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A 360° view of the inflammasome: mechanisms of activation, cell death, and disease

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Summary

Inflammasomes are critical sentinels of the innate immune system that respond to threats to the host through recognition of distinct molecules, known as pathogen- or damage-associated molecular patterns (PAMPs/DAMPs), or disruptions of cellular homeostasis, referred to as homeostasis-altering molecular processes (HAMPs) or effector-triggered immunity (ETI). Several distinct proteins nucleate inflammasomes, including NLRP1, CARD8, NLRP3, NLRP6, NLRC4/NAIP, AIM2, pyrin, and caspases-4/5/11. This diverse array of sensors strengthens the inflammasome response through redundancy and plasticity. Here, we present an overview of these pathways, outlining mechanisms of inflammasome formation, subcellular regulation, and pyroptosis, and discuss the wide-reaching effects of inflammasomes in human disease.

Keywords

Inflammasome; IL-1β; IL-18; pyroptosis; NLRP1; CARD8; NLRP3; NLRP6; NLRC4; AIM2; Pyrin; Caspase-1; Caspase-4; Caspase-5; Caspase-11; GSDMD

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J.P.-Y.T. is a cofounder of IMMvention Therapeutix which works on inflammasome inhibitors.

Introduction

In 2001, a member of the nucleotide-binding domain (NBD), leucine-rich repeat (LRR)-containing (NLR) protein family was found to stimulate caspase-1 activation and cause cell death[1]. Later, another group described how another member of the NLR family exhibited a similar function when coexpressed with an adaptor protein referred to as ASC (short for Apoptosis-associated Speck-like protein containing a Caspase activation and recruitment domain) and caspase-1, causing both cell death and IL-1β release[2]. Simultaneously, a biochemical study provided foundational information by demonstrating the formation of an NLR containing a pyrin domain (PYD) 1 (NLRP1)-dependent supramolecular organizing center (SMOC)[3] governing IL-1β processing, which the authors called the inflammasome[4]. Since these seminal studies, our understanding of the inflammasome and the pattern recognition receptors (PRRs) that nucleate its formation expanded substantially, though many aspects governing this critical innate immune signaling hub remain active areas of research.

Canonical inflammasomes are comprised of an activated PRR, ASC, and caspase-1. Several proteins nucleate inflammasome formation, including many in the NLR protein family, which contain a unique NBD referred to as NACHT, a name derived from proteins containing the domain: NLR family apoptosis inhibitory protein (NAIP), MHC class II transcription activator (CIITA), incompatibility locus protein from *Podospora anserina* (HET-E), and telomerase associated protein (TP-1)[5]. NLRs containing N-terminal PYDs are referred to as NLRPs, while NLRs with N-terminal caspase activation and recruitment domains (CARDs) are NLRCs. However, proteins outside of this family also nucleate inflammasomes. Inflammasome formation initiates autoproteolytic processing of caspase-1, instigating cleavage of its cellular substrates. These substrates include pro-IL-1β, pro-IL-18, and gasdermin D (GSDMD)[6–11]. After cleavage by caspase-1, the GSDMD N-terminus (GSDMD-NT) then oligomerizes to form pores in the plasma membrane, which mediate membrane depolarization and cell rupture. GSDMD pores also serve as conduits for IL-1β and IL-18 secretion, intrinsically linking release of these cytokines to disruption of cellular physiology[12,13]. Thus, inflammasome formation is a fundamental upheaval of cellular state that generates a robust pro-inflammatory response, serving as a key sentinel for pathogenic threats and damage to the host.

PRRs that nucleate inflammasomes respond to both pathogen-derived and host-derived molecules and activities. PRRs may bind directly to molecules from pathogens, or pathogen-associated molecular patterns (PAMPs), to initiate inflammasome formation. Examples of PAMPs that nucleate inflammasomes include bacterial products such as flagellin or lipopolysaccharide (LPS) or viral RNA. Similarly, PRRs may also detect the activities of pathogen effector proteins, a mechanism known as effector-triggered immunity (ETI)[14]. ETI was originally hypothesized as a mechanism of host defense in plants, in which a cellular R protein ‘guarded’ cellular targets of bacterial effectors to mediate disease resistance[15]. However, these principles are also observed in mammalian innate immunity, including the inflammasome response. Inflammasomes also form in response to host-derived signals. Disruption within the cellular environment is sufficient to activate inflammasome PRRs through recognition of homeostasis-altering molecular processes (HAMPs), such as

disturbance of cellular ion gradients or the cytoskeleton[16]. Likewise, damage to the host causes production of damage-associated molecular patterns (DAMPs), such as extracellular DNA or ATP, which also initiate inflammasome responses[3]. While some PRRs are highly specific for certain PAMPs/DAMPs/HAMPs or effector activities, other PRRs respond to a broad range of stimuli, and specific molecular signals that consistently mediate receptor activation remain elusive. Thus, inflammasome nucleation is a process with features of both plasticity and specificity that enables the host cells to respond to a wide range of signals. Furthermore, several cellular processes regulate inflammasome formation and pyroptosis, which converge to generate a range of responses arising from inflammasome formation. Though space constraints prevent a description of the less studied inflammasomes, the mechanisms of the major inflammasomes and their consequences in disease are described in detail below.

Threat Recognition and Inflammasome Nucleation

Diverse PAMPs/DAMPs and threats to cellular homeostasis nucleate canonical and non-canonical inflammasomes (Table 1). Inflammasome formation typically depends on two distinct signals: (I) primes the cell for inflammasome activation and (II) acts directly on a receptor/sensor to prompt inflammasome formation and pyroptosis. Together, these signals I and II define the nature of inflammasome and pyroptotic responses, as detailed below.

Priming

Typically, prior to inflammasome formation, a stimulus rewires the cellular state to license pathway activation, a stimulus known as a signal I or priming signal. Early work demonstrated that transcriptional upregulation of inflammasome components and cytokines, through stimulation nuclear factor-κB (NF-κB) gene transcription by toll-like receptor (TLR) agonists and tumor necrosis factor (TNF), promoted NLRP3 activation[17,18]. Because of this, transcriptional upregulation is utilized as an indicator of potential inflammasome activity, yet transcriptional upregulation alone is insufficient for inflammasome activation. Furthermore, other work has demonstrated that transcriptional priming is not strictly required for inflammasome activation[19,20] and has functions outside of transcriptional upregulation, including alteration of post-translational modifications (PTMs) on NLRP3 and other inflammasome components to promote activation[21,22]. As such, inflammasome activation is more dependent on priming in some contexts versus others. For instance, the inflammasome-secreted cytokines pro-IL-1β and pro-IL-18 have different expression patterns that influence sensitivity to priming signals. Pro-IL-18 is constitutively expressed in many cell types, while pro-IL-1β expression requires induction through TLR agonists, pro-inflammatory cytokines, and other inflammatory mediators[23]. Accordingly, IL-18 release is less dependent on priming than IL-1β[24]. Similarly, cell type and sensor identity play an important role in priming. While priming is necessary for NLRP3 inflammasome activation in murine bone marrow-derived macrophages (BMDMs) and other myeloid cell types, LPS stimulation of human monocytes leads to an alternative mechanism of inflammasome activation through direct interactions with TLR4 SMOCs, negating the requirement for additional priming signal[20]. Likewise, activation of the NLRP1 or CARD8 inflammasome by Val-boroPro (VbP) does not require a priming signal for IL-1β release[25,26]. Therefore,

the requirements for priming of inflammasome pathways prior to activation are context-dependent and vary between different cell types, stimuli, and sensors.

NLRP1 and CARD8

NLRP1 was the first identified inflammasome-nucleating protein[4] but only recent work expanded our understanding of this enigmatic sensor. Similar to other NLRPs, human NLRP1 (hNLRP1) has an N-terminal PYD, NACHT domain, and LRRs. Yet unlike other NLRs, these domains are followed by a function-to-find domain (FIIND) and a C-terminal CARD (Figure 1). The FIIND undergoes autoproteolytic cleavage that generates two fragments (N and C terminal), a process necessary for NLRP1 inflammasome responses[27,28]. In humans, CARD8 also contains this FIIND-CARD motif and nucleates inflammasomes[25,29]. Divergent from humans, mice have three paralogs of *NLRP1*, *Nlrp1a, Nlrp1b*, and *Nlrp1c*, that lack N-terminal PYDs and no paralog of *CARD8*. Expression and alleles of these paralogs vary between murine strains, as does their responsiveness to different stimuli.

Early work identified *Bacillus anthracis* Lethal Toxin (LT) as a mediator of pyroptosis in murine macrophages[30], a process abrogated by proteasome inhibitors[31] and inhibitors of N-end rule-mediated degradation[32]. Later, specific alleles[33] of *Nlrp1b* were identified to mediate this response through cleavage of its N-terminus[34,35] (Figure 1). This N-terminal cleavage event led to ubiquitination and N-end rule-mediated functional degradation of the NLRP1 N-terminus, freeing the C-terminal fragment (CTf) to mediate inflammasome formation[36,37]. Similar to cleavage by LT, the *Shigella flexneri* protein IpaH7.8 E3 ubiquitin ligase ubiquitinates the murine NLRP1b N terminus to promote its functional degradation and mediate CTf inflammasome nucleation[37]. Though it should be noted that neither of these bacterial products appear to affect hNLRP1 directly. However, we know that functional degradation of NLRP1 is a common mechanism of activation of this PRR across species (Figure 1). For example, the addition of artificial cleavage sites in the N-termini of murine NLRP1a (mNLRP1a), mNLRP1b, and hNLRP1 promotes inflammasome activation and IL-1β release[38]. More recently, several viral proteases were shown to cleave the N-terminus of hNLRP1, leading to its functional degradation and formation of a CTf inflammasome[39–41]. Similarly, the human immunodeficiency virus (HIV)-1 protease was shown to cleave CARD8, nucleating inflammasomes in T cells and myeloid cells[42].

Though pathogen-derived NLRP1 stimuli differ across species and alleles, all functional NLRP1 alleles respond to the inhibition of dipeptidyl peptidases 8 and 9 (DPP8/9)[25,43] (Figure 1). Cryo-EM studies revealed DPP9 forms an inhibitory, ternary (2:1) complex with both full-length human NLRP1 and the human NLRP1 CTf[44,45]. The CTf occupies the DPP9 active site, and upon DPP9 inhibition by Val-boroPro (VbP), the CTf is freed leading to inflammasome formation. The related PRR, CARD8, is similarly sequestered by DPP9 and forms an inflammasome upon DPP8/9 inhibitor treatment[25,29,46] (Figure 1). Regulation of NLRP1 may be a critical function of DPP9, as spontaneous inflammation resulting from mutation or loss of DPP9 is rescued by loss of NLRP1 and other inflammasome components[47].

Though CARD8 and hNLRP1 have seemingly redundant activation mechanisms, the dependence of the inflammasome response to VbP varies by cell type in humans. CARD8 mediates this response in T cells and myeloid cells[26,29,46], while hNLRP1 mediates this response in epithelial cell types[25]. While mNLRP1b functions in myeloid cells, hNLRP1 has emerged as an epithelial innate immune sensor, forming inflammasomes in human keratinocytes[25,48] and airway epithelial cells[39,41]. In epithelial cells, hNLRP1 detects diverse stimuli, including viral protease activity[39–41], RNA virus replication[49–51], ultraviolet (UV) radiation[51], ribotoxic stress[50,51], and shifts in cellular redox potential[52]. Detection of UV radiation and ribotoxic stress occur through activation of the p38/MAPK and ZAKα kinases, which activate hNLRP1 through hyperphosphorylation of the linker region between the hNLRP1 pyrin and NACHT domains (Figure 1)[50,51]. Activation of these kinases through cellular stress also mediates NLRP1 detection of the DNA mimetic poly(dA:dT)[53]. Though one report indicates the hNLRP1 N terminus directly binds viral RNA to initiate inflammasome formation[49], many infectious stimuli of NLRP1 and CARD8 mediate responses by instigating functional degradation of the N-terminus, which can occur through its cleavage[39,40] or ubiquitination[36,37]. This detection of pathogen activities, rather than binding specific PAMPs or DAMPs, is a form of ETI that has led some to speculate that NLRP1 may act as a guard protein[15,54]. In this model, the N-terminus of NLRP1 or CARD8 acts as a “decoy” or “tripwire” that when modified by pathogen effectors is degraded to release the inflammasome-nucleating CTf[15,37,42,55]. Similarly, NLRP1 and CARD8 detect changes in cellular homeostasis through recognition of HAMPs, including phosphorylation[50,51] and DPP9 inhibition[25,43,46]. Thus, these sensors detect diverse signals to mediate inflammasome formation. Future work will shed further light on the mechanisms of NLRP1/CARD8 activation, their sensory capacity in tissue injury and infection, and the role that DPP9 plays in these processes. For more information on NLRP1 and CARD8, readers can refer to an excellent recent review[55].

NLRP3

Highly expressed in myeloid cell types, NLRP3 is the best-studied inflammasome-nucleating sensor. While many different stimuli mediate NLRP3 activation, these mechanisms converge on changes in ion flux[56], organelle dysfunction[57], and shifts in metabolic flux[58]. While some work has linked NLRP3 activation to direct binding of nucleic acids[59,60], a recent study indicated that NLRP3 is the primary mediator of the inflammasome response to double-stranded DNA (dsDNA) in human monocytes, activated through ion gradient depolarization initiated by cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING)-driven lytic cell death[61]. Indeed, NLRP3 is reported to respond to the gamut of innate immune stimuli, recognizing HAMPs from cellular dysfunction, binding PAMPs/DAMPs in the form of nucleic acids, and mediating ETI by responding to pore-forming toxins that disrupt cellular ion gradients[62,63]. How such diverse signals converge on a singular mechanism to activate NLRP3 remains an active area of research. NLRP3 activation also has been observed as functioning in concert with other inflammasome PRRs, including AIM2[64,65] and NLRC4[66,67], in specific contexts. While some work indicates that NLRP3 directly interacts with other PRRs to create a dual inflammasomes[68,69], these observations using microscopy and gene-deletion experiments may reflect pathway redundancy rather than direct molecular interaction. Regardless,

these properties highlight NLRP3 as a critical mediator of inflammasome formation. For further discussion of NLRP3 biology, we refer interested readers to several superb reviews[62,63,70,71].

Recently, several cryo-EM studies revealed the inactive and active structures of NLRP3[72–74]. In its inactive form, NLRP3 forms a large multimeric cage[73,74]. Murine NLRP3 forms a dodecameric cage that shields the NLRP3 PYD to inhibit premature activation and promotes NLRP3 association with the *trans*-Golgi network (TGN)[74], while inactive human NLRP3 forms a similar decameric structure[73]. In its active conformation, human NLRP3 forms a decameric disc structure, freeing the PYD to interact with ASC and nucleate the inflammasome[72]. Future work will determine how different stimuli initiate conformational changes between these active and inactive structures, which may offer new therapeutic targets.

NLRP6

First observed to stimulate caspase-1 and NF-κB activation in overexpression systems[75], NLRP6 is reported to act as an inflammasome nucleating PRR in addition to other functions. NLRP6 is highly expressed in the colonic epithelium[78–80] and the gastrointestinal immune environment[76–78]. Loss of NLRP6 was found to abrogate mucus production in colonic goblet cells[79], promote the development of a colitogenic microbiota in dextran sodium sulfate (DSS)-induced colitis[78], and maintain the colonic microbiota through a relationship with microbiota-derived metabolites[80]. However, this role in maintaining the colonic microbiota is debated, as others were unable to recapitulate these findings[81–83]. In response to pathogens, loss of NLRP6 increased murine susceptibility to viral infection[84] and colonic tumorigenesis[76,77]. Findings in response to colonic bacterial infection show that NLRP6 protects the host against some bacterial infections[79], while it reduces host defense against others[85,86]. These studies in animal models highlight the nuanced and context-dependent role of NLRP6 in various diseases.

Furthering this notion, mechanisms of NLRP6 activity vary between studies and ligands described (Figure 2). Some report a suppressive role for NLRP6 in dampening NF-κB and MAPK responses to *Listeria monocytogenes* infection[86]. However, other phenotypes are dependent also on ASC, caspase-1, and IL-18, implicating an NLRP6 inflammasome[79,80,85]. In Gram-positive bacterial infection, this response is mediated by lipoteichoic acid (LTA) binding to NLRP6 to nucleate inflammasomes[85,87]. However, in RNA virus infection, NLRP6 detects viral RNA through an interaction with the RNA helicase DHX15 to promote IFN responses[84,87]. A recent study suggested that NLRP6 may accomplish both of these activities through liquid-liquid phase separation (LLPS)[87]. In this work, NLRP6 bound dsRNA or LTA directly to promote LLPS and form liquid condensates with ASC or DHX15 with the former driving inflammasome formation and the latter promoting interferon responses[87]. Therefore, more research is necessary to clarify the molecular cues driving the wide range of reported actions of the NLRP6 inflammasome and other SMOCs it nucleates.

NLRC4/NAIP

NLRC4 was the first inflammasome sensor demonstrated to cause both caspase-1 activation and cell death[1] and plays a key role in the innate immune response to bacterial pathogens[88–90]. Early work demonstrated that loss of NLRC4 blocked cell death following *Salmonella typhimurium* infection[88] and identified that cytosolic delivery of bacterial flagellin was sufficient to initiate this response[91,92]. However, NLRC4 does not bind flagellin directly. Rather, it relies on the sensory activity of NAIPs, specifically *Naip1-6* in mice and a single *NAIP* in humans. Murine *Naip*2 and *Naip5* were initially identified as candidate genes for *Legionella pneumophila* pathogenesis or resistance[93], a function later found to also depend on NLRC4[94]. Murine NAIP5 (mNAIP5), mNAIP6, and human NAIP (hNAIP) bind bacterial flagellin in the cytosol[95–97], which then interacts with NLRC4 to form an inflammasome. In addition to flagellin, NAIPs recognize components of bacterial type III secretion systems (T3SS). Individual murine NAIPs recognize distinct T3SS protein ligands, namely the rod protein, detected by mNAIP2[95,96], and needle protein, detected by mNAIP1[98]. However, hNAIP recognizes both the T3SS rod and needle proteins in addition to flagellin[95,98–100](Figure 2). Cryo-EM structures revealed how NAIPs nucleate the assembly of the NLRC4 inflammasome. Multiple groups showed that a single copy of mNAIP2 bound to the *S. typhimurium* rod protein nucleates a multi-subunit disk structure containing a single mNAIP2 and 10 monomers of NLRC4[101,102], corroborating earlier EM work that indicated a similar arrangement for the mNAIP5/NLRC4 inflammasome[103]. These higher-order assemblages leave the CARD of NLRC4 free to recruit caspase-1 and promote its oligomerization, demonstrating how these inflammasomes can form in the absence of ASC. While ASC is not strictly required for NLRC4 inflammasome formation, loss of ASC leads to inefficient caspase-1 cleavage and diminished IL-1β release, indicating that ASC enhances these responses[104,105]. Some work has implicated phosphorylation of NLRC4 at serine 533 as a requirement for its activation[106], while the structure of the autoinhibited, inactive NLRC4 also contains this PTM[107]. Yet, others have not observed this requirement[108,109], leaving the role of this PTM unclear[106,107].

While expressed in macrophages and other myeloid cell types, NLRC4 is also expressed in intestinal epithelial cells (IECs). In murine models of infection, loss of NLRC4 expression in the epithelium but not the bone marrow led to a loss of control of *S. typhimurium* and *Citrobacter rodentium* infection[110,111]. In the intestinal epithelium, NLRC4 promotes pyroptosis and IL-18 release in response to *S. typhimurium* and mediates cell death and expulsion of infected IECs[111,112]. Caspase-1 was dispensable in this process, which could also utilize caspase-8[112]. Similarly, NLRC4 prevented *Shigella* colonization and mediated infected cell expulsion in IEC monolayer cultures, and loss of NLRC4 in the intestinal epithelium led to shigellosis in mice[113,114]. Taken together, these studies point toward a pivotal role for NLRC4 in the innate immune and cell death responses in the intestinal epithelium.

While most work focused on the response to bacterial pathogens, recent studies implicate NLRC4 in mechanisms of sterile inflammation. Many different cell types form inflammasomes in response to DAMPs via NLRC4, including lysophosphatidylcholine (LPC) in microglia and astrocytes[67], hyperosmotic stress in BMDMs[66], and short

interspersed nuclear element (SINE) RNAs in retinal pigmented epithelial cells[69]. Unlike other NLRC4 inflammasome assemblies, the RNA helicase DDX17 was reported to mediate NLRC4 response to SINE RNAs, rather than NAIPs, suggesting the NLRC4 inflammasome may interface with multiple PRRs to mediate inflammasome responses. Notably, all of these DAMPs activated both NLRC4 and NLRP3[66,67,69]. Understanding the molecular requirements of NLRC4 activation, the extent of signals that activate NLRC4, and the role of NLRC4 in different cell types will be important areas for further research.

AIM2

AIM2 (absent in melanoma 2) was first described as a tumor suppressor[115] but was later found to bind cytosolic dsDNA to nucleate an inflammasome in human cell lines and murine BMDMs[116–118]. AIM2 is a member of the IFN-inducible HIN-200 family of proteins with an N-terminal PYD and a C-terminal HIN-200 domain. Prior to DNA binding, AIM2 exists in an autoinhibited conformation with interactions between the PYD and HIN-200 domain[119]. The HIN-200 domain binds dsDNA in a sequence-independent manner but requires a minimal length reported between 70–80bp for recognition[120,121]. Structural data reveals that the AIM2 HIN-200 domain oligomerizes along dsDNA[121,122], which then frees the AIM2 PYD to form helical assemblies that bind ASC to form an inflammasome[123,124]. Since its identification as a DNA sensor, AIM2 was found to mediate inflammasome responses to bacterial and viral pathogens, including cytomegalovirus (CMV)[125], vaccinia virus (VACV)[125], human papillomavirus (HPV)[126], *Francisella tularensis*[125,127], and *L. monocytogenes*[125,128,129] (Figure 3). AIM2 also detects self-derived DNA with noted roles in the immune response to tumorigenesis[130,131], radiation-induced tissue damage[132], and the DNA-damage response in mouse models of neurodevelopment[133], polyarthritis[134], and atherosclerosis[135].

Crosstalk with other innate immune sensors and cellular homeostasis regulate AIM2 activity. Notably, AIM2 interfaces with another DNA sensing pathway, the cGAS-STING pathway, which initiates a type I IFN response to cytosolic dsDNA[136]. cGAS-STING signaling can promote AIM2 inflammasome priming through IFN-stimulated upregulation of AIM2[137,138]. Conversely, AIM2 inflammasomes inhibit cGAS-STING signaling[139–142]. Mechanistically, cGAS-STING signaling is abrogated by AIM2 inflammasomes through caspase-1-mediated cleavage of cGAS[140] and inhibition of cGAS activity through disruption of intracellular K^+ levels caused by GSDMD pore formation[139]. AIM2 also coordinates with NLRP3, and multiple reports indicate both proteins are required for inflammasome responses in many contexts, including bacterial infection[143,144], *Plasmodium* infection[64], and STING agonist stimulation[138]. AIM2 is also implicated in a hybrid cell death pathway consisting of simultaneous activation of pyroptosis, apoptosis, and necroptosis, called PANoptosis[145], in which AIM2 is reported to form a complex with pyrin and ZBP1 to execute this form of inflammatory cell death[146]. Furthermore, changes in cellular metabolism govern AIM2 responses. For instance, excessive synthesis of cholesterol can trigger mitochondrial DNA (mtDNA) release and AIM2 activation[147]. Similarly, another study reported that upregulation of the M2 isoform of pyruvate kinase to promote glycolysis in macrophages initiates both AIM2 and NLRP3 inflammasome responses[148].

AIM2 has roles in immunity outside of the inflammasome response. In the murine azoxymethane/DSS (AOM/DSS) model of colorectal cancer, AIM2 loss led to a greater tumor burden than the loss of ASC, and AIM2 was found to suppress AKT activation through interaction with DNA-dependent protein kinase (DNA-PK) to control tumor development[130] and suppress intestinal stem cell proliferation[131]. Another group found AIM2 suppression of DNA-PK-AKT signaling in microglia decreased inflammation in experimental autoimmune encephalomyelitis (EAE)[149]. However, two other groups described conventional DNA and inflammasome-mediated roles of AIM2 in murine DSS colitis[150,151]. AIM2 also enhances the stability of T regulatory cells in EAE through suppression of AKT-mTOR signaling and alteration of immune metabolism[152]. Furthermore, AIM2 was shown to bind neutrophil extracellular traps, leading to DNase-resistant nucleoprotein fibers that can serve as autoantigens in systemic lupus erythematosus[153]. These studies suggest that AIM2 has inflammasome-independent functions and may function as a rheostat in various inflammatory processes. Future work will determine how both inflammasome-dependent and -independent functions of AIM2 inform the immune response and its relevance in human biology.

Pyrin

Pyrin is encoded by *MEFV* and was first identified as the genetic determinant of Familial Mediterranean fever (FMF)[154,155]. Pyrin was found to interact with ASC in a yeast-two hybrid screen[156] and is considered a member of the tripartite motif-containing (TRIM) family of proteins. However, unlike canonical TRIM proteins, pyrin has an N-terminal PYD rather than a RING E3 ubiquitin ligase domain. This N-terminal PYD mediates its interaction with ASC, while the following zinc finger (bBox), coiled-coil (CC), and C-terminal B30.2/SPRY domains regulate Pyrin activation. Though its role in inflammasome formation was debated for many years[157–159], missense mutations linked to FMF in pyrin led to gain-of-function inflammasome activation in mice independent of NLRP3[160]. Later, pyrin was shown to sense inactivation of the RhoA GTPase mediated by bacterial toxins[161], solidifying its role as an inflammasome-nucleating innate immune sensor.

Pyrin associates with actin filaments[162] and senses perturbations in the actin cytoskeleton through its relationship with RhoA. RhoA and other Rho GTPases regulate actin and microtubule dynamics to control cell shape, motility, and polarity[163]. Intracellular pathogens may disrupt these cytoskeletal dynamics to promote replication, as observed with bacterial toxins[161], activating pyrin inflammasome formation. A loss-of-function mutation in Wdr1, an actin depolymerization cofactor, led to spontaneous pyrin inflammasome activation[164]. Mechanistically, pyrin is maintained in an inactive state through phosphorylation of Ser208/242 in humans and Ser205/241 in mice by the RhoA-dependent kinases PKN1/2[165,166]. 14-3-3 proteins bind these PTMs, placing pyrin in an inactive state[164,166]. Disruption of RhoA function leads to pyrin dephosphorylation and loss of association with 14-3-3 proteins. However, pathogens triggering this response may also evade it, as different *Yersinia* species inhibit pyrin detection through YopM-mediated promotion of PKN1/2-mediated phosphorylation[167,168]. Pyrin also associates with microtubules[166]. Recently, a study demonstrated that microtubule-dependent trafficking of pyrin through HDAC6 activity was necessary for inflammasome formation[169], highlighting the complex

relationship between pyrin and the cytoskeleton. Through the detection of changes in RhoA function, pyrin initiates inflammasome formation upon disruption of cellular homeostasis, sensing HAMPs and mediating ETI (Figure 3). Future work will determine the range of pathogens and cytoskeletal disruptions sensed by this critical innate immune sensor.

Non-canonical caspases

Originally identified as caspase-1 homologs[170–173], human caspases-4 and −5 and murine caspase-11 are unique among the inflammasome sensors, acting as both PRRs and effectors. Similar to other caspases, caspases-4/5 and caspase-11 are zymogens activated through autoproteolysis and trigger cell death in overexpression systems[170,171,173,174]. However, rather than binding ASC, the CARDs of these caspases directly bind LPS to mediate their oligomerization and autoproteolytic cleavage[175], forming a non-canonical inflammasome. These PRRs play an important role in the immune response to bacteria[176–179] and intracellular LPS[175,180,181] (Figure 3).

Non-canonical caspases have distinct requirements for activation. Unlike caspase-1, caspase-11 expression is induced by type I IFNs[182,183], and loss of type I IFN signaling diminishes caspase-11 activation during bacterial infection[184]. This response is also critical for caspase-11 access to its ligand, because IFN-inducible GTPases that lyse pathogen-containing vacuoles mediate caspase-11 sensing of LPS in the cytosol[185]. Indeed, access to ligands is critical for non-canonical inflammasome formation. Human guanylate binding protein-1 (hGBP1) facilitates caspase-4 LPS detection through a “detergent-like” mechanism that exposes lipid A from the outer membrane of gram-negative bacteria[186–188]. Another mechanism of cytosolic LPS entry is through host proteins, as uptake of high-mobility group box 1 (HMGB1)-bound LPS mediates caspase-11 activation[189]. Furthermore, caspases-4/5/11 do not process proIL-1β into its mature form[177,190] but cause cell death through cleavage of GSDMD[191,192]. Because caspases-4/5/11 do not directly cleave IL-1β, the release of this cytokine depends on subsequent caspase-1 activation. Mechanistically, caspase-11 induces K^+ efflux, through cleavage of GSDMD and subsequent pore formation, to in turn activate NLRP3 and IL-1β release[6,192]. Understanding the complex relationship between NLRP3 and non-canonical inflammasome activation is an important topic for further research.

Non-canonical caspases have PRR activity beyond LPS detection. Caspase-11 was shown to bind oxidized phospholipids derived from 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine (PAPC) (oxPAPC), a class of DAMPs released from dying cells, to elicit IL-1β release and pyroptosis[193]. However, another group reported that oxPAPC binds caspase-4 and caspase-11 to inhibit noncanonical inflammasome activation[194]. These discrepancies may be due to differences between specific oxPAPCs moieties[195], and future work is needed to resolve these conflicting reports. Furthermore, caspase-11 activation is linked to actin cytoskeleton dynamics. Loss of caspase-11 led to defects in cellular migration, through interaction with actin-interacting protein 1 (Aip1)[196]. Another study observed that caspase-11 promoted fusion of the *Legionella pneumophila*-containing phagosome with the lysosome through Aip1-mediated remodeling of filamentous actin[197].

As a whole, these studies suggest that the non-canonical inflammasomes may have roles outside of LPS detection.

Cellular Orchestration of Inflammasomes and Pyroptosis

Following inflammasome formation, caspase-1 activation mediates the processing and release of pro-IL-1β and pro-IL-18 and pyroptotic cell death. Several regulatory events govern each step of inflammasome formation and execution of cell death following activation of an inflammasome sensor, as described below.

Cellular coordination of inflammasomes with organelles

Inflammasomes form a singular, macromolecular structure within the cell following PRR activation, and several cellular events coordinate the formation of these SMOCs to potentiate cytokine release and pyroptotic cell death. While these regulatory events are studied mostly in the context of the NLRP3 inflammasome (Figure 4), cell biology may govern many aspects of other receptors as they condense into singular inflammasomes.

Prior to activation, NLRP3 preferentially associates with cell membranes through electrostatic interactions with membrane phospholipids[74,198,199]. NLRP3 associates with multiple organelles, including the endoplasmic reticulum (ER)[200], the mitochondria[199,201–203] and the TGN[74,198,204]. Likewise, NLRP3 stimuli, including bacterial toxins and viral infection, are reported to cause the dispersal of the TGN in an NLRP3-dependent manner[74,198,204]. Interactions with phosphatidylinositol-4-phosphate (PI(4)P) direct NLRP3 localization through a polybasic motif in an N-terminal linker region between the PYD and NACHT domains, a process necessary for inflammasome formation and pyroptosis[74,198]. Two recent reports demonstrated that the PI(4)P+ vesicles that NLRP3 is recruited to following activation are endosomal in origin, containing canonical markers of the early endosome in addition to markers found on endosomes and TGN[205,206]. The authors demonstrated that NLRP3 stimuli disrupt ER-endosome membrane contact sites, leading to PI(4)P accumulation and disruption of endosome-TGN trafficking. Following these events, the NLRP3 inflammasome forms at the microtubule organizing center (MTOC), a trafficking event dependent on the α-tubulin deacetylase HDAC6[169]. At the MTOC, NLRP3 is reported to interact with the mitotic kinase NEK7[207–209]. While studies in murine cells indicate NEK7 is required for NLRP3 activation[207–209], investigation in human macrophages revealed that IKK-β priming promoted NLRP3 recruitment to PI(4)P and that NEK7 was dispensable in the presence of IKK-β post-translational priming[210]. Collectively, these studies demonstrate that NLRP3 activation is intrinsically tied to organelle biology and highlight the essential role that membrane component lipids and trafficking play in this process. These observations with NLRP3 mandate a better understanding of how organelle biology and spatial regulation govern the formation of all other inflammasomes.

Membrane rupture during pyroptosis

Pyroptosis is a lytic form of cell death that disrupts plasma membrane integrity and releases pro-inflammatory cytokines. The pore-forming protein GSDMD mediates this lytic cell death following inflammasome activation. Prior to cleavage, GSDMD exists in an

autoinhibited conformation with its C-terminus preventing the activity of the cytotoxic N-terminus. Caspase-1 and caspases-4/5/11 cleave GSDMD at its interdomain linker to free the N-terminus[6–8], causing conformation change that mediates interaction with membrane component lipids, including PIPs, phosphatidylserine, and cardiolipin[8,9]. This allows the GSDMD-NT to form a 31-fold to 34-fold oligomeric pore in the plasma membrane[211]. Reported to measure roughly 12–20nm in diameter[10,11], the GSDMD pore facilitates membrane depolarization through disruption of ion gradients and release of selected cargoes, including mature IL-1β and IL-18[12,13]. The GSDMD pore excludes molecules larger than its diameter and acidic molecules, as its interior surface is negatively charged[211]. This leads to the preferential release of mature IL-1β and IL-18 over their pro-forms, as mature IL-1β and IL-18 are more basic than their precursors[211,212]. Thus, GSDMD pore formation is a critical step in the execution of pyroptosis (Figure 5).

GSDMD pore formation is regulated by other cellular pathways. For instance, fumarate accumulation leads to the succination of GSDMD at Cys191 in humans (Cys192 in mice), limiting GSDMD processing[213]. Similarly, while protease processing governs GSDMD activation, the mTOR Ragulator-Rag complex promotes its oligomerization through reactive oxygen species (ROS) production[214]. Additionally, the GSDMD pore can permeabilize the mitochondrial outer membrane, which can alter cell death processes by activating necroptosis through the release of mitochondrial ROS (mtROS)[215] or the cGAS-STING pathway through mtDNA release[216]. Furthermore, during *Yersinia* infection in macrophages, activated caspase-8 mediates GSDMD cleavage to initiate pyroptotic cell death[217,218].

GSDMD pores do not permit the release of larger molecules associated with membrane rupture, such as lactate dehydrogenase (LDH) and other large DAMPs. While membrane rupture was considered a passive event, a recent study identified that ninjurin-1 (NINJ1) was essential for pyroptotic LDH release[219]. NINJ1 is a widely expressed cell-surface protein that mediates plasma membrane rupture in lytic cell death, including necroptosis and pyroptosis. Upon inflammasome activation, NINJ1 oligomerizes through interactions between conserved α-helices to facilitate membrane rupture, though the specific mechanism that triggers NINJ1 oligomerization remains unclear. NINJ1 oligomerization facilitates the release of large DAMPs, like HMGB1 and LDH. Of note, *Ninj1*$^{-/-}$ BMDMs had intact GSDMD pores and secreted similar amounts of IL-1β and IL-18 to WT BMDMs, indicating NINJ1 is dispensable for pro-inflammatory cytokine release[219]. Thus, GSDMD and NINJ1 coordinate membrane permeabilization and rupture following inflammasome activation. Future work will determine if other proteins mediate membrane rupture and the regulatory processes governing this process.

Pyroptosis and Cell Death

Recent work suggests that GSDMD pore formation, IL-1β release, and the initiation of pyroptosis do not necessitate cell death. One group reported that stimulation with oxPAPC led to caspase-11 activation in dendritic cells (DCs), causing IL-1β secretion but not cell death[193]. This phenotype was specific to bone marrow-derived DCs, as IL-1β release from BMDMs was not observed in this study with cytosolic delivery of oxPAPC. Similar observations were made with OatA-deficient *Staphylococcus aureus* infection of BMDM,

where cells retained mitochondrial potential and the ability to phagocytose[12]. Others found that N-acetylglucosamine (NAG), a subunit of bacterial peptidoglycan, activated NLRP3 inflammasomes but did not cause cell death in BMDMs[220]. Similarly, *Salmonella* infection in neutrophils promoted NLRC4 inflammasome activation, leading to IL-1β release without promoting pyroptotic cell death[221]. Thus, both cell type and the nature of stimuli influence cell death outcomes downstream of inflammasome formation.

One mechanism of muting cell death is through membrane repair (Figure 5). In BMDMs, Ca^{2+} influx stimulated by GSDMD-NT pore formation was found to recruit endosomal sorting complexes required for transport (ESCRT)-III machinery to patch the perforated plasma membrane and inhibition of this process increased cell death and decreased membrane integrity[222]. Another recent study showed that caspase-7 cleaved and activated acid sphingomyelinase (ASM) to generate ceramide to mediate membrane repair by promoting endocytic uptake of GSDMD pores[223]. Taken together, these studies suggest that GSDMD pores in the plasma membrane can be repaired to decrease the rate of cell death, though more work is necessary to understand the full extent of regulation of GSDMD pores and their execution of cell death.

Cross-talk between pyroptosis and other cell death pathways

Recent studies have highlighted the plasticity between cell death pathways and suggest pyroptosis is not exclusively inflammasome-induced. Other members of the gasdermin (GSDM) family form pores on the plasma membrane in other cell death contexts. GSDME expression can switch TNF- or chemotherapy-induced apoptosis to lytic pyroptosis via cleavage by caspase-3 and plasma membrane pore formation[224]. Similarly, granzyme B released by CD8+ T and natural killer (NK) cells mediated GSDME cleavage in tumor target cells[225], and granzyme A released from cytotoxic lymphocytes was shown to cleave GSDMB to promote pyroptosis in target cells[226]. Finally, several inflammasome-nucleating proteins are instigated in PANoptosis, a hybrid form of cell death pathways, apoptosis, pyroptosis, and necroptosis[145], including NLRP3[227] and AIM2[146].

Function of inflammasomes in disease

Inflammasomes have wide-reaching roles in human health, including genetic diseases, infections, and sterile inflammation (Table 1). Inflammasome responses support the development of adaptive immunity by providing inflammatory cytokines that promote T cell responses, a topic recently reviewed in detail[228]. This section is not exhaustive but rather serves to speak to the breadth of inflammasome activity in disease. For further information, we encourage the readers to refer to more specialized reviews on this topic[228–231].

Genetic Diseases

Inflammasomes require extensive regulation to ensure that pyroptotic cytokine release only occurs in appropriate contexts. Because of this, mutations in inflammasome components may cause heritable autoinflammatory disorders, including periodic fever syndromes, collectively referred to as “inflammasomopathies.” Discoveries that gain-of-function mutations in specific inflammasome receptors are linked to heritable diseases were

foundational to the characterization of these genes and to the development of treatments to curtail their activities.

NLRP3 mutations are linked to a disease continuum, collectively referred to as cryopyrin-associated periodic fever syndromes (CAPS) or cryopyrinopathies[232], which cause spontaneous NLRP3 activation. This spectrum of diseases ranges from familial cold autoinflammatory syndrome (FCAS), characterized by fever after cold exposure[232], to Muckle-Wells syndrome (MWS), typified by rash, limb pain, and periodic fevers[232], to the severe chronic infantile neurologic cutaneous articular (CINCA) syndrome or neonatal onset multi-system inflammatory disease (NOMID), classified by neonatal onset of chronic fevers, rashes, and headaches that can cause sterile meningitis and other life-threatening conditions[232]. Over 250 mutations in NLRP3 are associated with these conditions, a majority in the NACHT domain (https://infevers.umai-montpellier.fr/web/search.php?n=4). Left untreated, these diseases drastically affect quality of life and promote the development of secondary conditions, including hearing loss and amyloidosis.

Development of anti-IL-1 therapies were major advances in the treatment of CAPS[232]. These therapies include the IL-1 receptor antagonist (IL-1Ra) anakinra, a recombinant IL-1Ra that blocks IL-1R signaling; the anti-IL-1 'Trap' rilonacept, an IL-1R and Fc fusion protein that acts as a soluble decoy receptor to abrogate IL-1 signaling; and the anti-IL-1β monoclonal antibody canakinumab, a monoclonal antibody that binds to circulating IL-1β to block signaling[233]. With anakinra treatment as the current standard of care[232], these therapies drastically improve patient quality of life and decrease disease-associated damage.

Mutations in *MEFV*, the gene encoding pyrin, are linked to FMF syndrome, a genetic periodic fever syndrome marked by self-limited fever and serositis episodes[154,155]. Over 300 mutations in *MEFV* are linked to FMF (https://infevers.umai-montpellier.fr/web/search.php?n=1) with a majority in the C-terminal B.30.2/SPRY domain, which are thought to cause gain-of-function. A key study demonstrated that the addition of the human B30.2 domain harboring FMF mutations to murine *Mefv* led to spontaneous inflammation in mice[160]. Since 1972, colchicine, an inhibitor of microtubule polymerization, has been the cornerstone of FMF treatment, though the development of anti-IL-1 therapeutics has offered relief to those resistant to colchicine therapy[234].

Other inflammasome sensors are linked to genetic diseases. Single nucleotide polymorphisms (SNPs) in *NLRP1* are linked to various skin conditions, including vitiligo, psoriasis, and atopic dermatitis[235–238]. Mutations in *NLRP1* are linked also to multiple self-healing palmoplantar carcinoma and familial keratosis lichenoides chronica (FKLC) and were shown to promote spontaneous NLRP1 oligomerization, leading to a gain-of-function[48]. NLRP1 gain-of-function mutations are also linked to juvenile-onset recurrent respiratory papillomatosis (JRRP)[239] and NLRP1-associated autoinflammation with arthritis and dyskeratosis[240]. Similarly, gain of function mutations in *NLRC4* are linked to macrophage activation syndrome (MAS), enterocolitis, and periodic fevers[241–243], and a disease caused by one such *NLRC4* mutation has been successfully treated using a combination of anakinra and IL-18 binding protein (BP)[244]. Thus, gain-of-function mutations in inflammasome sensors can lead to genetic diseases of varying severity (Table

1), and many of these diseases are effectively treated by anti-IL-1 therapies, though their efficacy is not universal.

Infectious Diseases

Both adaptive immune responses and deleterious inflammatory responses to microorganisms, including bacteria, viruses, and fungi, rely on and are affected by inflammasome activation and subsequent pyroptosis. Though we only discuss it briefly here, this expansive topic was covered by multiple recent reviews[228,229,245].

Several PRRs mediate inflammasome responses during infection (Table 1). Often, a single pathogen nucleates multiple inflammasomes, whether through the production of multiple PAMPs/DAMPs/HAMPs or ETI. One example is the intracellular bacterial pathogen *L. pneumophila*, which activates caspase-11/4/5 by binding LPS[178,179,197], NLRC4/NAIP through detection of flagellin[95,96], and NLRP3 indirectly through activation of caspase-11[179]. Similarly, NLRP6 recognition of LTA initiates inflammasomes upon *L. monocytogenes*[85] infection, which also activates AIM2 and NLRP3[128,144]. Furthermore, anthrax LT mediates N-terminal cleavage of murine NLRP1b[34,35], yet in mice lacking sensitive *Nlrp1b* alleles, *B. anthracis* nucleates NLRP3 inflammasome activation through RIPK-1 and caspase-8[246]. Detection of infection by multiple PRRs ensures inflammasome formation occurs, as pathogen evasion mechanisms may circumvent any singular receptor. However, in instances where pathogen evasion mechanisms bypass several inflammasomes, single receptors may play a key role in pathogen clearance. In this regard, host genetics may sway disease outcomes. For instance, recent evidence suggests that outbreaks of *Y. pestis* promoted the inheritance of hyperactive pyrin alleles which overcome YopM-mediated inhibition of pyrin inflammasome formation[247]. Thus, overlapping sensors create a layered security system for pathogen detection, promoting favorable host outcomes in the face of immune evasion.

However, inflammasome activation in microbial infection can be a double-edged sword. For instance, during influenza A virus (IAV) infection, NLRP3 initiates a beneficial inflammatory response, promoting innate and adaptive immune responses to fight off infection[248–250]. By contrast, excessive inflammasome activity results in an overzealous inflammation that can cause the host's demise. Notably, administration of the NLRP3 inhibitor, MCC950[251], early after IAV infection leads to hyper-susceptibility to the virus, while treatment at a later time reduces lung inflammation[252]. In addition to activating the NLRP3 inflammasome, the IAV proteins NS1[253] and PB1-F2[254] inhibit NLRP3 activation. Similarly, multiple mechanisms of activating NLRP3 during IAV infection have been defined, including ion gradient depolarization through the activity of the IAV protein M2[255], and crosstalk with other cell death pathways through interaction with ZBP1[227]. Such contrasting functions compounded by pathogen evasion and crosstalk with other cell death pathways illustrate the complexity of inflammasome's role in infection, as it coordinates a powerful defense against infection but uncontrolled responses may cause unresolved inflammatory disease.

One timely example of these principles is the inflammasome response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Coronavirus disease 2019

(COVID-19). In airway epithelial cells, the SARS-CoV-2 Nsp5 protease was suggested to both activate and inhibit NLRP1 inflammasome activation, leading to no IL-1β release from these ACE2+ viral host cells[41]. In human monocytes, Fcγ receptor-mediated entry of SARS-CoV-2 instigates modest AIM2 and NLRP3 inflammasome responses[256], while other studies suggested other mechanisms of SARS-CoV-2 replication-mediated inflammasome activation in monocytes and macrophages[257,258]. More recently, DNA DAMPs produced by the SARS-CoV-2-infected airway epithelium were shown to stimulate robust IL-1β release from leukocytes in co-culture[259], demonstrating that inflammasome activation during viral infection extends beyond recognition of viral replicative activity within host cells. Thus, different mechanisms of pathogen encounter may shape the potential for inflammasome formation in a tissue-specific manner, and some of these responses may be more critical for protection than others. Treatment with anakinra shows efficacy in moderate to severe COVID-19 when given to patients with elevated serum levels of soluble urokinase plasminogen receptor (suPAR)[260,261]. Identifying which inflammasomes mediate protective versus pathologic responses in COVID-19 would allow for targeting of only detrimental inflammation, which may show broader treatment efficacy in different patient groups. Overall, understanding which inflammasomes guide disease outcomes in humans is essential for the development of effective inflammasome-targeting therapeutics.

Sterile Inflammation

Inflammasomes also play a key role in sterile inflammation. DAMPs produced by cellular stress or injury can mediate both inflammasome priming and activation. DAMPs that prime the inflammasome include HMGB1, DNA, and IL-1α[262,263], while DAMPs that activate inflammasomes include ATP[264,265], uric acid crystals[266], and DNA[132–135]. Many DAMPs, such as HMGB1 and ATP, are released following lytic cell death, a major contributor to sterile inflammation. Similarly, mitochondrial dysfunction is linked to sterile inflammasome activation through ROS production, mtDNA release, and metabolic shifts[57,58,267], and ER stress and other organelle dysfunction may also activate inflammasomes[57]. Thus, many molecular mechanisms mediate inflammasome responses in sterile disease.

Sustained or overzealous inflammasome activation is implicated in chronic inflammatory diseases, such as inflammatory bowel disease and dermatitis, and autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis[230,268,269] (Table 1). The many inflammatory and autoimmune diseases associated with inflammasome activation are discussed in several outstanding recent reviews[71,230,268,269]. The contributions of inflammasomes in many inflammatory and autoimmune diseases are shown clearly in murine models, where inflammasome components are targeted by gene deletion, and elevated inflammasome components and/or IL-1β are found in many corresponding human diseases. However, direct demonstration of the significance of these responses in human diseases is challenging to verify. Alleviation of symptoms by pharmacologic inhibition of inflammasomes would constitute important confirmation of the importance of this pathway in human diseases, but the causal effect of genetic mutations in inflammasome genes on human diseases remains the most powerful validation of their importance.

Inflammasomes also mediate important aspects of the immune response to cancer. ATP release from dying tumor cells promotes NLRP3 activation to generate $CD8^+$ T cell anti-tumor immune responses[270]. Likewise, non-canonical inflammasome agonists reported to induce IL-1β release but not cell death in DCs also promoted anti-tumor CD8+ T cell responses in murine cancer models[271]. Conversely, inflammasome responses are also observed to have detrimental effects in cancer models. For instance, overexpression of human IL-1β in mice leads to the spontaneous development of tumors[272], and NLRP3 expression in specific murine cancer models hinders NK cell anti-metastatic function[273]. Similarly, silencing AIM2 in DCs enhances antigen-specific T cell anti-tumor responses through STING activation[142], while AIM2 inflammasome activation by DNA from phagocytosed tumor cells converts macrophages into an immunosuppressive phenotype[274]. Similarly, NLRP1[275], NLRP3[276], and NLRP6[76,77] are all implicated in the control of colitis-associated tumorigenesis in mice. Thus, the inflammasome response in cancer is as nuanced as the disease itself. For further discussion, readers can refer to a recent review[70].

Inflammasomes also contribute to metabolic diseases. NLRP3 deletion alleviates the development of atherosclerotic plaques in different animal models[277], and oxidized low-density lipoprotein (oxLDL), which is associated with atherosclerosis[278], activates NLRP3 by functioning as both signals I and II[277]. The importance of this activation extends to obesity[279] and insulin resistance[280] in type 2 diabetes (T2D)[281]. In human macrophages, endothelial cells, or vascular smooth muscle cells, TNF, which is elevated in obesity, primes inflammasomes[282], increasing NLRP3 expression in the liver and adipose tissue of old mice or obese mice[283]. IL-1β disrupts insulin signaling and decreases the expression of insulin receptor substrate 1 (IRS1), resulting in decreased insulin-mediated glucose uptake and insulin resistance[284]. In models of diet-induced obesity, high-fat diet activates NLRP3 in adipose tissue macrophages (ATMs) to secrete IL-1β, leading to insulin resistance in adipocytes[285]. Ceramide produced by ATMs in obese mice can also trigger the inflammasome[286]. Similarly, saturated fatty acids can activate the NLRP3 inflammasome[285], and this activation pathway has been shown in T2D[287], nonalcoholic fatty liver disease (NAFLD)[288], and chronic kidney disease[289]. However, despite all of these associations, blockade of IL-1 signaling has not shown success in treating diabetes, and in a murine model, treatment with the NLRP3 inhibitor, MCC950, did not prevent the onset of T2D pathology[290]. Thus, the specific role of the inflammasome in metabolic diseases in humans remains unclear and an active area of research.

The NLRP3 inflammasome is also implicated in neurologic diseases[291], including amyloid-associated Alzheimer's disease[292], age-related macular degeneration[293,294], and Parkinson's disease[295,296]. Inflammasome activation in neurodegenerative diseases is mediated by DAMPs, including mitochondrial dysfunction, lysosomal damage, and extracellular ATP[291]. However, specific protein moieties accumulated in some of these diseases, including amyloid-β (Aβ) fibers and oligomers in Alzheimer's disease[297] and α-synuclein in Parkinson's disease[295], activate NLRP3, linking the inflammasome directly to disease pathology. Similarly, the accumulation of *Alu* RNA elements in the retinal pigmented epithelium activates the NLRP3/NLRC4 inflammasomes in mouse models of age-related macular degeneration[69,293]. Though apparent in mouse models, causal links to human neurogenerative diseases warrant further investigation. Overall, inflammasomes have far-

reaching effects in sterile inflammatory diseases, and in many instances, contribute to disease pathology. The therapeutic blockade of inflammasomes using either biologics or small molecule inhibitors is a robust area of research covered by outstanding reviews[62,71,298].

Conclusion

Inflammasomes are critical initiators of inflammation and adaptive immunity with far-reaching effects on human health and disease. Inflammasome activation is an innate immune response that fundamentally alters the cellular state, through the initiation of pyroptosis, cell death, and inflammatory cytokine release. A host of PRRs govern inflammasome activation in the cytosol and respond to threats to cellular integrity and infection in the form discrete molecules, namely PAMPs/DAMPs, and changes in cellular processes, specifically HAMPs and ETI. Some inflammasome sensors are well-characterized, such as NLRP3, while our understanding of other sensors is more nascent, such as NLRP6. Yet, all of these PRRs have clear roles in different diseases and tissues, mandating more extensive study. Similarly, some stimuli, such as dsDNA and viral RNA, are reported to activate multiple inflammasomes in different contexts, thus understanding which PRRs respond to specific moieties in different disease states is an important topic for further investigation. Regulation of inflammasomes is not limited to their nucleation, as both cell biology and metabolic state govern inflammasome formation and the execution of cell death. Observations of inflammasomes in living cells and regulation of pyroptosis through modulation of GSDMD pores show that cell death outcomes can be altered and are context-dependent. Similarly, cross-talk between cell death pathways highlights the nuance and plasticity in cell fate decisions. Thus, while our understanding of inflammasomes has expanded significantly since their discovery, many questions remain regarding the activation and execution of inflammasome formation and pyroptosis and the role of inflammasomes in human diseases. Because inflammasomes have both detrimental and beneficial responses in human diseases, developing a toolkit of therapeutics that target individual inflammasome PRRs will allow for refined disease interventions. Achieving such a goal will require a holistic understanding of different inflammasome pathways and subsequent cell death responses in different disease contexts.

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Inflammasomes are critical initiators of inflammation and adaptive immunity with far reaching effects on human health and disease. This review provides a 360-degree view on the mechanisms of inflammasome formation, subcellular regulation, and their effects on cell death and disease.

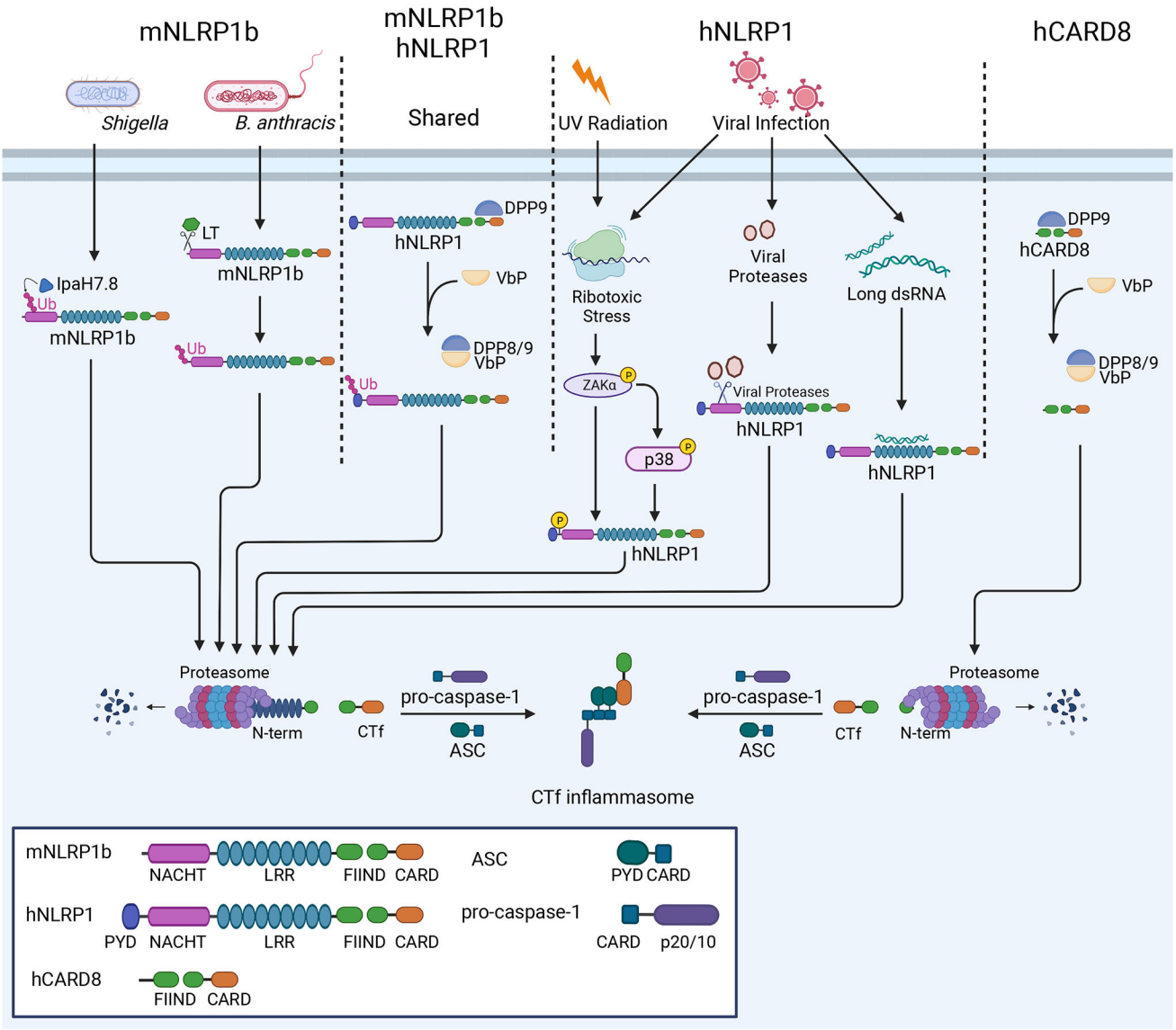

Figure 1: Distinct and shared mechanisms of murine NLRP1b (mNLRP1b) and human NLRP1 (hNLRP1) and human CARD8.

NLRP1 activation mechanisms vary between specific alleles in the murine population and between species. Some mNLRP1b alleles are sensitive to *B. anthracis* LT and *S. flexneri* effector IpaH7.8, which cleave or ubiquitinate mNLRP1b, respectively, instigating proteasomal degradation of the mNLRP1b N-terminus and formation of the mNLRP1b CTf inflammasome. Both mNLRP1b and hNLRP1 respond to DPP8/9 inhibition through Val-boroPro (VbP), leading to Ctf inflammasome formation. hNLRP1, but not mNLRP1b, responds to viral proteases, ribotoxic stress, and viral RNA to promote CTf inflammasome formation. hCARD8 responds to Val-boroPro similarly to mNLRP1b and hNLRP1 and forms CTf inflammasome.

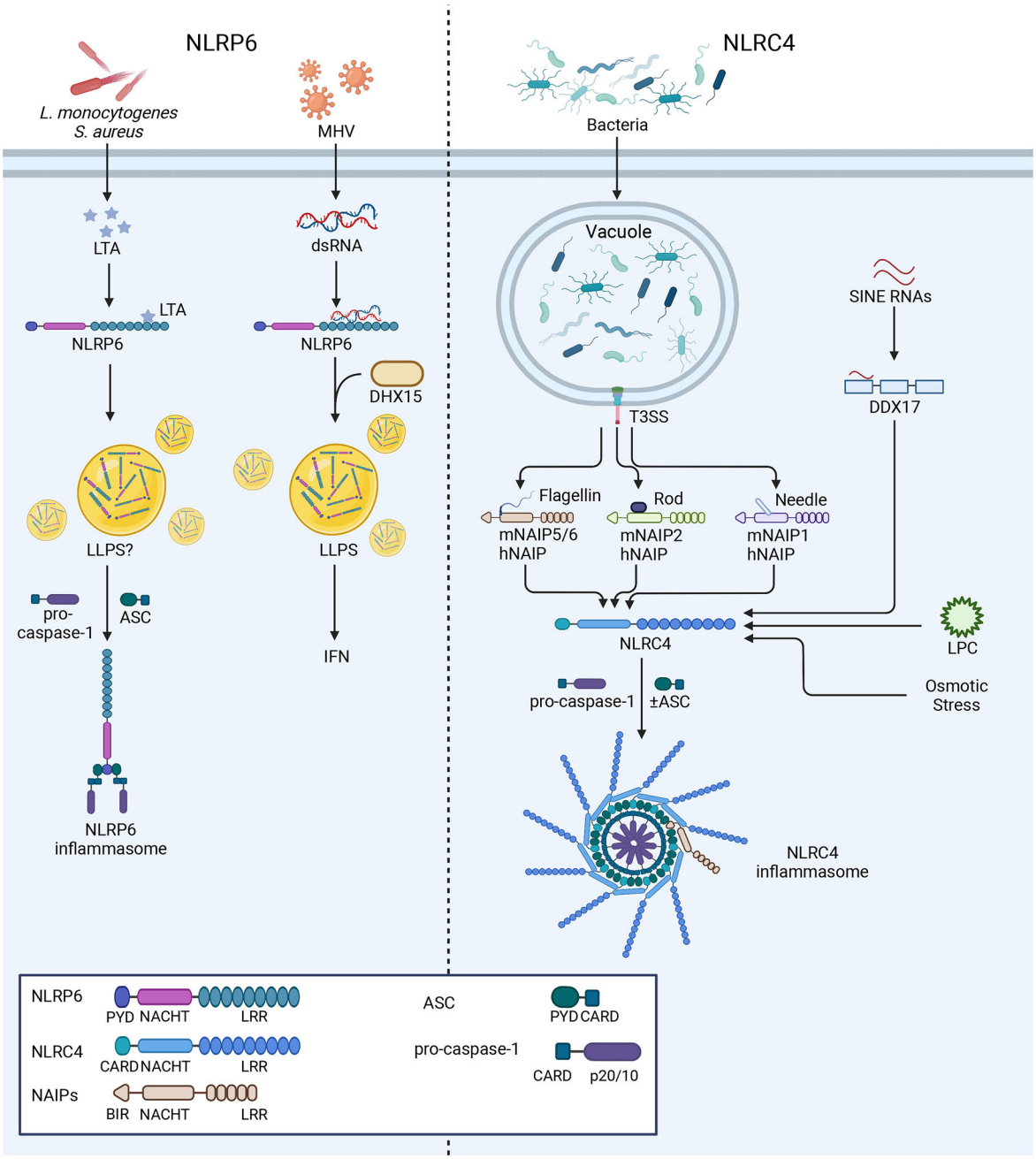

Figure 2: Mechanisms of NLRP6 and NLRC4 inflammasome activation

Left: NLRP6 responds to both LTA from bacterial infections and viral RNA from mouse hepatitis virus (MHV). In response to LTA, NLRP6 nucleates an inflammasome, while the response to RNA is mediated by DHX15 and promotes IFN production. LLPS is reported to govern both of these responses. Right: NLRC4 and hNAIP or mNAIP1–6 form inflammasomes upon recognition of flagellin or T3SS components from bacterial infections, as described in the text. More recent reports suggest that NLRC4 may also recognize sterile stimuli, including SINE RNAs through DDX17 activity, osmotic stress, and LPC. NLRC4 inflammasomes may form with or without ASC.

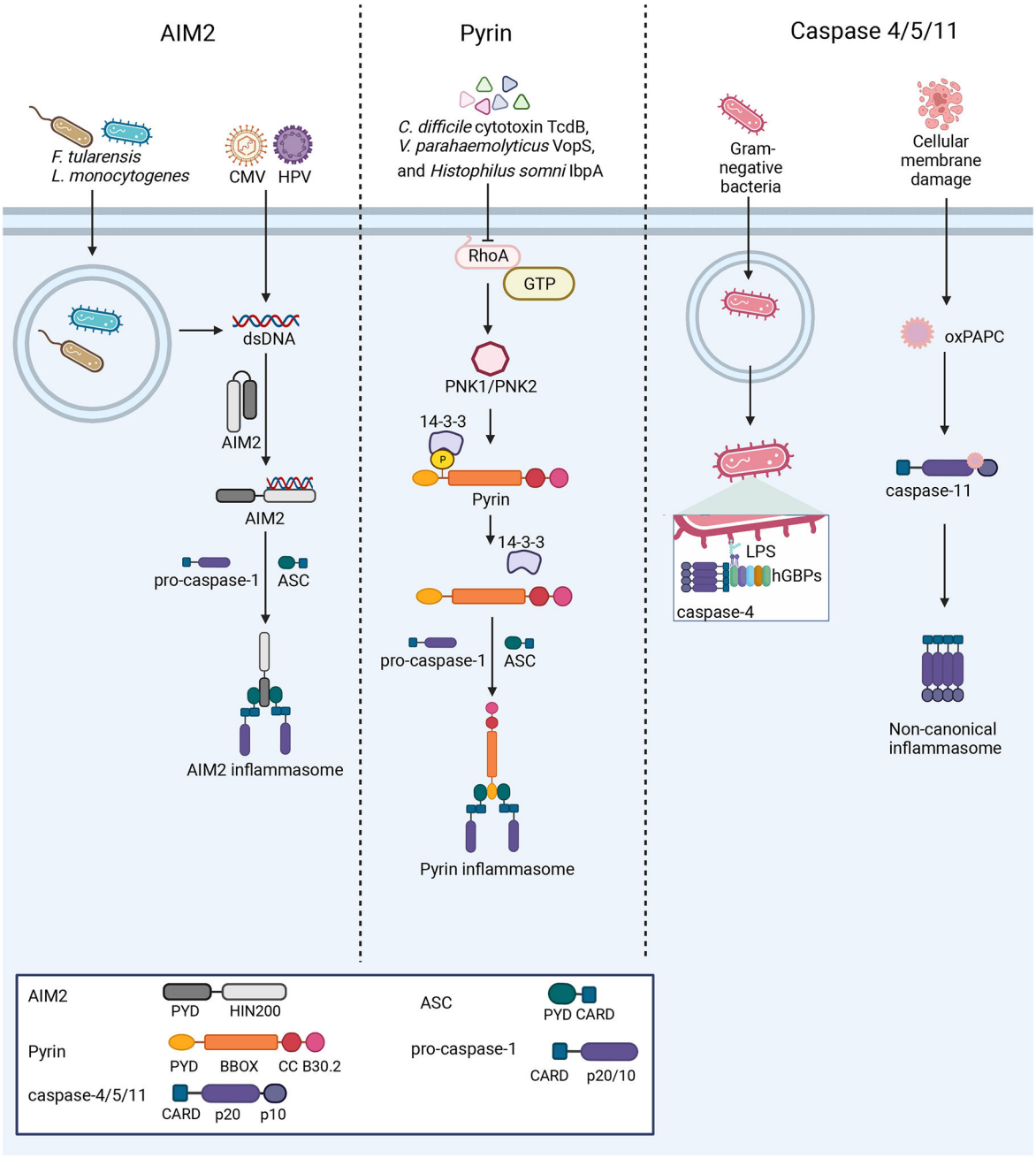

Figure 3: Nucleation of the AIM2, pyrin, and non-canonical inflammasomes

Left: AIM2 detects dsDNA from a variety of sources, including bacterial and viral infections. Upon dsDNA binding, AIM2 oligomerizes along the dsDNA and interacts with ASC to form the inflammasome. Center: At steady-state, pyrin is kept in an inactive conformation through phosphorylation by PKN1/2 and interaction of 14-3-3 proteins with this PTM. Several bacterial toxins activate the pyrin inflammasome through inactivation of the RhoA GTPase, which in turn causes pyrin to be dephosphorylated and nucleate inflammasome formation. Right: Murine caspase-11 and human caspases-4/5 act as PRRs. Guanylate-binding proteins (GBPs) assemble on the surface of Gram-negative bacteria after

escape from the vacuole, exposing Lipid A moieties from LPS. This GBP coat then serves as a platform for caspase-4 recruitment and activation[186–188]. The binding of LPS or oxPAPC by these caspases promotes their activation and downstream inflammasome formation.

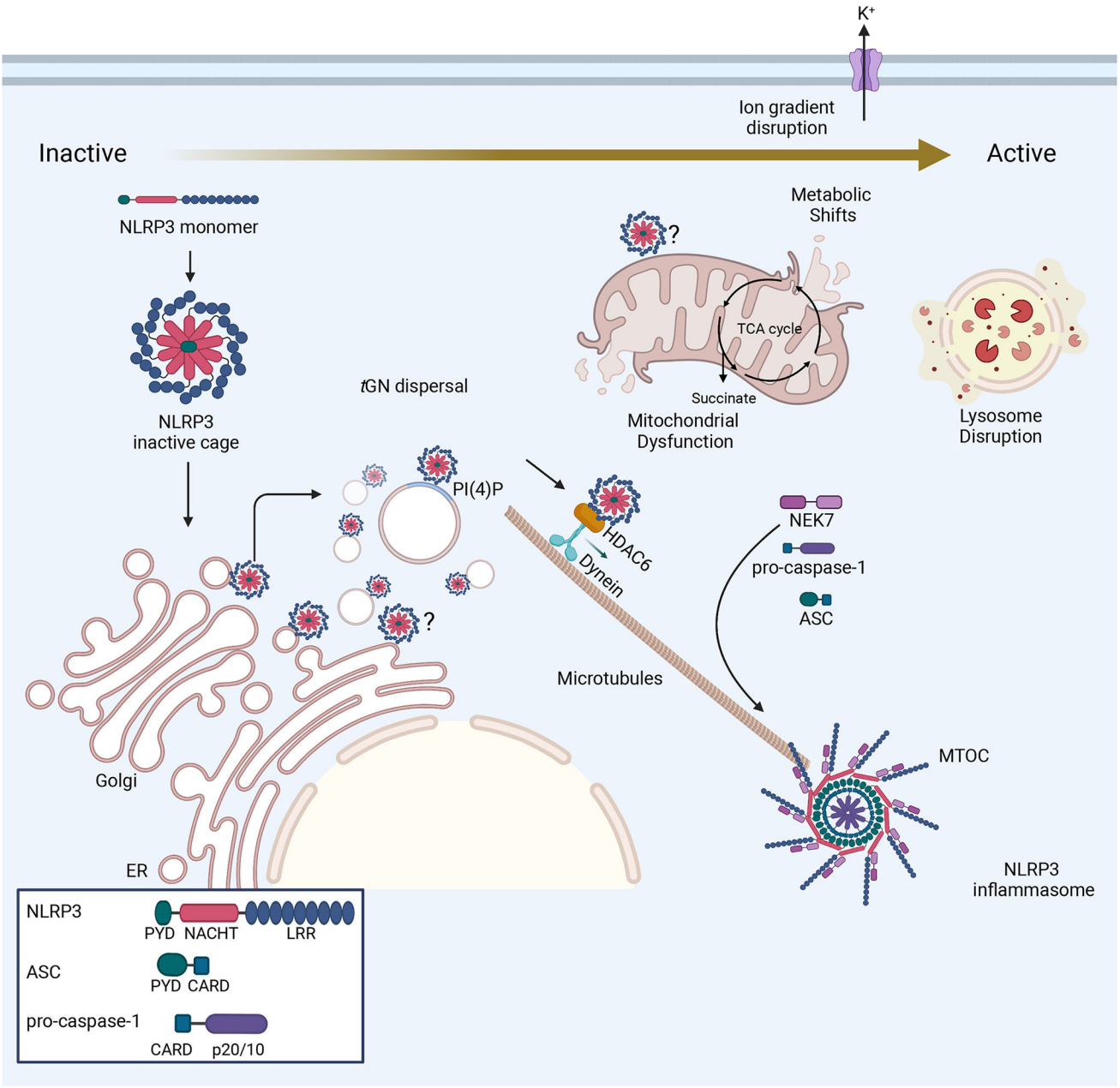

Figure 4: Cellular orchestration of the NLRP3 inflammasome

Prior to activation, NLRP3 exists in an inactivate cage conformation and is reported to associate with many different organelles, including the mitochondria and the ER. Recent work revealed that NLRP3 associates with the TGN through electrostatic interactions with the membrane component lipid PI(4)P[74,198], and a new study describes how these PI(4)P+ vesicles are endosomal in origin, displaying markers of early endosomes and the TGN[205,206]. Upon its activation through ion gradient disruption, organelle dysfunction, or metabolic shifts, NLRP3 mediates the dispersal of the TGN and traffics along microtubules in a manner dependent on HDAC6 and dynein. At the MTOC, NLRP3 associates with NEK7, and NLRP3 monomers assemble into a decameric inflammasome[72].

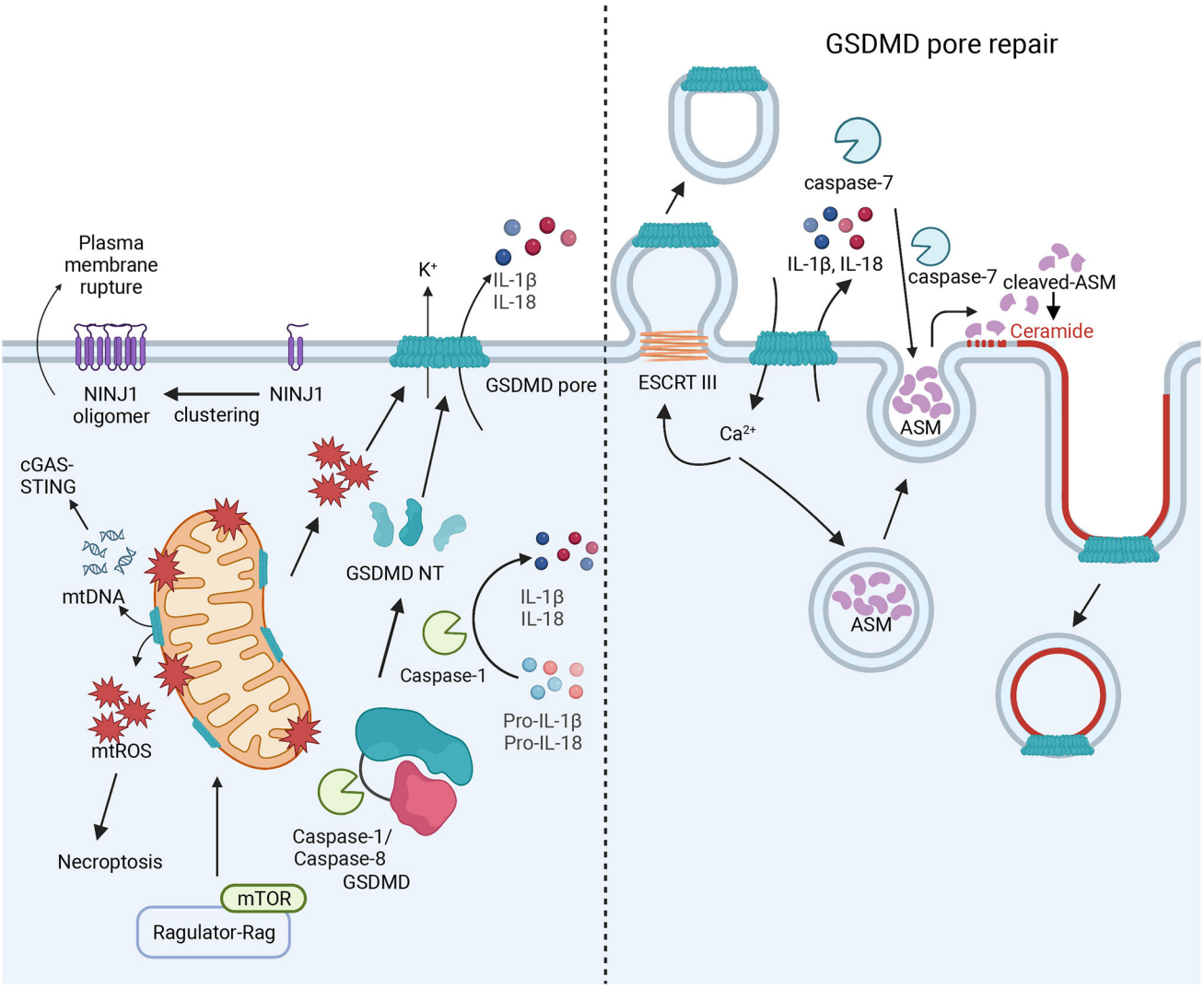

Figure 5: Regulation of cell membrane rupture following inflammasome activation

Left: Caspase-1 cleaves IL-1β/IL-18 and GSDMD to free its N-terminal (GSDMD-NT) fragment. The GSDMD-NT forms a pore on the plasma membrane, releasing IL-1β/IL-18 and disrupting cellular ion gradients to execute pyroptosis. Mitochondrial ROS downstream of Ragulator-Rag-mTORC1 activity regulates GSDMD-NT pore formation and loss of these signals prevents GSDMD NT oligomerization. GSDMD-NT pores may also form on the mitochondria through interaction with cardiolipin, causing the release of mtDNA that can activate cGAS/STING signaling and ROS that can trigger necroptosis. Inflammasomes also promote NINJ1 oligomerization in the plasma to perpetuate membrane rupture and cell death. Right: GSDMD-NT pores can be repaired through ESCRT-III-mediated cell membrane budding, triggered by Ca^{2+} influx. GSDMD-NT pores may also be repaired through caspase-7 activity. Caspase-7 and ASM are released into the extracellular space, where caspase-7 cleaves ASM to activate it. This causes the enrichment of ceramide on the plasma membrane through ASM activity, which promotes internalization of the microdomains on the plasma membrane that contain GSDMD pores. Both of these

mechanisms lead to decreased prevalence of GSDMD pores on the plasma membrane and may explain how some cells do not die following inflammasome activation.

Table 1:

Diversity and redundancy of inflammasome responses in different diseases and tissues

Inflammasome	Cell Types	Disease and Pathogen Associations	Activation Mechanism(s)	
			Molecules Detected (PAMPs/DAMPs)	Processes Detected (HAMPs/ETI)
NLRP1	Murine myeloid cells[30,55], human airway epithelial cells[39,41], human keratinocytes[25,48,237]	*B. anthracis* (murine)[30], *S. flexneri* (murine)[37], viral infections (e.g., HRV, SARS-CoV-2, SFV)[39–41,49], vitiligo[236], psoriasis[237], atopic dermatitis[238], MSPC[48], FKLC[48], JRRP[239], arthritis[240], dyskeratosis[240]	Viral dsRNA[49]	DPP8/9 inhibition[25,43], ubiquitination by *S. flexneri* IpaH7.8[37], cleavage by *B. anthracis* LT[34,35], cleavage by viral proteases[39–41], ribotoxic and cellular stress[50,51,53]
CARD8	Human T cells[26,46], human myeloid cells[29]	HIV-1[42]		DPP8/9 inhibition[25,29,46], cleavage by HIV-1 protease[42]
NLRP3	Myeloid cells (monocytes, neutrophils, macrophages, DCs)[63,138,299], oligodendroc ytes[291], astrocytes[67], endothelial cells[216], retinal pigmented epithelial cells[69]	Viral infections (e.g., IAV, SARS-CoV-2)[62,63,248–250,256–258], bacterial infections (e.g., *L. monocytogenes, L. pneumophila*)[62,63,144,179], fungal infections (e.g., *C. albicans*, *A. fumigatus*)[245], atherosclerosis[277], T2D[281,285,286], obesity[285,286,288], NAFLD[288], chronic kidney disease[289], AD[291,292,297], AMD[293,294], PD[295,296], CAPS[232], gout[266], cancer[70,270,273,276], RA[269]	Nucleic acids (e.g., oxidized DNA, viral RNA)[59,60,62], monosodium urate crystals[266], cGAMP[138], LPC[67], alum, silica[17], β-glucans, hyphae, mannan, zymosan, Aβ fibers[297], α-synuclein[295], ceramides[286], saturated fatty acids[285], oxLDL[277], cholesterol crystals[277]	K^+ efflux (e.g., bacterial toxins, viral pore-forming proteins, P2X7R activation by ATP, GSDMD pore formation)[56], Ca^{2+} flux[56], Cl^- efflux[56], TGN disruption[57,198], mitochondrial or lysosomal dysfunction[57], loss of ER-endosome membrane contact sites[205,206], metabolic shifts (e.g., fatty acid synthesis)[58], hyperosmotic stress[66]
NLRP6	Myeloid cells[85], colonic epithelial cells[76–78], colonic goblet cells[79]	Bacterial infections (e.g., *L. monocytogenes*, *C. rodentium*)[85], viral infections (e.g., ECMV, MHV)[84,87], colitis[78], cancer[76,77]	LTA[85], viral RNA[84,87]	
NAIP/NLRC4	Myeloid cells[88,89], intestinal epithelial cells[110–114], astrocytes[67], retinal pigmented epithelial cells[69]	Bacterial infections (e.g., *L. pneumophila*, *S. typhimurium*, *P. aeruginosa*)[88–90,93,94], AMD[69], MAS[241,242], colitis[243], periodic fever syndromes[242]	hNAIP: bacterial flagellin and T3SS needle and rod proteins[95,97–100]; mNAIP1: T3SS needle protein[98]; mNAIP2: T3SS rod protein[95,96]; mNAIP5/6: bacterial flagellin[95,96]; DDX17: SINE RNA[69] LPC[67]	Hyperosmotic stress[66]
AIM2	Myeloid cells[116–118], keratinocytes[126], T regulatory cells[152]	Bacterial infections (e.g., *L. monocytogenes*, *F. tularensis*)[125,127–129], viral infections (e.g., CMV, VACV, HPV, SARS-CoV-2)[125,126,256], *Plasmodium* infection[64], *A. fumigatus* infection[245], radiation-induced tissue damage[132], polyarthritis[134], atherosclerosis[135], cancer[130,131,274], EAE[149,152], colitis[150,151], SLE[153]	dsDNA[116–118]	
Pyrin	Myeloid cells[154,155]	FMF[154,155], bacterial infection (e.g., *Y. pestis*, *C. difficile*)[161,167,168,247]		Disruption of the actin cytoskeleton (e.g., bacterial toxins, loss of function mutation in Wdr1)[161,166]

Inflammasome	Cell Types	Disease and Pathogen Associations	Activation Mechanism(s)	
			Molecules Detected (PAMPs/DAMPs)	Processes Detected (HAMPs/ETI)
Caspase-4/5/11	Myeloid cells[175], epithelial cells[175], keratinocytes[175], endothelial cells[300]	Bacterial infections (e.g., *L. pneumophila, S. typhimurium*)[176–179]	LPS[175,180,181], oxPAPC[193]	

Abbreviations used: AD, Amyloid-associated Alzheimer's disease; AIM2, absent in melanoma 2; AMD, Age-related macular degeneration; ATP, adenosine triphosphate; CAPS, Cryopyrin-associated periodic syndrome; CARD8, caspase-activation and recruitment domain-containing protein 8; CINCA, Chronic infantile neurological cutaneous and articular; cGAMP, cyclic GMP-AMP; CMV, cytomegalovirus; DAMP, damage-associated molecular pattern; DDX17, DEAD box helicase 17; dsDNA, double-stranded DNA; dsRNA, double-stranded RNA; DPP8/9, dipeptidyl peptidase 8/9; EAE, Experimental autoimmune encephalomyelitis; ECMV, encephalomyocarditis virus; ER, endoplasmic reticulum; ETI, effector-triggered immunity; FCAS, familial cold autoinflammatory syndrome; FKLC, Familial keratosis lichenoides chronica; FMF, Familial Mediterranean fever syndrome; GSDMD, gasdermin D; HAMP, homeostasis-altering molecular process; HPV, human papillomavirus; HRV, human rhinovirus; IAV, Influenza A virus; JRRP, Juvenile-onset recurrent respiratory papillomatosis; LPS, lipopolysaccharide; LPC, lysophosphatidylcholine; LT, lethal toxin; LTA, lipoteichoic acid; MAS, Macrophage activation syndrome; MHV, mouse hepatitis virus; MSPC, Multiple self-healing palmoplantar carcinoma; MWS, Muckle–Wells syndrome; NAFLD, Nonalcoholic fatty liver disease; NAIP, NLR family apoptosis inhibitory protein; NLRC4, NLR family CARD-containing protein 4; NLRP1, NLR family Pyrin-containing protein 1; NLRP3, NLR family Pyrin-containing protein 3; NLRP6, NLR family Pyrin-containing protein 6; NOMID, Neonatal-onset multisystem inflammatory disease; oxLDL, oxidized low density lipoprotein; oxPAPC, oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphorylcholine; P2X7R, P2X7 receptor; PAMP, pathogen-associated molecular pattern; PD, Parkinson's disease; RA, rheumatoid arthritis; SARS-CoV-2, severe acute respiratory coronavirus 2; SFV, Semliki Forest virus; SINE RNAs: Short interspersed nuclear element RNAs; SLE, systemic lupus erythematosus; T2D, Type 2 diabetes; T3SS, type 3 secretion system; TGN, *trans* Gogli Network; UV, Ultraviolet; VACV, vaccinia virus; Wdr1, WD repeat containing protein 1