73]. Although the NLRP12 activation mechanisms remain unknown, NLRP12 ligand generation requires the presence of virulence-associated type III secretion systems, suggesting NLRP12 activation may involve sensing damage associated with type III secretion. However, even if NLRP12 is involved in in vivo resistance against *Yersinia* infection, NLRP3 activation is required in both *Yersinia* and *Plasmodium* infections, suggesting that differential NLR activation might contribute to optimal protection and host defenses [74].

7. Pyrin

Pyrin encoded by *MEFV* is expressed largely in granulocytes, eosinophils, and monocytes. Early structural investigations of Pyrin revealed a nuclear role, indicated by the presence of a bZIP transcription factor domain and two overlapping nuclear localization signals [75]. Although full-length Pyrin is primarily found in the cytosol, later studies looking into its localization and function discovered the colocalization of the N-terminal Pyrin fraction with microtubules and the actin cytoskeleton [76].

The Pyrin C-terminal B30.2 domain is of particular significance because most familial Mediterranean fever (FMF)-associated mutations cluster there and functional data suggest that this domain is necessary for the molecular pathways causing FMF. In vitro overexpression studies demonstrated direct interaction between caspase-1 and pyrin B30.2 but others examining the impact of FMF-related mutations on the binding affinity of B30.2 to caspase-1 produced contradictory findings [77][78].

The ligand or signals that activate Pyrin have long been unknown. In 2014, Xu et al. [79] showed that Pyrin is able to sense pathogen-induced changes in the host Rho guanosine triphosphatases (Rho GTPases) (**Figure 1**). For example, the *Clostridium difficile* virulence factor TcdB, which glycosylates and subsequently inhibits the activity of a minor Rho GTPase called RhoA, can activate the Pyrin inflammasome [80]. When exposed to wildtype TcdB, bone-marrow-derived macrophages show a potent Pyrin-mediated inflammasome response, enhanced caspase-1 activity, and pyroptosis, which does not occur upon exposure to mutant TcdB. Inhibition of RhoA is not restricted to TcdB, as other bacterial toxins also, such as C3 (*Clostridium botulinum*), pertussis toxin (*Bordetella pertussis*), VopS (*Vibrio parahaemolyticus*), IbpA (*Histophilus somni*), and TecA (*Burkholderia cenocepacia*), can distinctly modify the RhoA switch I region domain [81][82][83]. Due to the lack of direct interaction between Pyrin and RhoA, Pyrin is believed to be activated by an indirect signal downstream of RhoA, rather than through direct recognition of specific RhoA modifications. Given that Rho GTPases regulate many aspects of actin cytoskeleton dynamics, it is, therefore, hypothesized that changes in the cytoskeleton organization might trigger Pyrin. Moreover, Pyrin activation relies on the RhoA-dependent serine/threonine-protein kinases PKN1 and PKN2, that directly phosphorylate Pyrin at Ser208 and Ser242 [84]. As a result, the chaperone proteins 14-3-3ε and 14-3-3τ interact with phosphorylated Pyrin, preventing the development of an active inflammasome and maintaining Pyrin in an

inactive state. Bacterial toxins that inactivate RhoA result in decreased PKN1 and PKN2 activity and decreased amounts of phosphorylated Pyrin, which frees pyrin from 14-3-3 inhibition and promotes the development of an active Pyrin inflammasome. Studies of the autoinflammatory disorder caused by mevalonate kinase (MVK) deficiency offered more proof that the Pyrin inflammasome regulation mechanism described there is accurate. The mevalonate pathway is an important metabolic pathway that generates several metabolites, including geranylgeranyl pyrophosphate. This metabolite acts as a substrate for the geranylgeranylation of proteins, a post-translational lipid modification. RhoA is geranylgeranylated, and its translocation from the cytosol to the cellular membrane, which is required for activation, is dependent on this post-translational modification. Inhibiting the MVK pathway in bone-marrow-derived macrophages causes the release of membrane-bound RhoA and Pyrin inflammasome-dependent production of IL-1β [84]. By adding geranylgeranyl pyrophosphate, or by chemically activating PKN1 and PKN2, the synthesis of IL-1 was prevented.

Recent research has identified a previously unknown regulatory and molecular connection between AIM2, Pyrin, and ZBP1, which promotes the formation of the AIM2 PANoptosome, a multiprotein complex that includes various inflammasome sensors and cell death regulators [85].

8. NLRC4

NLRC4 was first described in 2001 as an activator and recruiter of caspase-1 upon bacterial pathogen sensing. Indeed, NLRC4 combines with pro-caspase-1 via CARD–CARD interactions to induce its processing and activation [86]. Specifically, the NLRC4 CARD interacts with the ASC adaptor protein CARD, thus linking NLRC4-ASC with caspase-1 to mediate downstream signaling [87]. Indeed, the CARD domain of ASC is necessary for recruiting caspase-1 to ASC specks, ensuring correct pro-IL-1β and pro-IL-18 proteolytic cleavage and activation [88][89][90], thus triggering proteolytic processing and oligomerization of GSDMD leading to pyroptosis [91]. NLRC4 is mainly expressed in myeloid cells, astrocytes, retinal pigmented epithelial cells, and intestinal epithelial cells [92].

NLRC4 forms an inflammasome complex with NAIP proteins, comprising three N-terminal baculovirus IAP-repeat domains, a central NACHT, and a C-terminal LRR [93], and acts as an upstream sensor of bacterial ligands in the cytoplasm. As such, the NAIP-NLRC4 inflammasome recognizes cytoplasmic bacterial ligands (mainly Gram-negative bacteria) and induces an inflammatory response via caspase-1 activation and pyroptosis. The NAIP-NLRC4 inflammasome in human and murine macrophages is activated by flagellin [94][95][96] and the type III [97][98] or type IV secretion system [99][100] proteins through direct recognition via NAIP proteins. It has been shown in mice that IFN regulatory factor 8 is responsible for the transcriptional induction of *Nlrc4* and *Naip 1*, *2*, *5*, and *6* [101]. The formation of the NAIP-NLRC4 inflammasome is quite peculiar. NLRC4 activation starts with the formation of a ligand-bound NAIP complex that changes the conformation of an NLRC4 monomer, exposing the "catalytic surface" of the active monomer, allowing it to interact with the "acceptor surface" of an inactive NLRC4 monomer. This contact activates a second monomer responsible for engaging more NLRC4 monomers, thus triggering the formation of an NLRC4 coil [87][102][103][104]. Consequently, NLRC4 oligomerization induces ASC and caspase-1 recruitment. NLRC4 inflammasome activation is finely regulated by phosphorylation and ubiquitination events [105][106].

NLRC4 was initially thought to induce inflammation by activating the caspase-1, IL-1β, and IL-18 cascade and promoting GSDMD maturation. Later data showed, however, that an artificial NAIP5-NLRC4 activator can induce the release of arachidonic acid by activating the calcium-dependent phospholipase A2 [107]. Arachidonic acid, in turn, stimulates the rapid production of prostaglandins and leukotrienes. The mechanism of arachidonic acid release and its link with NLRC4 activation is still unclear; however, more than 1000 possible targets of caspase-1 have been identified that might cooperate in NLRC4 activation to activate numerous downstream signals involved in the inflammatory response [87].

9. AIM2

Unlike other inflammasome activators, dsDNA can activate an ASC-dependent, but NLRP3-independent, inflammasome, the AIM2 inflammasome [108]. AIM2 is expressed by myeloid cells, keratinocytes, and T regulatory cells [92], and it is composed of an N-terminal PYD domain and a C-terminal hematopoietic expression, IFN-inducible, and nuclear localization (HIN) domain that senses dsDNA. An HIN-dependent interaction between AIM2 and dsDNA is enabled by two, high-affinity dsDNA binding folds in the HIN domain. Under homeostatic conditions, PYD and HIN form an intramolecular complex that inhibits inflammasome activation; this inhibition is relieved when the HIN domain binds dsDNA. Hence, the PYD can interact with ASC, allowing it to polymerize and thereby activate AIM2 [109][110].

The interaction between dsDNA and the AIM2 complex is independent of the DNA sequence or its origin, but the DNA must be at least 80 base pairs long to be sensed by the HIN domain [111]. Indeed, host DNA (including mitochondrial DNA, damaged nuclear DNA, and exosome-secreted host DNA released in the cytosol) and intracellular viral and bacterial DNAs released upon microbial infections, can all trigger AIM2-dependent innate immunity [112][113][114]. The AIM2 inflammasome has canonical and non-canonical activation mechanisms (**Figure 1**) [115]. Canonical activation, which mostly occurs during viral infections [116], is rapid and does not involve type I IFN activation [117]. By this mechanism, dsDNA is directly recognized by AIM2, triggering the formation of the inflammasome. Non-canonical activation, conversely, depends on IFN activity and is principally involved in bacterial infections [118]. Unlike canonical activation, non-canonical activation is thought to involve intracellular bacteria that escape the vacuoles and release small amount of DNA, thereby activating cyclic-GMP-AMP synthase and IFI204, which are two components of the cascade that drive IFN secretion [119]. At this point, secreted type I IFN exits the cells where it binds IFN receptors, driving the downstream activation of immunity-related GTPase family member b10 and guanylate-binding proteins, which, in turn, induce bacteriolysis releasing large quantities of bacterial DNA that are eventually recognized by the AIM2 inflammasome [120][121]. Unlike other DNA sensors involved in IFN induction, AIM2 inflammasome assembly following detection of cytosolic dsDNA drives the proteolytic maturation of IL-1β and IL-18 and the maturation of GSDMD, which induces pyroptosis [109][122][123].

To prevent cytokine overexpression and cell death, AIM2 inflammasome activation must be tightly regulated; this regulation is achieved through PYD:PYD or CARD:CARD interactions [124]. The presence of three human PYD-only (POP) genes (*POP1*, *POP2*, and *POP3*) suggests that POPs may negatively regulate inflammasomes [125][126][127]. POP1 and POP2 are broad-spectrum inhibitors that interfere with inflammasome assembly by interacting with ASC

PYD. Conversely, POP3 specifically inhibits AIM2 by binding to AIM2 PYD, consequently blocking the AIM2 and ASC interaction [126].

Pathogens have evolved strategies to escape AIM2 inflammasome activation. For example, the human cytomegalovirus virion protein pUL83 by interacting with AIM2 inhibits its activation [124]. Huang et al. demonstrated that THP-1-derived macrophages infected with HCMV showed increased levels of AIM2 at early stages of infections, but 24 h post-infection AIM2 decreased to basal levels. They investigated the effect of pUL83 on AIM2 in recombinant HEK293T cells expressing AIM2, ASC, pro-caspase-1, and pro-IL-1β and found that, upon induction of AIM2 activation, the expression of pUL83 led to a drastic reduction in AIM2, pro-caspase-1, and pro-IL-1β levels. These results demonstrate that pUL83 is responsible for reducing AIM2 response leading to downstream reduction of caspase-1 and IL-1β cleavage [128]. Moreover, since AIM2 inflammasome becomes active every time it senses cytosolic dsDNA, some bacterial pathogens can escape AIM2 recognition by maintaining their structural integrity [129].

References

1. Martinon, F.; Burns, K.; Tschopp, J. The Inflammasome. Mol. Cell 2002, 10, 417–426.

2. Sastalla, I.; Crown, D.; Masters, S.L.; McKenzie, A.; Leppla, S.H.; Moayeri, M. Transcriptional Analysis of the Three Nlrp1 Paralogs in Mice. BMC Genom. 2013, 14, 188.

3. Chavarría-Smith, J.; Vance, R.E. The NLRP1 Inflammasomes. Immunol. Rev. 2015, 265, 22–34.

4. D'Osualdo, A.; Weichenberger, C.X.; Wagner, R.N.; Godzik, A.; Wooley, J.; Reed, J.C. CARD8 and NLRP1 Undergo Autoproteolytic Processing through a ZU5-Like Domain. PLoS ONE 2011, 6, e27396.

5. Finger, J.N.; Lich, J.D.; Dare, L.C.; Cook, M.N.; Brown, K.K.; Duraiswami, C.; Bertin, J.J.; Gough, P.J. Autolytic Proteolysis within the Function to Find Domain (FIIND) Is Required for NLRP1 Inflammasome Activity. J. Biol. Chem. 2012, 287, 25030–25037.

6. Frew, B.C.; Joag, V.R.; Mogridge, J. Proteolytic Processing of Nlrp1b Is Required for Inflammasome Activity. PLoS Pathog. 2012, 8, e1002659.

7. van Opdenbosch, N.; Gurung, P.; vande Walle, L.; Fossoul, A.; Kanneganti, T.-D.; Lamkanfi, M. Activation of the NLRP1b Inflammasome Independently of ASC-Mediated Caspase-1 Autoproteolysis and Speck Formation. Nat. Commun. 2014, 5, 3209.

8. Yang, X.; Zhou, J.; Liu, C.; Qu, Y.; Wang, W.; Xiao, M.Z.X.; Zhu, F.; Liu, Z.; Liang, Q. KSHV-Encoded ORF45 Activates Human NLRP1 Inflammasome. Nat. Immunol. 2022, 23, 916–926.

9. Hollingsworth, L.R.; Sharif, H.; Griswold, A.R.; Fontana, P.; Mintseris, J.; Dagbay, K.B.; Paulo, J.A.; Gygi, S.P.; Bachovchin, D.A.; Wu, H. DPP9 Sequesters the C Terminus of NLRP1 to

Repress Inflammasome Activation. Nature 2021, 592, 778–783.

10. Huang, M.; Zhang, X.; Toh, G.A.; Gong, Q.; Wang, J.; Han, Z.; Wu, B.; Zhong, F.; Chai, J. Structural and Biochemical Mechanisms of NLRP1 Inhibition by DPP9. Nature 2021, 592, 773–777.

11. Chui, A.J.; Okondo, M.C.; Rao, S.D.; Gai, K.; Griswold, A.R.; Johnson, D.C.; Ball, D.P.; Taabazuing, C.Y.; Orth, E.L.; Vittimberga, B.A.; et al. N-Terminal Degradation Activates the NLRP1B Inflammasome. Science (1979) 2019, 364, 82–85.

12. Sandstrom, A.; Mitchell, P.S.; Goers, L.; Mu, E.W.; Lesser, C.F.; Vance, R.E. Functional Degradation: A Mechanism of NLRP1 Inflammasome Activation by Diverse Pathogen Enzymes. Science (1979) 2019, 364, eaau1330.

13. Xu, H.; Shi, J.; Gao, H.; Liu, Y.; Yang, Z.; Shao, F.; Dong, N. The N-end Rule Ubiquitin Ligase UBR2 Mediates NLRP1B Inflammasome Activation by Anthrax Lethal Toxin. EMBO J. 2019, 38, e101996.

14. Zhong, F.L.; Robinson, K.; Teo, D.E.T.; Tan, K.-Y.; Lim, C.; Harapas, C.R.; Yu, C.-H.; Xie, W.H.; Sobota, R.M.; Au, V.B.; et al. Human DPP9 Represses NLRP1 Inflammasome and Protects against Autoinflammatory Diseases via Both Peptidase Activity and FIIND Domain Binding. J. Biol. Chem. 2018, 293, 18864–18878.

15. Bauernfried, S.; Scherr, M.J.; Pichlmair, A.; Duderstadt, K.E.; Hornung, V. Human NLRP1 Is a Sensor for Double-Stranded RNA. Science (1979) 2021, 371, eabd0811.

16. Xu, J.; Núñez, G. The NLRP3 Inflammasome: Activation and Regulation. Trends Biochem. Sci. 2023, 48, 331–344.

17. Heneka, M.T.; McManus, R.M.; Latz, E. Inflammasome Signalling in Brain Function and Neurodegenerative Disease. Nat. Rev. Neurosci. 2018, 19, 610–621.

18. Bauernfeind, F.G.; Horvath, G.; Stutz, A.; Alnemri, E.S.; MacDonald, K.; Speert, D.; Fernandes-Alnemri, T.; Wu, J.; Monks, B.G.; Fitzgerald, K.A.; et al. Cutting Edge: NF-KB Activating Pattern Recognition and Cytokine Receptors License NLRP3 Inflammasome Activation by Regulating NLRP3 Expression. J. Immunol. 2009, 183, 787–791.

19. Franchi, L.; Eigenbrod, T.; Núñez, G. Cutting Edge: TNF-α Mediates Sensitization to ATP and Silica via the NLRP3 Inflammasome in the Absence of Microbial Stimulation. J. Immunol. 2009, 183, 792–796.

20. Mariathasan, S.; Weiss, D.S.; Newton, K.; McBride, J.; O'Rourke, K.; Roose-Girma, M.; Lee, W.P.; Weinrauch, Y.; Monack, D.M.; Dixit, V.M. Cryopyrin Activates the Inflammasome in Response to Toxins and ATP. Nature 2006, 440, 228–232.

21. Muñoz-Planillo, R.; Kuffa, P.; Martínez-Colón, G.; Smith, B.L.; Rajendiran, T.M.; Núñez, G. K+ Efflux Is the Common Trigger of NLRP3 Inflammasome Activation by Bacterial Toxins and Particulate Matter. Immunity 2013, 38, 1142–1153.

22. Martinon, F.; Pétrilli, V.; Mayor, A.; Tardivel, A.; Tschopp, J. Gout-Associated Uric Acid Crystals Activate the NALP3 Inflammasome. Nature 2006, 440, 237–241.

23. Hornung, V.; Bauernfeind, F.; Halle, A.; Samstad, E.O.; Kono, H.; Rock, K.L.; Fitzgerald, K.A.; Latz, E. Silica Crystals and Aluminum Salts Activate the NALP3 Inflammasome through Phagosomal Destabilization. Nat. Immunol. 2008, 9, 847–856.

24. Dostert, C.; Pétrilli, V.; Van Bruggen, R.; Steele, C.; Mossman, B.T.; Tschopp, J. Innate Immune Activation Through Nalp3 Inflammasome Sensing of Asbestos and Silica. Science (1979) 2008, 320, 674–677.

25. Eigenbrod, T.; Dalpke, A.H. Bacterial RNA: An Underestimated Stimulus for Innate Immune Responses. J. Immunol. 2015, 195.

26. Skeldon, A.; Saleh, M. The Inflammasomes: Molecular Effectors of Host Resistance Against Bacterial, Viral, Parasitic, and Fungal Infections. Front. Microbiol. 2011, 2, 15.

27. Greaney, A.J.; Leppla, S.H.; Moayeri, M. Bacterial Exotoxins and the Inflammasome. Front. Immunol. 2015, 6, 570.

28. Seoane, P.I.; Lee, B.; Hoyle, C.; Yu, S.; Lopez-Castejon, G.; Lowe, M.; Brough, D. The NLRP3–Inflammasome as a Sensor of Organelle Dysfunction. J. Cell Biol. 2020, 219, e202006194.

29. Perregaux, D.; Gabel, C.A. Interleukin-1 Beta Maturation and Release in Response to ATP and Nigericin. Evidence That Potassium Depletion Mediated by These Agents Is a Necessary and Common Feature of Their Activity. J. Biol. Chem. 1994, 269, 15195–15203.

30. Walev, I.; Klein, J.; Husmann, M.; Valeva, A.; Strauch, S.; Wirtz, H.; Weichel, O.; Bhakdi, S. Potassium Regulates IL-1β Processing Via Calcium-Independent Phospholipase A2. J. Immunol. 2000, 164, 5120–5124.

31. Walev, I.; Reske, K.; Palmer, M.; Valeva, A.; Bhakdi, S. Potassium-Inhibited Processing of IL-1 Beta in Human Monocytes. EMBO J. 1995, 14, 1607–1614.

32. Pétrilli, V.; Papin, S.; Dostert, C.; Mayor, A.; Martinon, F.; Tschopp, J. Activation of the NALP3 Inflammasome Is Triggered by Low Intracellular Potassium Concentration. Cell Death Differ. 2007, 14, 1583–1589.

33. Groß, C.J.; Mishra, R.; Schneider, K.S.; Médard, G.; Wettmarshausen, J.; Dittlein, D.C.; Shi, H.; Gorka, O.; Koenig, P.-A.; Fromm, S.; et al. K + Efflux-Independent NLRP3 Inflammasome Activation by Small Molecules Targeting Mitochondria. Immunity 2016, 45, 761–773.

34. Kayagaki, N.; Stowe, I.B.; Lee, B.L.; O'Rourke, K.; Anderson, K.; Warming, S.; Cuellar, T.; Haley, B.; Roose-Girma, M.; Phung, Q.T.; et al. Caspase-11 Cleaves Gasdermin D for Non-Canonical Inflammasome Signalling. Nature 2015, 526, 666–671.

35. Yang, D.; He, Y.; Muñoz-Planillo, R.; Liu, Q.; Núñez, G. Caspase-11 Requires the Pannexin-1 Channel and the Purinergic P2X7 Pore to Mediate Pyroptosis and Endotoxic Shock. Immunity 2015, 43, 923–932.

36. Pelegrin, P.; Surprenant, A. Pannexin-1 Mediates Large Pore Formation and Interleukin-1β Release by the ATP-Gated P2X7 Receptor. EMBO J. 2006, 25, 5071–5082.

37. Piccini, A.; Carta, S.; Tassi, S.; Lasiglié, D.; Fossati, G.; Rubartelli, A. ATP Is Released by Monocytes Stimulated with Pathogen-Sensing Receptor Ligands and Induces IL-1β and IL-18 Secretion in an Autocrine Way. Proc. Natl. Acad. Sci. USA 2008, 105, 8067–8072.

38. Shi, J.; Zhao, Y.; Wang, K.; Shi, X.; Wang, Y.; Huang, H.; Zhuang, Y.; Cai, T.; Wang, F.; Shao, F. Cleavage of GSDMD by Inflammatory Caspases Determines Pyroptotic Cell Death. Nature 2015, 526, 660–665.

39. Gaidt, M.M.; Ebert, T.S.; Chauhan, D.; Schmidt, T.; Schmid-Burgk, J.L.; Rapino, F.; Robertson, A.A.B.; Cooper, M.A.; Graf, T.; Hornung, V. Human Monocytes Engage an Alternative Inflammasome Pathway. Immunity 2016, 44, 833–846.

40. Laudisi, F.; Viganò, E.; Mortellaro, A. Tyrosine Kinases: The Molecular Switch for Inflammasome Activation. Cell Mol. Immunol. 2014, 11, 129–131.

41. He, Y.; Franchi, L.; Núñez, G. TLR Agonists Stimulate Nlrp3-Dependent IL-1β Production Independently of the Purinergic P2X7 Receptor in Dendritic Cells and In Vivo. J. Immunol. 2013, 190, 334–339.

42. Song, N.; Liu, Z.-S.; Xue, W.; Bai, Z.-F.; Wang, Q.-Y.; Dai, J.; Liu, X.; Huang, Y.-J.; Cai, H.; Zhan, X.-Y.; et al. NLRP3 Phosphorylation Is an Essential Priming Event for Inflammasome Activation. Mol. Cell 2017, 68, 185–197.e6.

43. Seok, J.K.; Kang, H.C.; Cho, Y.-Y.; Lee, H.S.; Lee, J.Y. Regulation of the NLRP3 Inflammasome by Post-Translational Modifications and Small Molecules. Front. Immunol. 2021, 11, 618231.

44. He, Y.; Zeng, M.Y.; Yang, D.; Motro, B.; Núñez, G. NEK7 Is an Essential Mediator of NLRP3 Activation Downstream of Potassium Efflux. Nature 2016, 530, 354–357.

45. Shi, H.; Wang, Y.; Li, X.; Zhan, X.; Tang, M.; Fina, M.; Su, L.; Pratt, D.; Bu, C.H.; Hildebrand, S.; et al. NLRP3 Activation and Mitosis Are Mutually Exclusive Events Coordinated by NEK7, a New Inflammasome Component. Nat. Immunol. 2016, 17, 250–258.

46. Zheng, D.; Kern, L.; Elinav, E. The NLRP6 Inflammasome. Immunology 2021, 162, 281–289.

47. Hara, H.; Seregin, S.S.; Yang, D.; Fukase, K.; Chamaillard, M.; Alnemri, E.S.; Inohara, N.; Chen, G.Y.; Núñez, G. The NLRP6 Inflammasome Recognizes Lipoteichoic Acid and Regulates Gram-Positive Pathogen Infection. Cell 2018, 175, 1651–1664.e14.

48. Leng, F.; Yin, H.; Qin, S.; Zhang, K.; Guan, Y.; Fang, R.; Wang, H.; Li, G.; Jiang, Z.; Sun, F.; et al. NLRP6 Self-Assembles into a Linear Molecular Platform Following LPS Binding and ATP Stimulation. Sci. Rep. 2020, 10, 198.

49. Wang, P.; Zhu, S.; Yang, L.; Cui, S.; Pan, W.; Jackson, R.; Zheng, Y.; Rongvaux, A.; Sun, Q.; Yang, G.; et al. Nlrp6 Regulates Intestinal Antiviral Innate Immunity. Science (1979) 2015, 350, 826–830.

50. Li, G.; Tian, X.; Lv, D.; Zhang, L.; Zhang, Z.; Wang, J.; Yang, M.; Tao, J.; Ma, T.; Wu, H.; et al. NLRP7 Is Expressed in the Ovine Ovary and Associated with in Vitro Pre-Implantation Embryo Development. Reproduction 2019, 158, 415–427.

51. Khare, S.; Dorfleutner, A.; Bryan, N.B.; Yun, C.; Radian, A.D.; de Almeida, L.; Rojanasakul, Y.; Stehlik, C. An NLRP7-Containing Inflammasome Mediates Recognition of Microbial Lipopeptides in Human Macrophages. Immunity 2012, 36, 464–476.

52. Radian, A.D.; Khare, S.; Chu, L.H.; Dorfleutner, A.; Stehlik, C. ATP Binding by NLRP7 Is Required for Inflammasome Activation in Response to Bacterial Lipopeptides. Mol. Immunol. 2015, 67, 294–302.

53. Bednash, J.S.; Weathington, N.; Londino, J.; Rojas, M.; Gulick, D.L.; Fort, R.; Han, S.; McKelvey, A.C.; Chen, B.B.; Mallampalli, R.K. Targeting the Deubiquitinase STAMBP Inhibits NALP7 Inflammasome Activity. Nat. Commun. 2017, 8, 15203.

54. Kinoshita, T.; Wang, Y.; Hasegawa, M.; Imamura, R.; Suda, T. PYPAF3, a PYRIN-Containing APAF-1-like Protein, Is a Feedback Regulator of Caspase-1-Dependent Interleukin-1β Secretion. J. Biol. Chem. 2005, 280, 21720–21725.

55. Grenier, J.M.; Wang, L.; Manji, G.A.; Huang, W.-J.; Al-Garawi, A.; Kelly, R.; Carlson, A.; Merriam, S.; Lora, J.M.; Briskin, M.; et al. Functional Screening of Five PYPAF Family Members Identifies PYPAF5 as a Novel Regulator of NF-KB and Caspase-1. FEBS Lett. 2002, 530, 73–78.

56. Messaed, C.; Chebaro, W.; Roberto, R.B.D.; Rittore, C.; Cheung, A.; Arseneau, J.; Schneider, A.; Chen, M.F.; Bernishke, K.; Surti, U.; et al. NLRP7 in the Spectrum of Reproductive Wastage: Rare Non-Synonymous Variants Confer Genetic Susceptibility to Recurrent Reproductive Wastage. J. Med. Genet. 2011, 48, 540–548.

57. Lech, M.; Avila-Ferrufino, A.; Skuginna, V.; Susanti, H.E.; Anders, H.J. Quantitative Expression of RIG-like Helicase, NOD-like Receptor and Inflammasome-Related mRNAs in Humans and Mice. Int. Immunol. 2010, 22, 717–728.

58. Imamura, R.; Wang, Y.; Kinoshita, T.; Suzuki, M.; Noda, T.; Sagara, J.; Taniguchi, S.; Okamoto, H.; Suda, T. Anti-Inflammatory Activity of PYNOD and Its Mechanism in Humans and Mice. J. Immunol. 2010, 184, 5874–5884.

59. Vacca, M.; Böhme, J.; Zambetti, L.P.; Khameneh, H.J.; Paleja, B.S.; Laudisi, F.; Ho, A.W.S.; Neo, K.; Leong, K.W.K.; Marzuki, M.; et al. NLRP10 Enhances CD4+ T-Cell-Mediated IFNγ Response via Regulation of Dendritic Cell-Derived IL-12 Release. Front. Immunol. 2017, 8, 1462.

60. Clay, G.M.; Valadares, D.G.; Graff, J.W.; Ulland, T.K.; Davis, R.E.; Scorza, B.M.; Zhanbolat, B.S.; Chen, Y.; Sutterwala, F.S.; Wilson, M.E. An Anti-Inflammatory Role for NLRP10 in Murine Cutaneous Leishmaniasis. J. Immunol. 2017, 199, 2823–2833.

61. Wang, Y.; Hasegawa, M.; Imamura, R.; Kinoshita, T.; Kondo, C.; Konaka, K.; Suda, T. PYNOD, a Novel Apaf-1/CED4-like Protein Is an Inhibitor of ASC and Caspase-1. Int. Immunol. 2004, 16, 777–786.

62. Próchnicki, T.; Vasconcelos, M.B.; Robinson, K.S.; Mangan, M.S.J.; De Graaf, D.; Shkarina, K.; Lovotti, M.; Standke, L.; Kaiser, R.; Stahl, R.; et al. Mitochondrial Damage Activates the NLRP10 Inflammasome. Nat. Immunol. 2023, 24, 595–603.

63. Zheng, D.; Mohapatra, G.; Kern, L.; He, Y.; Shmueli, M.D.; Valdés-Mas, R.; Kolodziejczyk, A.A.; Próchnicki, T.; Vasconcelos, M.B.; Schorr, L.; et al. Epithelial Nlrp10 Inflammasome Mediates Protection against Intestinal Autoinflammation. Nat. Immunol. 2023, 24, 585–594.

64. Allen, I.C.; Wilson, J.E.; Schneider, M.; Lich, J.D.; Roberts, R.A.; Arthur, J.C.; Woodford, R.-M.T.; Davis, B.K.; Uronis, J.M.; Herfarth, H.H.; et al. NLRP12 Suppresses Colon Inflammation and Tumorigenesis through the Negative Regulation of Noncanonical NF-KB Signaling. Immunity 2012, 36, 742–754.

65. Williams, K.L.; Taxman, D.J.; Linhoff, M.W.; Reed, W.; Ting, J.P.-Y. Cutting Edge: Monarch-1: A Pyrin/Nucleotide-Binding Domain/Leucine-Rich Repeat Protein That Controls Classical and Nonclassical MHC Class I Genes. J. Immunol. 2003, 170, 5354–5358.

66. Williams, K.L.; Lich, J.D.; Duncan, J.A.; Reed, W.; Rallabhandi, P.; Moore, C.; Kurtz, S.; Coffield, V.M.; Accavitti-Loper, M.A.; Su, L.; et al. The Caterpillar Protein Monarch-1 Is an Antagonist of Toll-like Receptor-, Tumor Necrosis Factor α-, and Mycobacterium Tuberculosis-Induced Pro-Inflammatory Signals. J. Biol. Chem. 2005, 280, 39914–39924.

67. Lich, J.D.; Williams, K.L.; Moore, C.B.; Arthur, J.C.; Davis, B.K.; Taxman, D.J.; Ting, J.P.-Y. Cutting Edge: Monarch-1 Suppresses Non-Canonical NF-KB Activation and P52-Dependent Chemokine Expression in Monocytes. J. Immunol. 2007, 178, 1256–1260.

68. Hornick, E.E.; Banoth, B.; Miller, A.M.; Zacharias, Z.R.; Jain, N.; Wilson, M.E.; Gibson-Corley, K.N.; Legge, K.L.; Bishop, G.A.; Sutterwala, F.S.; et al. Nlrp12 Mediates Adverse Neutrophil Recruitment during Influenza Virus Infection. J. Immunol. 2018, 200, 1188–1197.

69. Ulland, T.K.; Jain, N.; Hornick, E.E.; Elliott, E.I.; Clay, G.M.; Sadler, J.J.; Mills, K.A.M.; Janowski, A.M.; Volk, A.P.D.; Wang, K.; et al. Nlrp12 Mutation Causes C57BL/6J Strain-Specific Defect in Neutrophil Recruitment. Nat. Commun. 2016, 7, 13180.

70. Zamoshnikova, A.; Groß, C.J.; Schuster, S.; Chen, K.W.; Wilson, A.; Tacchini-Cottier, F.; Schroder, K. NLRP12 Is a Neutrophil-Specific, Negative Regulator of in Vitro Cell Migration but Does Not Modulate LPS- or Infection-Induced NF-KB or ERK Signalling. Immunobiology 2016, 221, 341–346.

71. Lukens, J.R.; Gurung, P.; Shaw, P.J.; Barr, M.J.; Zaki, M.H.; Brown, S.A.; Vogel, P.; Chi, H.; Kanneganti, T.-D. The NLRP12 Sensor Negatively Regulates Autoinflammatory Disease by Modulating Interleukin-4 Production in T Cells. Immunity 2015, 42, 654–664.

72. Gurung, P.; Kanneganti, T.-D. NLRP12 in Autoimmune Diseases. Oncotarget 2015, 6, 19950–19951.

73. Vladimer, G.I.; Weng, D.; Paquette, S.W.M.; Vanaja, S.K.; Rathinam, V.A.K.; Aune, M.H.; Conlon, J.E.; Burbage, J.J.; Proulx, M.K.; Liu, Q.; et al. The NLRP12 Inflammasome Recognizes Yersinia Pestis. Immunity 2012, 37, 96–107.

74. Tuladhar, S.; Kanneganti, T.-D. NLRP12 in Innate Immunity and Inflammation. Mol. Asp. Med. 2020, 76, 100887.

75. The International FMF Consortium Ancient Missense Mutations in a New Member of the RoRet Gene Family Are Likely to Cause Familial Mediterranean Fever. Cell 1997, 90, 797–807.

76. Mansfield, E.; Chae, J.J.; Komarow, H.D.; Brotz, T.M.; Frucht, D.M.; Aksentijevich, I.; Kastner, D.L. The Familial Mediterranean Fever Protein, Pyrin, Associates with Microtubules and Colocalizes with Actin Filaments. Blood 2001, 98, 851–859.

77. Chae, J.J.; Wood, G.; Masters, S.L.; Richard, K.; Park, G.; Smith, B.J.; Kastner, D.L. The B30.2 Domain of Pyrin, the Familial Mediterranean Fever Protein, Interacts Directly with Caspase-1 to Modulate IL-1β Production. Proc. Natl. Acad. Sci. USA 2006, 103, 9982–9987.

78. Papin, S.; Cuenin, S.; Agostini, L.; Martinon, F.; Werner, S.; Beer, H.-D.; Grütter, C.; Grütter, M.; Tschopp, J. The SPRY Domain of Pyrin, Mutated in Familial Mediterranean Fever Patients, Interacts with Inflammasome Components and Inhibits ProIL-1β Processing. Cell Death Differ. 2007, 14, 1457–1466.

79. Xu, H.; Yang, J.; Gao, W.; Li, L.; Li, P.; Zhang, L.; Gong, Y.-N.; Peng, X.; Xi, J.J.; Chen, S.; et al. Innate Immune Sensing of Bacterial Modifications of Rho GTPases by the Pyrin Inflammasome. Nature 2014, 513, 237–241.

80. Just, I.; Selzer, J.; Wilm, M.; von Eichel-Streiber, C.; Mann, M.; Aktories, K. Glucosylation of Rho Proteins by Clostridium Difficile Toxin B. Nature 1995, 375, 500–503.

81. Mostowy, S.; Shenoy, A.R. The Cytoskeleton in Cell-Autonomous Immunity: Structural Determinants of Host Defence. Nat. Rev. Immunol. 2015, 15, 559–573.

82. Kamanova, J.; Kofronova, O.; Masin, J.; Genth, H.; Vojtova, J.; Linhartova, I.; Benada, O.; Just, I.; Sebo, P. Adenylate Cyclase Toxin Subverts Phagocyte Function by RhoA Inhibition and Unproductive Ruffling. J. Immunol. 2008, 181, 5587–5597.

83. Aubert, D.F.; Xu, H.; Yang, J.; Shi, X.; Gao, W.; Li, L.; Bisaro, F.; Chen, S.; Valvano, M.A.; Shao, F. A Burkholderia Type VI Effector Deamidates Rho GTPases to Activate the Pyrin Inflammasome and Trigger Inflammation. Cell Host Microbe 2016, 19, 664–674.

84. Park, Y.H.; Wood, G.; Kastner, D.L.; Chae, J.J. Pyrin Inflammasome Activation and RhoA Signaling in the Autoinflammatory Diseases FMF and HIDS. Nat. Immunol. 2016, 17, 914–921.

85. Lee, S.; Karki, R.; Wang, Y.; Nguyen, L.N.; Kalathur, R.C.; Kanneganti, T.-D. AIM2 Forms a Complex with Pyrin and ZBP1 to Drive PANoptosis and Host Defence. Nature 2021, 597, 415–419.

86. Li, Y.; Fu, T.-M.; Lu, A.; Witt, K.; Ruan, J.; Shen, C.; Wu, H. Cryo-EM Structures of ASC and NLRC4 CARD Filaments Reveal a Unified Mechanism of Nucleation and Activation of Caspase-1. Proc. Natl. Acad. Sci. USA 2018, 115, 10845–10852.

87. Wen, J.; Xuan, B.; Liu, Y.; Wang, L.; He, L.; Meng, X.; Zhou, T.; Wang, Y. Updating the NLRC4 Inflammasome: From Bacterial Infections to Autoimmunity and Cancer. Front. Immunol. 2021, 12, 702527.

88. Broz, P.; Newton, K.; Lamkanfi, M.; Mariathasan, S.; Dixit, V.M.; Monack, D.M. Redundant Roles for Inflammasome Receptors NLRP3 and NLRC4 in Host Defense against Salmonella. J. Exp. Med. 2010, 207, 1745–1755.

89. Man, S.M.; Tourlomousis, P.; Hopkins, L.; Monie, T.P.; Fitzgerald, K.A.; Bryant, C.E. Salmonella Infection Induces Recruitment of Caspase-8 to the Inflammasome To Modulate IL-1β Production. J. Immunol. 2013, 191, 5239–5246.

90. Man, S.M.; Hopkins, L.J.; Nugent, E.; Cox, S.; Glück, I.M.; Tourlomousis, P.; Wright, J.A.; Cicuta, P.; Monie, T.P.; Bryant, C.E. Inflammasome Activation Causes Dual Recruitment of NLRC4 and NLRP3 to the Same Macromolecular Complex. Proc. Natl. Acad. Sci. USA 2014, 111, 7403–7408.

91. Sundaram, B.; Kanneganti, T.-D. Advances in Understanding Activation and Function of the NLRC4 Inflammasome. Int. J. Mol. Sci. 2021, 22, 1048.

92. Barnett, K.C.; Li, S.; Liang, K.; Ting, J.P.-Y. A 360° View of the Inflammasome: Mechanisms of Activation, Cell Death, and Diseases. Cell 2023, 186, 2288–2312.

93. Man, S.M.; Kanneganti, T.-D. Regulation of Inflammasome Activation. Immunol. Rev. 2015, 265, 6–21.

94. Ren, T.; Zamboni, D.S.; Roy, C.R.; Dietrich, W.F.; Vance, R.E. Flagellin-Deficient Legionella Mutants Evade Caspase-1- and Naip5-Mediated Macrophage Immunity. PLoS Pathog. 2006, 2, e18.

95. Franchi, L.; Amer, A.; Body-Malapel, M.; Kanneganti, T.-D.; Özören, N.; Jagirdar, R.; Inohara, N.; Vandenabeele, P.; Bertin, J.; Coyle, A.; et al. Cytosolic Flagellin Requires Ipaf for Activation of Caspase-1 and Interleukin 1β in Salmonella-Infected Macrophages. Nat. Immunol. 2006, 7, 576–582.

96. Miao, E.A.; Alpuche-Aranda, C.M.; Dors, M.; Clark, A.E.; Bader, M.W.; Miller, S.I.; Aderem, A. Cytoplasmic Flagellin Activates Caspase-1 and Secretion of Interleukin 1β via Ipaf. Nat. Immunol. 2006, 7, 569–575.

97. Kofoed, E.M.; Vance, R.E. Innate Immune Recognition of Bacterial Ligands by NAIPs Determines Inflammasome Specificity. Nature 2011, 477, 592–595.

98. Zhao, Y.; Yang, J.; Shi, J.; Gong, Y.-N.; Lu, Q.; Xu, H.; Liu, L.; Shao, F. The NLRC4 Inflammasome Receptors for Bacterial Flagellin and Type III Secretion Apparatus. Nature 2011, 477, 596–600.

99. Zamboni, D.S.; Kobayashi, K.S.; Kohlsdorf, T.; Ogura, Y.; Long, E.M.; Vance, R.E.; Kuida, K.; Mariathasan, S.; Dixit, V.M.; Flavell, R.A.; et al. The Birc1e Cytosolic Pattern-Recognition Receptor Contributes to the Detection and Control of Legionella Pneumophila Infection. Nat. Immunol. 2006, 7, 318–325.

100. Amer, A.; Franchi, L.; Kanneganti, T.-D.; Body-Malapel, M.; Özören, N.; Brady, G.; Meshinchi, S.; Jagirdar, R.; Gewirtz, A.; Akira, S.; et al. Regulation of Legionella Phagosome Maturation and Infection through Flagellin and Host Ipaf. J. Biol. Chem. 2006, 281, 35217–35223.

101. Karki, R.; Lee, E.; Place, D.; Samir, P.; Mavuluri, J.; Sharma, B.R.; Balakrishnan, A.; Malireddi, R.K.S.; Geiger, R.; Zhu, Q.; et al. IRF8 Regulates Transcription of Naips for NLRC4 Inflammasome Activation. Cell 2018, 173, 920–933.e13.

102. Mathur, A.; Hayward, J.A.; Man, S.M. Molecular Mechanisms of Inflammasome Signaling. J. Leukoc. Biol. 2017, 103, 233–257.

103. Hu, Z.; Zhou, Q.; Zhang, C.; Fan, S.; Cheng, W.; Zhao, Y.; Shao, F.; Wang, H.-W.; Sui, S.-F.; Chai, J. Structural and Biochemical Basis for Induced Self-Propagation of NLRC4. Science (1979) 2015, 350, 399–404.

104. Zhang, L.; Chen, S.; Ruan, J.; Wu, J.; Tong, A.B.; Yin, Q.; Li, Y.; David, L.; Lu, A.; Wang, W.L.; et al. Cryo-EM Structure of the Activated NAIP2-NLRC4 Inflammasome Reveals Nucleated Polymerization. Science (1979) 2015, 350, 404–409.

105. Kumar, Y.; Radha, V.; Swarup, G. Interaction with Sug1 Enables Ipaf Ubiquitination Leading to Caspase 8 Activation and Cell Death. Biochem. J. 2010, 427, 91–104.

106. Raghawan, A.K.; Sripada, A.; Gopinath, G.; Pushpanjali, P.; Kumar, Y.; Radha, V.; Swarup, G. A Disease-Associated Mutant of NLRC4 Shows Enhanced Interaction with SUG1 Leading to Constitutive FADD-Dependent Caspase-8 Activation and Cell Death. J. Biol. Chem. 2017, 292, 1218–1230.

107. von Moltke, J.; Trinidad, N.J.; Moayeri, M.; Kintzer, A.F.; Wang, S.B.; van Rooijen, N.; Brown, C.R.; Krantz, B.A.; Leppla, S.H.; Gronert, K.; et al. Rapid Induction of Inflammatory Lipid Mediators by the Inflammasome in Vivo. Nature 2012, 490, 107–111.

108. Muruve, D.A.; Pétrilli, V.; Zaiss, A.K.; White, L.R.; Clark, S.A.; Ross, P.J.; Parks, R.J.; Tschopp, J. The Inflammasome Recognizes Cytosolic Microbial and Host DNA and Triggers an Innate Immune Response. Nature 2008, 452, 103–107.

109. Hornung, V.; Ablasser, A.; Charrel-Dennis, M.; Bauernfeind, F.; Horvath, G.; Caffrey Daniel, R.; Latz, E.; Fitzgerald, K.A. AIM2 Recognizes Cytosolic dsDNA and Forms a Caspase-1-Activating Inflammasome with ASC. Nature 2009, 458, 514–518.

110. Fernandes-Alnemri, T.; Yu, J.-W.; Datta, P.; Wu, J.; Alnemri, E.S. AIM2 Activates the Inflammasome and Cell Death in Response to Cytoplasmic DNA. Nature 2009, 458, 509–513.

111. Wang, B.; Yin, Q. AIM2 Inflammasome Activation and Regulation: A Structural Perspective. J. Struct. Biol. 2017, 200, 279–282.

112. Di Micco, A.; Frera, G.; Lugrin, J.; Jamilloux, Y.; Hsu, E.-T.; Tardivel, A.; De Gassart, A.; Zaffalon, L.; Bujisic, B.; Siegert, S.; et al. AIM2 Inflammasome Is Activated by Pharmacological Disruption of Nuclear Envelope Integrity. Proc. Natl. Acad. Sci. USA 2016, 113, E4671–E4680.

113. Lugrin, J.; Martinon, F. The AIM2 Inflammasome: Sensor of Pathogens and Cellular Perturbations. Immunol. Rev. 2018, 281, 99–114.

114. Wang, L.; Sun, L.; Byrd, K.M.; Ko, C.-C.; Zhao, Z.; Fang, J. AIM2 Inflammasome's First Decade of Discovery: Focus on Oral Diseases. Front. Immunol. 2020, 11, 1487.

115. Man, S.M.; Karki, R.; Kanneganti, T.-D. AIM2 Inflammasome in Infection, Cancer, and Autoimmunity: Role in DNA Sensing, Inflammation, and Innate Immunity. Eur. J. Immunol. 2016, 46, 269–280.

116. Shrivastava, G.; León-Juárez, M.; García-Cordero, J.; Meza-Sánchez, D.E.; Cedillo-Barrón, L. Inflammasomes and Its Importance in Viral Infections. Immunol. Res. 2016, 64, 1101–1117.

117. Ma, Z.; Ni, G.; Damania, B. Innate Sensing of DNA Virus Genomes. Annu. Rev. Virol. 2018, 5, 341–362.

118. Hayward, J.A.; Mathur, A.; Ngo, C.; Man, S.M. Cytosolic Recognition of Microbes and Pathogens: Inflammasomes in Action. Microbiol. Mol. Biol. Rev. 2018, 82, e00015-18.

119. Storek, K.M.; Gertsvolf, N.A.; Ohlson, M.B.; Monack, D.M. CGAS and Ifi204 Cooperate To Produce Type I IFNs in Response to Francisella Infection. J. Immunol. 2015, 194, 3236–3245.

120. Man, S.M.; Karki, R.; Sasai, M.; Place, D.E.; Kesavardhana, S.; Temirov, J.; Frase, S.; Zhu, Q.; Malireddi, R.K.S.; Kuriakose, T.; et al. IRGB10 Liberates Bacterial Ligands for Sensing by the AIM2 and Caspase-11-NLRP3 Inflammasomes. Cell 2016, 167, 382–396.e17.

121. Meunier, E.; Wallet, P.; Dreier, R.F.; Costanzo, S.; Anton, L.; Rühl, S.; Dussurgey, S.; Dick, M.S.; Kistner, A.; Rigard, M.; et al. Guanylate-Binding Proteins Promote Activation of the AIM2 Inflammasome during Infection with Francisella Novicida. Nat. Immunol. 2015, 16, 476–484.

122. Bürckstümmer, T.; Baumann, C.; Blüml, S.; Dixit, E.; Dürnberger, G.; Jahn, H.; Planyavsky, M.; Bilban, M.; Colinge, J.; Bennett, K.L.; et al. An Orthogonal Proteomic-Genomic Screen Identifies AIM2 as a Cytoplasmic DNA Sensor for the Inflammasome. Nat. Immunol. 2009, 10, 266–272.

123. Mantovani, A.; Dinarello, C.A.; Molgora, M.; Garlanda, C. Interleukin-1 and Related Cytokines in the Regulation of Inflammation and Immunity. Immunity 2019, 50, 778–795.

124. Wang, B.; Bhattacharya, M.; Roy, S.; Tian, Y.; Yin, Q. Immunobiology and Structural Biology of AIM2 Inflammasome. Mol. Asp. Med. 2020, 76, 100869.

125. Dorfleutner, A.; Bryan, N.B.; Talbott, S.J.; Funya, K.N.; Rellick, S.L.; Reed, J.C.; Shi, X.; Rojanasakul, Y.; Flynn, D.C.; Stehlik, C. Cellular Pyrin Domain-Only Protein 2 Is a Candidate Regulator of Inflammasome Activation. Infect. Immun. 2007, 75, 1484–1492.

126. Khare, S.; Ratsimandresy, R.A.; de Almeida, L.; Cuda, C.M.; Rellick, S.L.; Misharin, A.V.; Wallin, M.C.; Gangopadhyay, A.; Forte, E.; Gottwein, E.; et al. The PYRIN Domain–Only Protein POP3 Inhibits ALR Inflammasomes and Regulates Responses to Infection with DNA Viruses. Nat. Immunol. 2014, 15, 343–353.

127. Stehlik, C.; Krajewska, M.; Welsh, K.; Krajewski, S.; Godzik, A.; Reed, J.C. The PAAD/PYRIN-Only Protein POP1/ASC2 Is a Modulator of ASC-Mediated Nuclear-Factor-KappaB and pro-Caspase-1 Regulation. Biochem. J. 2003, 373, 101–113.

128. Huang, Y.; Ma, D.; Huang, H.; Lu, Y.; Liao, Y.; Liu, L.; Liu, X.; Fang, F. Interaction between HCMV PUL83 and Human AIM2 Disrupts the Activation of the AIM2 Inflammasome. Virol. J. 2017, 14, 34.

129. Bauernfeind, F.; Hornung, V. Of Inflammasomes and Pathogens – Sensing of Microbes by the Inflammasome. EMBO Mol. Med. 2013, 5, 814–826.