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Cytosolic Recognition of Microbes and Pathogens: Inflammasomes in Action

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SUMMARY Infection is a dynamic biological process underpinned by a complex interplay between the pathogen and the host. Microbes from all domains of life, including bacteria, viruses, fungi, and protozoan parasites, have the capacity to cause infection. Infection is sensed by the host, which often leads to activation of the inflammasome, a cytosolic macromolecular signaling platform that mediates the release of the proinflammatory cytokines interleukin-1β (IL-1β) and IL-18 and cleavage of the pore-forming protein gasdermin D, leading to pyroptosis. Host-mediated sensing of the infection occurs when pathogens inject or carry pathogen-associated molecular patterns (PAMPs) into the cytoplasm or induce damage that causes cytosolic liberation of danger-associated molecular patterns (DAMPs) in the host cell. Recognition of PAMPs and DAMPs by inflammasome sensors, including NLRP1, NLRP3, NLRC4, NAIP, AIM2, and Pyrin, initiates a cascade of events that culminate in inflammation and cell death. However, pathogens can deploy virulence factors capable of minimizing or evading host detection. This review presents a comprehensive overview of the mechanisms of microbe-induced activation of the inflammasome and the functional consequences of inflammasome activation in infectious diseases. We also explore the microbial strategies used in the evasion of inflammasome sensing at the host-microbe interaction interface.

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INTRODUCTION

Bacteria, fungi, viruses, and protozoa are capable of causing infection, potentially leading to death of the host. The host immune system acts as a guardian and defends the body from challenge by pathogens. Both innate and adaptive immune systems contribute to the killing and clearance of invading microbes. Pattern recognition receptors (PRRs) of the innate immune system initiate sensing of pathogens and danger signals by recognizing pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), respectively. Activation of PRRs induces a cascade of inflammatory host responses that, in most cases, rapidly resolve the infection (1). However, inflammation is a double-edged sword and can result in the development of autoimmunity, inflammatory diseases, and cancer.

PRRs evoke diverse antimicrobial activities by initiating activation of the transcription factor NF-κB, mitogen-activated protein kinase (MAPK), and interferon (IFN) signaling pathways, leading to the transcription of hundreds of genes that collectively induce an antipathogen state in the cell. PRRs include the family members Toll-like receptors (TLRs), C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs), NOD-like receptors (NLRs), AIM2-like receptors (ALRs), and cytoplasmic DNA and RNA sensors (2–4). Both membrane-bound and cytoplasmic sensors function synergistically to mount an effective antimicrobial response against invading microbes. TLRs and CLRs are membrane-bound receptors which detect PAMPs and DAMPs on the cell surface and within endosomes. ALRs, NLRs, RLRs, and cytoplasmic DNA and RNA sensors recognize PAMPs and DAMPs that have reached the cytoplasm of the cell, which is achieved via either infection by pathogens or damage to organelles of the host cell leading to the release of endogenous DAMPs.

Certain NLRs and ALRs assemble inflammasome complexes in response to PAMPs and DAMPs (5). The inflammasome is a multiprotein complex which regulates activation of the cysteine protease caspase-1, leading to proteolytic processing and secretion of the proinflammatory cytokines interleukin-1β (IL-1β) and IL-18. In addition, this multimeric complex induces an inflammatory form of cell death called pyroptosis (6). An inflammasome complex comprises one or more sensors (NLRs, ALRs, or Pyrin), the adaptor protein apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC), and caspase-1 (7, 8) (Fig. 1A). On stimulation with PAMPs or DAMPs, an inflammasome sensor is activated and associates with ASC, thereby leading to oligomerization of ASC and formation of a filamentous scaffold (9, 10). ASC filaments interact with inactive procaspase-1 monomers to facilitate proximity-induced activation of caspase-1 (9, 10). This sensor–ASC–caspase-1 scaffold can readily be visualized endogenously as a cytoplasmic speck of 0.8 to 1 μm in diameter (11–14). Furthermore, inflammasome specks act as DAMPs following their release by pyroptotic cells, resulting in amplification of inflammation (15, 16). Caspase-1 activated within the inflammasome complex executes pyroptosis by inducing cleavage of the propyroptotic factor gasdermin D (17–19), yielding a cleaved N-terminal fragment of gasdermin D that oligomerizes and forms pores on the host cell membrane (20–24) (Fig. 1B). The consequences of this event are cell swelling, lytic cell death, and liberation of cytoplasmic contents, including biologically active IL-1β and IL-18. Evidence suggests that the pores formed by gasdermin D allow passive release of IL-1β and DAMPs of less than 10 to 16 nm in diameter from the cytoplasm of macrophages to the extracellular space, even prior to lysis and death of the host cell (25–27). Self-cleavage of caspase-1 at the caspase activation and recruitment domain (CARD) linker region releases caspase-1 from the inflammasome complex, resulting in termination of caspase-1 activity (28).

Pathogens have evolved various immune evasion mechanisms. To counteract these evasion strategies, both extracellular and intracellular surveillance systems must overlap and operate in unity to provide efficient recognition of the pathogen. This review
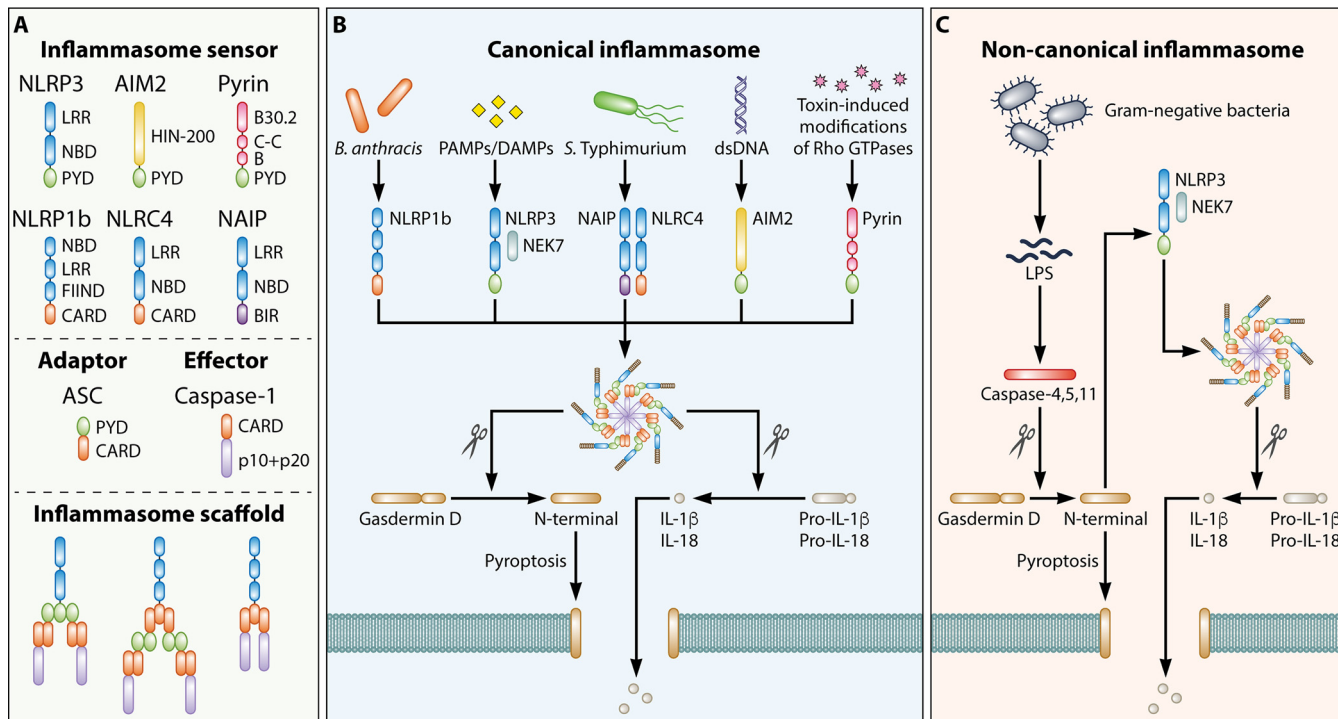
FIG 1 Architecture of inflammasome complexes. (A) Formation of an inflammasome complex is initiated by an inflammasome sensor. Inflammasome sensors carry a pyrin domain (PYD) and/or a caspase activation and recruitment domain (CARD). They may also carry a leucine-rich-repeat domain (LRR), a nucleotide-binding domain (NBD), a HIN-200 domain, a B30.2 domain, a coiled-coil domain (C-C), a B-box domain (B), a function-to-find domain (FIIND), or a baculovirus inhibitor of apoptosis repeat (BIR). Other inflammasome components include the inflammasome adaptor protein apoptosis-associated speck-like protein containing a CARD (ASC) and the effector protein caspase-1. A PYD-containing inflammasome sensor interacts with the PYD of ASC, allowing the CARD of ASC to interact with the CARD of caspase-1. A CARD-containing inflammasome sensor can interact with the CARD of ASC, whereby the PYD of ASC interacts with the PYD of an additional ASC. The CARD of ASC then interacts with the CARD of caspase-1. Alternatively, a CARD-containing inflammasome sensor may directly interact with caspase-1 via their respective CARDs. (B) Canonical inflammasome complexes are activated by a range of pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). Caspase-1 cleaves the pore-forming factor gasdermin D, whereby the N-terminal domain of gasdermin D forms pores in the host cell membrane. Caspase-1 also cleaves the proinflammatory cytokines pro-IL-1β and pro-IL-18, generating biologically active versions of these cytokines for release through the membrane pores generated by gasdermin D. The pores formed by gasdermin D also lead to lytic cell death via pyroptosis. (C) The noncanonical inflammasome is a pathway specifically activated by Gram-negative bacteria. In this pathway, lipopolysaccharides (LPS) are introduced into the cytoplasm during infection and sensed by human caspase-4 and caspase-5 and mouse caspase-11. These inflammatory caspases can also cleave gasdermin D, in a manner similar to that by caspase-1, leading to the induction of pyroptosis. The N-terminal domain of gasdermin D also induces activation of the NLRP3 inflammasome and the associated proteolytic cleavage of pro-IL-1β and pro-IL-18.

focuses on the diverse cytosolic innate immune recognition pathways of microorganisms, with a focus on inflammasome sensors and the respective families of PAMPs that they recognize. We also shed light on the downstream effector functions of the inflammasome that drive protection against infectious diseases.

GENERAL OVERVIEW OF INFLAMMASOME SENSING AND SIGNALING

Several cytoplasmic innate immune sensors form inflammasome complexes in response to PAMPs and DAMPs, including AIM2, NAIP, NLRC4, NLRP1, NLRP3, Pyrin, and caspase-11 (Fig. 1); further, mouse NLRP6, NLRP9b, and NLRP12 and human NLRP2, NLRP7, and IFN-inducible protein 16 (IFI16) have also been proposed to activate caspase-1 (5), although the ability of these sensors to form bona fide inflammasome complexes has remained uncertain (29). Inflammasome sensors initiate a generally proinflammatory signaling cascade upon activation; however, the molecular mechanisms regulating the activation of each sensor and the composition of each inflammasome complex are distinct.

Inflammasome sensors differ based on whether they are activated by direct interaction with a ligand or by indirect sensing of broader cellular perturbations (29). AIM2, NAIP, and caspase-11 directly bind to their cognate ligands, whereas NLRP1, NLRP3, and Pyrin respond to cellular perturbations (Fig. 1B). AIM2 binds exclusively to cytoplasmic double-stranded DNA (dsDNA), independent of the sequence of the dsDNA (30–33).

Similarly, NAIP proteins directly bind flagellin and components of the type III secretion systems (T3SS) of Gram-negative bacteria, such as *Salmonella enterica* serovar Typhimurium, leading to activation of the NLRC4 inflammasome (discussed below) (34, 35). Mouse caspase-11 and the two human analogs caspase-4 and caspase-5 are all sensors of cytoplasmic lipopolysaccharide (LPS) (36–39) (Fig. 1C). Direct interaction between the lipid A portion of LPS and the CARD of caspase-11 catalyzes oligomerization of caspase-11 and activation of the noncanonical NLRP3 inflammasome (36, 40–44). While caspase-11 cannot directly cleave pro-IL-1β and pro-IL-18, it can induce pyroptosis in the absence of caspase-1 by cleaving gasdermin D (40). Further, LPS-induced activation of caspase-11 leads to potassium efflux (45) or caspase-11-dependent cleavage of the membrane channel pannexin-1, followed by an ATP release that subsequently activates the purinergic receptor P2X7R and pyroptosis (46).

NLRP3 responds to cellular perturbations emanating from stimulation with PAMPs and DAMPs rather than through binding to an activating ligand (Fig. 1B). These cellular cues include lysosomal disruption and subsequent leakage of cathepsin B (47), potassium efflux via P2X7R (48–51), formation of pores on the cell membrane (52), translocation of cardiolipin from the inner to the outer mitochondrial membrane (53), production of reactive oxygen species (ROS) (54, 55), oxidized mitochondrial DNA (56), calcium influx and a reduction in cellular cyclic AMP (57–59), and alteration of the cell volume (60). While several molecular mechanisms involving homeostatic disruption have been proposed, a single unifying signal leading to NLRP3 inflammasome activation has yet to emerge.

Similar to NLRP3, NLRP1 and Pyrin respond to cellular perturbations rather than to direct binding to a specific ligand. The mechanism of NLRP1 activation is cleavage dependent; human NLRP1 and mouse NLRP1b are activated by any protein capable of inducing N-terminal proteolytic cleavage of NLRP1 (61–67), demonstrating that these inflammasome sensors are not specific to any single ligand. Activation of Pyrin is more complex. In homeostasis, Pyrin is phosphorylated on two serine residues by the RhoA effector serine-threonine kinases PKN1 and PKN2, promoting interaction between Pyrin and the regulatory proteins 14-3-3ε and 14-3-3τ (68–70). The interaction between Pyrin and 14-3-3 regulatory proteins holds Pyrin in an inactive state to prevent activation of the Pyrin inflammasome in unstimulated cells (70, 71). Rho-inactivating toxins and T3SS effectors produced by many bacteria inhibit the action of PKN1 and PKN2, thereby relieving phosphorylation of Pyrin and promoting activation of the Pyrin inflammasome (71–76) (Fig. 1B).

The requirement of the inflammasome adaptor protein ASC for the formation of an inflammasome complex also differs among inflammasome sensors (Fig. 1A). ASC is a bipartite protein comprised of a pyrin domain (PYD) and a CARD. AIM2, NLRP3, and Pyrin carry a PYD but not a CARD and must therefore bind ASC in order to recruit the CARD-bearing procaspase-1. In contrast, NLRP1 and NLRC4 carry a CARD and can therefore directly recruit procaspase-1 in the absence of ASC (77–80). However, optimal secretion of IL-1β is often achieved only when ASC is present in these inflammasome complexes (12, 13, 81), indicating the universal importance of ASC in inflammasome signaling.

Secretion of IL-1β and IL-18 and induction of pyroptosis have instrumental roles in eliciting, magnifying, and perpetuating inflammation and, in most cases, reducing the overall pathogen burden. Both cytokines serve as a bridge between the innate and adaptive immune systems: IL-1β is a potent promoter of inflammation, immune cell extravasation, and vasodilation with additional capabilities in modulating adaptive immunity (82), while IL-18 triggers local inflammation as well as IFN-γ production in natural killer (NK) cells, CD4$^+$ T$_H$1 cells, and CD8$^+$ cytotoxic T cells and augments the development of CD4$^+$ T$_H$2 cells (83). In addition to promoting the release of cytokines and DAMPs, another overarching function of pyroptosis is to expel an infected cell from the tissue (84, 85) or to expel pathogens from infected macrophages (86, 87). In contrast, neutrophils release IL-1β without undergoing pyroptosis (88), reflecting the different roles of immune cells in clearing pathogens. Thus, the inflammasome facili-
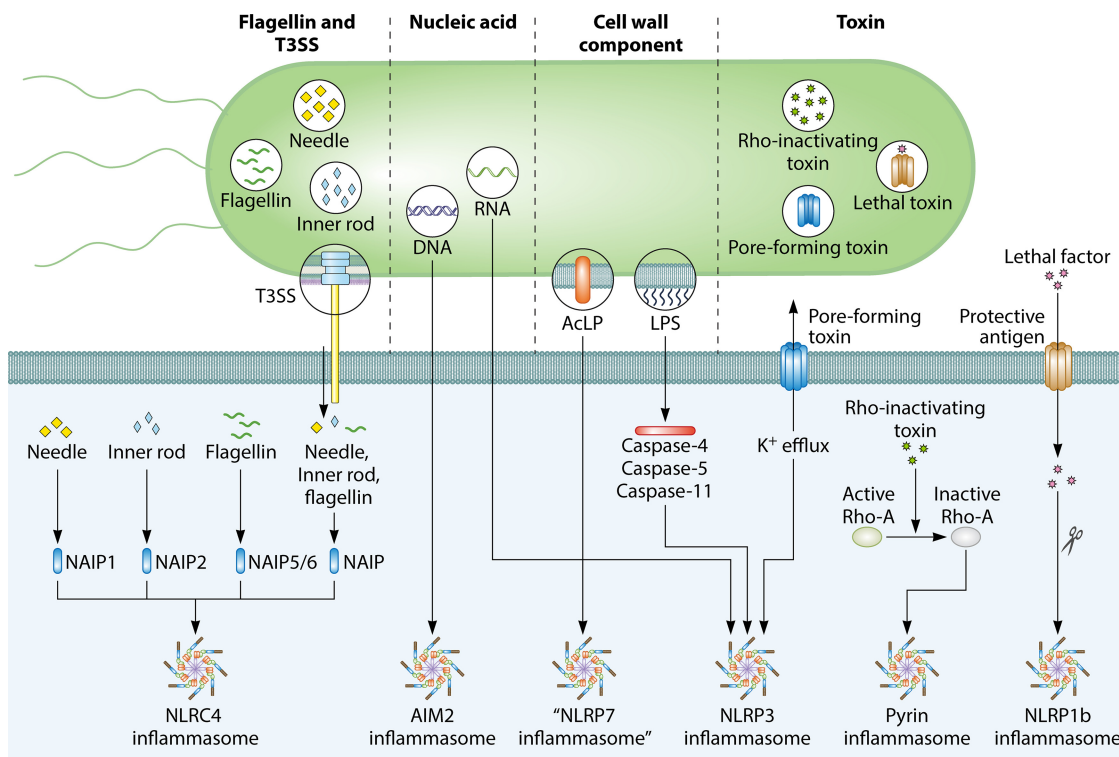
FIG 2 Major bacterial activators of the inflammasome. Four major groups of bacterial components trigger activation of the inflammasome. Flagellin and components of the type III secretion system (T3SS) can be injected into the cytoplasm of the host cell via the T3SS. The T3SS needle and inner rod proteins are sensed by mouse NAIP1 and NAIP2, respectively, whereas flagellin is sensed by mouse NAIP5 or NAIP6. The needle and inner rod proteins and flagellin are all sensed by human NAIP. Ligand-bound NAIPs recruit NLRC4 to the same complex to drive activation of the NLRC4 inflammasome. The bacterial nucleic acid molecules DNA and RNA can activate the AIM2 and NLRP3 inflammasomes, respectively. RNA-DNA hybrids derived from bacteria (not shown) can also activate the NLRP3 inflammasome. The cell wall components acylated lipopeptides (AcLP) might activate a putative NLRP7 inflammasome in human macrophages. Lipopolysaccharides (LPS) from the cell walls of Gram-negative bacteria activate human caspase-4 and caspase-5 and mouse caspase-11. These inflammatory caspases oligomerize and drive activation of the NLRP3 inflammasome. Pore-forming toxins produced by bacteria induce K^+ efflux, a physiological aberration sensed by the NLRP3 inflammasome. Rho-inactivating toxins inactivate the host GTPase RhoA, which relieves inhibition of Pyrin, leading to activation of the Pyrin inflammasome. The protective antigen of lethal toxin generates pores on the host cell membrane, allowing lethal factor to enter the cytoplasm and mediate cleavage of NLRP1b. Cleaved NLRP1b induces formation of the NLRP1b inflammasome.

tates disruption of the replicative niche exploited by intracellular pathogens and exposes them to potentially less favorable conditions (discussed below).

BACTERIA

A plethora of bacteria engage with and shape the development of the host immune system. Reflecting the coevolution of bacteria and the host immune system, host cells encode innate immune sensors capable of detecting and exploiting the conservation of key bacterial PAMPs (Fig. 2). In this section, we discuss several groups of bacterial PAMPs that are recognized by their respective inflammasome sensors and highlight some of the strategies employed by bacteria to block inflammasome activation.

LPS

The cell wall of bacteria functions to maintain bacterial cell integrity and resist osmotic stress. LPS, a key component of the outer membrane of Gram-negative bacteria, is composed of a lipid A portion, a core oligosaccharide, and an O antigen consisting of repeating glycan subunits. LPSs from many Gram-negative bacteria are recognized by human caspase-4, human caspase-5, or mouse caspase-11 (37–43, 89–91) (Table 1). Caspase-11 directly binds to the penta- or hexa-acylated lipid A portion of cytoplasmic LPS via its CARD, inducing self-oligomerization and activation (36, 44). Some Gram-negative bacteria, including *Porphyromonas gingivalis* (92), *Yersinia*

TABLE 1 Gram-negative bacteria produce PAMPs and DAMPs during infection that activate inflammasomes and other sensors

Bacterium	Inflammasome sensor(s) [activator(s)] [reference(s)]
Acholeplasma laidlawii	NLRP3 (unknown activator) (119), NLRP7 (acylated lipopeptide) (119), NLRP12 (unknown activator) (119)
Acinetobacter baumannii	NLRP3 (ROS, cathepsin release, K^+ efflux, P2X7R) (114, 347), caspase-11 (LPS) (112, 114)
Aeromonas hydrophila	NLRP3 (aerolysin, hemolysin, multifunctional repeat-in-toxin) (348)
Aeromonas trota	NLRP3 (aerolysin) (52), NLRC4 (unknown activator) (52)
Aeromonas veronii	NLRC4 (T3SS) (349), NLRP3 (aerolysin, T3SS) (349)
Aggregatibacter actinomycetemcomitans	NLRP3 (cytolethal distending toxin) (350)
Bordetella pertussis	NLRP3 (adenylate cyclase toxin, CyaA) (351), Pyrin (pertussis toxin) (74)
Brucella abortus	NLRP3 (mitochondrial ROS) (352, 353), AIM2 (dsDNA) (352–354)
Burkholderia cenocepacia	NLRP3 (T2SS, T4SS, T6SS) (355), mouse Pyrin (T6SS dependent) (72), human Pyrin (T6SS effector TecA) (73, 76)
Burkholderia pseudomallei	NLRC4 (T3SS rod BsaK, flagellin) (123, 356), NLRP3 (unknown activator) (356), caspase-11 (LPS) (42)
Burkholderia thailandensis	NAIP2-NLRC4 (T3SS rod BsaK) (35), human NAIP-NLRC4 (T3SS needle BsaL and rod BsaK) (35, 133), caspase-11 (LPS) (42)
Campylobacter jejuni	NLRP3 (unknown activator) (155)
Chlamydia pneumoniae	NLRP3 (mitochondrial dysfunction) (357, 358)
Chlamydia trachomatis	NLRP3 (LPS, mitochondrial ROS) (103, 359), AIM2 (dsDNA) (103, 359)
Chlamydia muridarum	Caspase-11 (LPS) (103), AIM2 (dsDNA) (103)
Chromobacterium violaceum	Human NAIP-NLRC4 (T3SS needle CprI) (35)
Citrobacter rodentium	NLRC4 (unknown activator) (360, 361), NLRP3 (T3SS independent) (360, 362), caspase-11 (LPS) (40, 104)
Escherichia coli	NLRC4 (T3SS rod EprJ and EscI) (123), NLRP3 (RNA-DNA hybrids, RNA) (177, 180), NLRP6 (unknown activator) (363), human NAIP-NLRC4 (T3SS needle EprJ) (35), caspase-11 (LPS) (40, 104)
Francisella tularensis	AIM2 (dsDNA) (100, 157–160, 162–165, 171, 364), NLRP3 (IgG-opsonized, inactivated F. tularensis LVS) (365–367), caspase-4 (LPS) (94)
Fusobacterium nucleatum	NLRP3 (mitochondrial ROS) (92, 368)
Helicobacter pylori	NLRP3 (ROS signaling, lysosomal destabilization, K^+ efflux, VacA) (369–373)
Histophilus somni	Pyrin (IbpA toxin) (72)
Klebsiella pneumoniae	NLRC4 (unknown activator) (374), NLRP3 (unknown activator) (375), caspase-11 (LPS) (113)
Legionella pneumophila	AIM2 (DNA) (173), NAIP5 and NAIP6-NLRC4 (flagellin) (35, 126, 139, 376, 377), caspase-4 (LPS) (37), caspase-11 (LPS) (91)
Neisseria gonorrhoeae	NLRP3 (lipooligosaccharide) (378)
Photorhabdus luminescens	NAIP5 and NAIP6-NLRC4 (flagellin) (35)
Porphyromonas gingivalis	NLRP3 (ATP, K^+ efflux, and cathepsin B) (379, 380), caspase-11 (LPS via OMVs) (381), AIM2 (dsDNA) (379)
Pseudomonas aeruginosa	NAIP5 and NAIP6-NLRC4 (flagellin) (35, 123, 382, 383), NAIP2-NLRC4 (T3SS rod PscI) (35, 123, 384), NLRP3 (exolysin toxin ExlA) (385), human NAIP-NLRC4 (T3SS rod PscI and needle PscF) (132), caspase-11 (LPS) (104)
Salmonella enterica serovar Typhimurium	Human NAIP-NLRC4 (T3SS needle PrgI and rod PrgJ, flagellin) (35, 127, 130, 133), mouse NAIP1-NLRC4 (T3SS needle) (131), mouse NAIP2-NLRC4 (T3SS rod PrgJ) (34, 35, 123, 186), mouse NAIP5 or NAIP6-NLRC4 (flagellin) (34, 35, 138), caspase-4 and caspase-5 (LPS) (38, 85), caspase-11 (LPS) (13, 14)
Serratia marcescens	NLRP3 (toxin ShlA)
Shigella flexneri	NAIP2-NLRC4 (T3SS rod MxiI) (123, 129), NLRP3 (unknown activator, Shiga toxin) (386, 387), NLRP1b (metabolic stress) (388), human NAIP-NLRC4 (T3SS needle MxiH and rod MxiI) (35, 130, 133)
Tannerella forsythia	NLRP3-caspase-11 (LPS via OMVs) (381), AIM2 (dsDNA) (381)
Treponema denticola	NLRP3 (surface protein Td92, caspase-11 via LPS in OMVs) (381, 389), AIM2 (dsDNA) (381)
Treponema pallidum	NLRP3? (TpF1-induced ATP release) (390)
Vibrio cholerae	NLRP3 (cholera toxin B, El Tor hemolysin HlyA, cytotoxin MARTX$_{Vc}$) (40, 184), caspase-11 (LPS) (40)
Vibrio parahaemolyticus	Pyrin (toxin VopS) (72)
Vibrio vulnificus	NLRP3 (hemolysin/cytolysin VvhA, cytotoxin MARTX$_{Vv}$) (184)
Yersinia spp.	NAIP5 and NAIP6-NLRC4 (flagellin) (35, 93), NLRP3 (T3SS effectors YopB and YopD) (93, 391–393), NLRP12 (T3SS) (394), Pyrin (YopE and YopT) (395, 396)

pestis (93), *Francisella tularensis* (44), and *Rhodobacter sphaeroides* (36), have altered lipid A structures that cannot activate mouse caspase-11. In contrast, human caspase-4 is able to recognize underacylated LPS from *F. tularensis* subsp. *novicida* and *Bacteroides vulgatus* in macrophages, in addition to detecting penta- or hexa-acylated lipid A (94). This interspecies difference in sensing of distinct LPS moieties may reflect differences in the CARDs of caspase-4 and caspase-11, which share 51% sequence identity (94). Whether caspase-5, which shares only 39% sequence identity with caspase-11 in the CARD (94), can sense a different repertoire of LPS variants or other PAMPs remains to be determined. These inflammatory caspases subsequently trigger activation of the NLRP3 inflammasome upon sensing LPS, giving rise to the nomenclature of the noncanonical NLRP3 inflammasome pathway (Fig. 1C) (40).

The entry of LPS into the cytoplasm is an important event that leads to activation of the noncanonical NLRP3 inflammasome. Several mechanisms have been discovered to explain how LPS might reach the cytoplasm of the host cell for sensing by caspase-11. Naturally cytoplasmic pathogens, such as *Burkholderia thailandensis* and *Burkholderia pseudomallei*, introduce LPS into the cytoplasm as they escape the pathogen-containing vacuole, thereby driving rapid and robust caspase-11 activation (42). However, vacuole-restricted bacteria, such as *Escherichia coli*, *Citrobacter roden-tium*, and *Vibrio cholerae*, can also activate the noncanonical NLRP3 inflammasome (14, 40, 90, 95, 96), implying the existence of alternative routes by which LPS can enter the cytoplasm. In the case of vacuole-restricted bacteria, type I IFN signaling, which is normally induced in response to infection, has an important role in the liberation of LPS in the cytoplasm. Type I IFNs upregulate the expression of host IFN-inducible GTPases, including guanylate-binding proteins (GBPs) and immunity-related GTPases (IRGs) (97). In mouse macrophages, GBPs colocalize with pathogen-containing vacuoles, where they facilitate lysis of the vacuolar membrane such that the bacteria and their associated LPS are released into the cytoplasm for detection by caspase-11 (98, 99). GBPs can also direct IRGB10 to the cell membrane of cytoplasm-exposed Gram-negative bacteria to induce bacteriolysis (100), thereby increasing the amount of free LPS, but also DNA (discussed further below), in the cytoplasm. Bioinformatic analysis of IRG family members identified an amphipathic helix on the C terminus of IRGB10 (100) that is a putative transmembrane region with antimicrobial potential. It is possible that the transmembrane region of IRGB10 may allow insertion into and destabilization of bacterial membranes. In mouse embryonic fibroblasts, pathogen-containing vacuoles carrying *Chlamydia trachomatis* are decorated with ubiquitin in an IRG-dependent manner (101). This ubiquitination facilitates GBP recruitment to the membrane and subsequent lysis of the pathogen-containing vacuole (101). Therefore, lysis of pathogen-containing vacuoles represents an important mechanism by which LPS from vacuole-restricted bacteria can enter the cytoplasm (102). However, it is noteworthy that in the case of the related bacterium *Chlamydia muridarum*, recruitment of GBPs to the pathogen-containing vacuole or the bacterial cell wall is not necessary for activation of the inflammasome (103), suggesting a further route by which ligands from this bacterium can be introduced into the cytoplasm.

Another mechanism by which LPS can be introduced into the cytoplasm in the absence of cytoplasmic invasion by bacteria is through outer membrane vesicles (OMVs). LPS encapsulated within OMVs, which are shed by Gram-negative bacteria (such as *E. coli*), can be endocytosed via a clathrin-mediated process (104). This process is followed by escape of the LPS from the endocytic compartment into the cytoplasm of mouse macrophages to induce caspase-11 activation (104). It has also been demonstrated that GBPs encoded on chromosome 3 or GBP2 is involved (105). Mechanistically, isoprenylated GBPs were found to associate with the surface of OMVs or with transfected LPS (106), suggesting that LPS is the PAMP which targets GBPs to bacterial membranes and OMVs. However, the exact mechanism by which GBPs facilitate release of LPS for sensing by caspase-11 remains poorly defined. It is possible that GBPs induce the rupture of OMVs to release LPS into the cytoplasm, perhaps by recruiting additional membrane-disrupting proteins, such as IRGB10 (100). Alternatively, GBPs bound to

TABLE 2 Gram-positive bacteria produce PAMPs and DAMPS during infection that activate inflammasomes and other sensors

Bacterium	Inflammasome sensor(s) [activator(s)] [reference(s)]
Bacillus anthracis	NLRC4 (unknown activator) (397), NOD2 and NLRP1 (muramyl dipeptide) (122), NLRP1 (lethal toxin) (61, 62, 190)
Bacillus amyloliquefaciens	NLRP3 (amylosin toxin) (398)
Clostridium difficile	NLRP3 (toxins TcdA and TcdB) (399), Pyrin (toxins TcdA and TcdB) (71, 72, 75)
Clostridium botulinum	Pyrin (C3 toxin) (72)
Lactobacillus casei	NLRP3 (cathepsin B release triggered by cell wall fragments) (120)
Listeria monocytogenes	AIM2 (dsDNA) (154, 400–403), NLRC4 (flagellin) (137, 400), NLRP3 (listeriolysin O?) (154, 187, 400), NLRP7 (acylated lipopeptide?) (119), NLRP1b (metabolic stress) (388)
Propionibacterium acnes	NLRP3 (mitochondrial ROS, ATP, K^+ efflux) (404–407)
Staphylococcus aureus	NLRP3 (α-, β-, and γ-hemolysins) (119, 185, 408), NLRP7 (acylated lipopeptide?) (119), AIM2 (dsDNA) (409), NLRC4 (cathepsin B release via alpha-toxin) (410)
Streptococcus agalactiae	NLRP3 (RNA, β-hemolysin) (178)
Streptococcus pyogenes	NLRP3 (streptolysin O, ADP-ribosyltransferase toxin, surface protein M1) (121, 411–413)
Streptococcus pneumoniae	AIM2 (dsDNA) (414, 415), NLRP3 (pneumolysin) (414, 416–420)

OMVs may directly facilitate binding of caspase-11 to LPS embedded in the OMV membrane.

Sensing of LPS via caspase-11 and activation of the noncanonical NLRP3 inflammasome can lead to a protective or detrimental outcome. For example, injection of LPS into mice induces lethality (18, 40, 41, 44, 107–110). In this case, caspase-11- and gasdermin D-mediated tissue damage and pyroptosis of endothelial cells in response to LPS have been proposed to be responsible for driving the lethality of endotoxemia (18, 40, 44, 95, 111). In contrast, caspase-11 provides host protection *in vivo* in response to infection by Gram-negative bacterial pathogens, including *S.* Typhimurium, enteropathogenic *E. coli*, *B. thailandensis*, *B. pseudomallei*, *Legionella pneumophila*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae* (42, 85, 89, 112–114). The increased susceptibility of mice lacking caspase-11 or gasdermin D to these bacteria can likely be attributed to defective activation of pyroptosis and an increased bacterial burden. Indeed, pyroptosis can induce extrusion of infected cells from the epithelium (85). In addition, pyroptosis can release intracellular bacteria into the extracellular milieu to promote phagocytosis and killing by neutrophils (86, 115–117) or can shed infected cells for removal by the host (84, 85). These different experimental systems provide insights into the outcome of caspase-11 activation by Gram-negative bacterial pathogens.

In humans, extracellular LPS has also been reported to trigger an alternative NLRP3 inflammasome pathway in monocytes (118). This pathway is propagated by TLR4–TRIF–RIPK1–FADD–caspase-8 signaling upstream of NLRP3 but differs from both the canonical and noncanonical NLRP3 inflammasomes in that activation of this pathway does not lead to pyroptosis or ASC speck formation and is not dependent on potassium efflux (118). Furthermore, the alternative NLRP3 inflammasome pathway appears to be species and cell type specific, as it is absent in mice and in human macrophages and dendritic cells (118). This TLR4-mediated sensing of extracellular LPS may initiate an early warning system for infection by secreting IL-1β without the cell undergoing pyroptosis. In this way, LPS, one of the strongest bacterium-derived activators of the immune system and inflammasomes, can trigger activation of inflammasome pathways without entering the cytoplasm of human monocytes.

Other Cell Wall Components

There is some evidence that bacterial cell wall components other than LPS, including lipopeptides and muramyl dipeptide, activate the inflammasome (Tables 1 to 3). Both Gram-negative and Gram-positive bacteria have acylated lipopeptides associated with their cell walls, which activate NLRP7 in human macrophages (119). Activation of NLRP7 has been reported to result in ASC-dependent caspase-1 activation and restriction of the replication of *Staphylococcus aureus* and *Listeria monocytogenes* (119); however, human macrophages lacking NLRP7 retain some inflammasome activation in response to bacterial infection (119). NLRP3 knockdown also results in decreased IL-1β

TABLE 3 Gram-variable bacteria produce PAMPs and DAMPs during infection that activate inflammasomes and other sensors

Bacterium	Inflammasome sensor(s) [activator(s)] [reference(s)]
Mycobacterium bovis	AIM2 (dsDNA) (421)
Mycobacterium marinum	NLRP3 (Esx-1, type VII secretion system) (422)
Mycobacterium tuberculosis	AIM2 (dsDNA) (423), NLRP3 (ESAT-6, dsRNA) (424, 425)
Mycoplasma pneumoniae	NLRP3 (ADP-ribosylation by CARDS toxin) (191, 192)
Mycoplasma spp.	NLRP7 (acylated lipopeptide) (119), NLRP3 (cathepsin B, K^+ efflux, ROS) (426, 427)

secretion upon *S. aureus* and *L. monocytogenes* infection (119), suggesting that NLRP7 may function redundantly with NLRP3 for inflammasome activation in these infections. Further studies are required to more fully elucidate the relative contributions of NLRP7 and NLRP3 to inflammasome activation in these instances.

Cell wall fragments derived from *Lactobacillus casei* elicit NLRP3 inflammasome activation in mouse vascular endothelial cells (120). Mechanistically, cell wall fragments increase lysosomal permeability and thereby facilitate release of cathepsin B into the cytoplasm to activate NLRP3 (120). The cell surface protein M1 of *Streptococcus pyogenes* can likewise activate the NLRP3 inflammasome upon clathrin-mediated endocytosis, in a manner dependent on potassium efflux (121). A further study suggests that the muramyl dipeptide of *Bacillus anthracis* is detected by its cognate cytosolic sensor, NOD2, which has been reported to recruit NLRP1 to mediate caspase-1 activation and secretion of IL-1β (122). However, the mechanistic relationship, if any, between NOD1 and NLRP1 activation remains unclear. Previous studies have shown that NLRP1 is activated by protease-specific cleavage of the N-terminal domain or the function-to-find domain; therefore, NOD2 binding to muramyl dipeptide potentially has some role in triggering this cleavage event. However, it is unlikely that muramyl dipeptide would induce direct cleavage of NLRP1. Taken together, these studies highlight the potential of cell wall components to trigger activation of multiple inflammasomes.

Flagellin and Secretion Systems

Motile bacteria frequently encode specialized organelles, called flagella, which facilitate bacterial movement and attachment. Repeating subunits of the monomeric flagellin protein are the main constituents of bacterial flagella (123). Many Gram-negative bacteria utilize a related but specialized apparatus, called a secretion system, to inject virulence factors into the host cytoplasm. While the virulence factors injected depend on the bacterial species, the secretion system apparatus itself is relatively conserved (124, 125).

Many flagellated bacteria trigger activation of the inflammasome via NAIP and NLRC4 (Tables 1 and 2). Cytoplasmic flagellin monomers are initially sensed by murine NAIP5 or NAIP6 (34, 35, 126) and the single human NAIP (127). A stretch of 35 amino acids from the C terminus of flagellin is required to trigger activation of the NLRC4 inflammasome (126). Mutating the inflammasome-activating flagellin residues abolishes motility in *L. pneumophila* (126), indicating that these residues are critical for flagellin function. Furthermore, structural analysis suggests that upon binding NAIP5, flagellin adopts a conformation similar to its structure in flagellar filaments (128), implying that mutating residues important for NAIP recognition would also disrupt formation of flagellar filaments.

Elements that constitute the T3SS apparatus can also be recognized directly by inflammasome sensors (Fig. 2). The T3SS rod proteins of many Gram-negative bacteria are sensed by the murine NAIP2 protein (34, 35, 123, 129) (Table 1); likewise, the T3SS needle proteins of many Gram-negative bacteria are sensed by NAIP1 in mice and by NAIP in humans (35, 130, 131) (Table 1). A further study has indicated that both the inner rod (PscI) and needle (PscF) T3SS proteins of *Pseudomonas aeruginosa* are sensed by human NAIP in macrophages and peripheral blood mononuclear cells (PBMCs) (132). An additional study broadened the role of human NAIP even further, with evidence that

NAIP can recognize the T3SS inner rod proteins of *S.* Typhimurium, *Shigella flexneri*, and *Burkholderia* spp., in addition to flagellin and T3SS needle proteins from these bacteria (133). These studies have therefore shown the single human NAIP protein to be a versatile sensor capable of interacting with multiple PAMPs.

Further studies have mapped the nucleotide-binding domain (NBD) of mouse NAIP2, -5, and -6 (134), as well as the LRR domain of NAIP5 (128, 135), as the region responsible for ligand specificity. The evolutionary and functional basis for the different specificities of murine and human NAIPs remains a mystery. Rodent NAIP paralogs are likely to have evolved from expansion or duplication of a single progenitor, with NAIP1, -2, and -3 representing one family and NAIP4, -5, -6, and -7 representing another (136). Furthermore, murine NAIPs have been reported to undergo extensive recombination within regions conferring ligand specificity (134), which may facilitate positive diversifying selection to combat the evolution of bacterial ligands. However, why mice encode several NAIP proteins with specificity for distinct bacterial ligands while humans encode a single NAIP capable of recognizing the same set of ligands remains uncertain.

Flagellin must be introduced into the cytoplasm for recognition by cytoplasmic NAIP proteins to occur. Certain bacteria, such as *L. monocytogenes*, invade the cytoplasm shortly after phagocytosis in order to replicate and thereby directly introduce flagellin and other PAMPs into the cytoplasm (137). However, other bacteria remain in a pathogen-containing vacuole, and their flagellin is therefore sequestered and not exposed to the cytoplasm. In these instances, the T3SS or T4SS apparatus can pierce the pathogen-containing vacuole membrane or host cell membrane to deliver virulence factors and effector proteins, some of which may include flagellin subunits, into the cytoplasm (124, 125). For example, infection with the vacuole-restricted bacteria *S.* Typhimurium and *L. pneumophila* triggers activation of the NLRC4 inflammasome, a process which requires a functional T3SS and T4SS, respectively (138, 139). During this process, flagellin subunits can be secreted into the host cytoplasm through these secretion systems (13, 138, 140).

Activated NAIPs subsequently bind NLRC4 to initiate inflammasome formation (Fig. 2). Mechanistically, an association between the ligand and NAIP induces NLRC4 binding, causing a conformational change in bound NLRC4 that exposes an oligomerization surface to which additional inactive NLRC4 subunits are recruited to initiate inflammasome formation (128, 141–143). Activation of the NAIP-NLRC4 inflammasome can lead to the recruitment of NLRP3 to the same inflammasome complex (14), which may require phosphorylation of NLRC4 at residue S533 (144–146). A further study has shown that the leucine-rich repeat-containing kinase LRRK2 complexes with NLRC4 in response to *S.* Typhimurium infection, leading to phosphorylation of NLRC4 at residue S533 and to activation of the NLRC4 inflammasome (147).

The ability of NAIP-NLRC4 to recognize flagellin and T3SS apparatus proteins provides host protection against many Gram-negative bacterial infections (13, 14, 148). NLRC4 is highly expressed in mouse enterocytes and intestinal immune cells (149). Studies focusing on *S.* Typhimurium infection of the intestinal epithelium have suggested the mechanism by which NLRC4 and pyroptosis mediate the host defense against bacterial infection. Specifically, *S.* Typhimurium-infected wild-type (WT) enterocytes are ejected from the intestinal epithelium via NLRC4-driven pyroptosis (84). This expulsion mechanism is accompanied by the release of eicosanoids and IL-18 and is dependent on NAIP-NLRC4, caspase-1, and caspase-8 (150, 151). Consistent with this observation, caspase-8 is recruited to the NAIP-NLRC4 inflammasome in response to *S.* Typhimurium infection (152); however, it is robustly activated only with the absence or inhibition of gasdermin D or caspase-1 (19, 153).

Phase variation, downregulation, and concealment of ligands are important mechanisms used by bacteria to avoid or minimize detection by the NAIP-NLRC4 inflammasome. For instance, *S.* Typhimurium switches expression of T3SS proteins from SPI-1 to SPI-2 upon reaching the pathogen-containing vacuole, facilitating the secretion of effector proteins that promote survival in the vacuole; importantly, the SPI-2 rod protein SsaI is not recognized by NAIP (123), further contributing to pathogen survival.

Further, a strain of *S.* Typhimurium that constitutively expresses flagellin is rapidly cleared in mice by the inflammasome pathway (86), suggesting that regulating flagellin expression is critical for bacterial survival. Similarly, *L. monocytogenes* flagellin expression is suppressed at 37°C (154), potentially allowing evasion of NLRC4 inflammasome detection in the gastrointestinal tract. Interestingly, the flagellins of *Campylobacter jejuni* and *Helicobacter pylori* fail to activate the NAIP-NLRC4 inflammasome (145, 155), most likely due to differences in flagellin sequence composition compared to that of flagellins produced by NLRC4-activating bacteria. These flagellins also fail to activate TLR5 (156), allowing these bacteria to evade detection by both known sensors of flagellin. Further, a T3SS-secreted effector protein of pathogenic *Yersinia* spp., YopK, can bind to its own T3SS translocon (93), thereby masking and preventing recognition of the T3SS by NAIPs. The prevalence of evasion mechanisms directed against the NAIP-NLRC4 inflammasome highlights the importance of this signaling axis in clearing Gram-negative bacterial infections.

Bacterial DNA

Both microbes and mammalian cells use the same basic biomolecules to encode genetic information. Mammalian cells have evolved mechanisms to distinguish self nucleic acids from nonself nucleic acids. DNA of host cells is normally sequestered inside the nucleus and mitochondria; such spatial separation allows cytosolic DNA sensors to respond only to PAMP- or DAMP-associated DNA in the cytoplasmic space (Fig. 2).

The inflammasome-forming DNA sensor AIM2 responds to infections by a range of Gram-negative, Gram-positive, and Gram-variable bacteria (Tables 1 to 3). The mechanism by which DNA, normally sequestered within the cell membrane and cell wall of bacteria, becomes exposed in the cytoplasm for inflammasome sensing during infection of a host cell has begun to be unraveled by use of the intracellular Gram-negative bacterium *Francisella novicida* as a model. Upon infection of the host cell, *F. novicida* is contained within a pathogen-containing vacuole; however, in order to replicate, *F. novicida* escapes from the pathogen-containing vacuole via a T6SS and invades the cytoplasm (157). Initial studies found that mutant strains of *F. novicida* that are unable to escape the pathogen-containing vacuole fail to activate the AIM2 inflammasome in macrophages and dendritic cells (158, 159). Furthermore, mutant strains of *F. novicida* that are prone to intracellular lysis exhibit an increased ability to trigger activation of the AIM2 inflammasome in macrophages (160). This finding suggests that bacteriolysis is an important mechanism in the liberation of bacterial DNA for AIM2 sensing.

Further studies have provided insights into the mechanisms by which *F. novicida* is lysed during infection. Type I IFN signaling is induced during infection with *F. novicida* and is required for inflammasome activation (161). This signaling cascade leads to the upregulation of IFN-inducible proteins, including GBPs and IRGs, by the transcription factor IRF1 (162). Evidence indicates that GBP members GBP2 and GBP5 target cytoplasmic *F. novicida* and recruit the IRG member IRGB10 to the bacterial cell membrane (100), where they instigate bacteriolysis to induce the release of bacterial DNA into the host cytoplasm for sensing by the AIM2 inflammasome (100, 162, 163). Consistent with the role of the AIM2 inflammasome in antibacterial host defense, mice lacking AIM2, GBPs, or IRGB10 are highly susceptible to infection by *F. novicida* and have an impaired ability to induce activation of the inflammasome (158, 162–167).

Cytoplasmic DNA sensing in certain human myeloid cells has been proposed to employ an alternative pathway that is independent of AIM2 (168). Upon *F. novicida* infection, cGAS and STING induce lysosomal cell death, potassium efflux, and subsequent activation of the NLRP3 inflammasome in an AIM2-independent manner (168). However, why AIM2 is not functional in human monocytes was not addressed in that study. Indeed, AIM2 is the major DNA-sensing inflammasome pathway in THP-1 cells, monocyte-derived dendritic cells, and keratinocytes in humans and in myeloid cells in mice (169, 170), suggesting that this alternative DNA-sensing inflammasome pathway

is cell type rather than species specific. Further, this alternative pathway may have some capability to compensate the AIM2 inflammasome pathway in human monocytes when it is inhibited by certain virulence factors.

Several bacteria strategically prevent DNA release and activation of the AIM2 inflammasome to ensure survival and dissemination in the infected host. *F. novicida* encodes a lipid II flippase, MviN, and a CRISPR-Cas system to enhance the integrity of the bacterial envelope and to resist bacteriolysis and subsequent release of DNA (171, 172). Similarly, *L. pneumophila* produces an effector protein, SdhA, that helps to maintain membrane integrity of the pathogen-containing vacuole (173). In the absence of SdhA, more *L. pneumophila* DNA is released into the host cytoplasm, activating the AIM2 inflammasome and pyroptosis within 5 h of infection of human macrophages (173). It is likely that other cytosolic bacteria have similar strategies to limit the amount of free bacterial DNA in the cytoplasm. For example, *S. flexneri* encodes an E3 ubiquitin ligase, IpaH9.8, which mediates ubiquitination and degradation of mouse and human GBPs (174–176). Given the importance of GBPs in mediating bacteriolysis, IpaH9.8 potentially prevents GBP-induced binding to bacteria and subsequent bacteriolysis and DNA release. Additional searches for similar cytosolic bacterial virulence factors that promote degradation of GBPs and IRGs or DNA sensors would further unveil the complexity of the microbial DNA sensing pathway.

Bacterial RNA and Other Bacterial Nucleic Acids

Bacterial RNA species activate multiple cytoplasmic RNA sensors, including the inflammasome sensor NLRP3 and the noninflammasome RLRs and non-RLR helicases. Purified total RNAs derived from both Gram-positive and Gram-negative bacteria trigger activation of the NLRP3 inflammasome in mouse macrophages (177, 178). In addition, both mRNA and RNA-DNA hybrids of *E. coli* activate NLRP3 in mouse macrophages and dendritic cells (179, 180). Further studies indicate that bacterial mRNA, tRNA, and rRNA are all capable of activating NLRP3 in human macrophages (181). It has been proposed that bacterial RNA might serve as an important "vita-PAMP" to signify the presence of viable microbes to host sensors (179). mRNA from bacteria, but not that from eukaryotic cells, activates the NLRP3 inflammasome, and 3′ polyadenylation of bacterial mRNA abolishes its inflammasome-activating activity (179), suggesting that the 3′ end of bacterial mRNA might be important for NLRP3 engagement and that polyadenylation of host RNA might be sufficient to suppress immune recognition of self RNA. However, the mechanism by which NLRP3 senses and is activated by bacterial RNA remains poorly defined.

Two hypotheses have been postulated to describe how bacterial RNA species might activate NLRP3. First, bacterial RNA and RNA-DNA hybrids colocalize with NLRP3 and caspase-1 inflammasome specks in mouse macrophages infected with *E. coli* (180), providing some evidence that NLRP3 may interact with bacterial RNA. However, whether this finding reflects a direct interaction between NLRP3 and bacterial RNA or the requirement of an RNA-binding mediator has yet to be shown conclusively. Second, the RNA helicase DHX33 may function as an upstream sensor of bacterial mRNA and subsequently interact with and activate NLRP3 (182, 183). Further studies are therefore required to elucidate whether cytoplasmic bacterial RNA activates NLRP3 directly, through an additional sensor, such as DHX33, or via a mechanism involving nonspecific homeostatic disruption. It would also be interesting to investigate how bacterial RNA molecules gain access to the cytoplasm to more fully elucidate the molecular mechanisms governing the host response to bacterial RNA.

Toxins

Bacteria encode an arsenal of toxins that modify the function, metabolism, and physiology of the host cell to favor bacterial infection. However, the host immune system can sense some bacterial toxins and activate the inflammasome in response to bacterial infection. Inflammasome activation by bacterial toxins is generally achieved through the pore-forming and/or enzymatic activity of the toxin (Fig. 2).

Many bacterial toxins function by forming pores in the host cell membrane. Certain pore-forming toxins produced by both Gram-positive and Gram-negative bacteria are indirectly sensed by the NLRP3 inflammasome (Tables 1 and 2). Mechanistically, toxin-induced pore formation in the host cell membrane can cause potassium efflux (51), which in turn activates the NLRP3 inflammasome (Fig. 2). Indeed, potassium efflux has been proposed as a common upstream activator of the NLRP3 inflammasome in response to bacterial toxins (51). However, the presence of other bacterial PAMPs in concert with potassium efflux appears to be important for NLRP3 inflammasome activation by some pore-forming toxins. For instance, the Gram-negative pathogenic bacteria *V. cholerae* and *Vibrio vulnificus* (184) and the Gram-positive bacterium *S. aureus* (185) produce hemolysin toxins that induce potassium efflux in macrophages. Culture supernatants derived from *V. cholerae* can trigger potassium efflux and activation of caspase-1 via the NLRP3 inflammasome in macrophages; however, purified hemolysin induces substantially less caspase-1 activation (184). It is possible that other bacterial PAMPs, such as peptidoglycan, may provide a priming signal (signal 1) to upregulate inflammasome components, while toxin-induced potassium efflux acts as the inflammasome-activating signal (signal 2). In this way, hemolysins may function in concert with other bacterial virulence factors to maximally activate the NLRP3 inflammasome.

Introducing pores into the pathogen-containing vacuole membrane can also permit bacterial escape, and subsequent release of PAMPs, into the cytoplasm for innate immune sensing. For instance, the *L. monocytogenes* toxin listeriolysin O is required for bacterial invasion of the cytoplasm from the pathogen-containing vacuole (186). A mutant strain of *L. monocytogenes* lacking listeriolysin O fails to induce IL-1β secretion in macrophages (186), likely due to inflammasome-activating PAMPs remaining sequestered in the pathogen-containing vacuole. A further study implicated listeriolysin O-mediated rupture of phagosomes and release of cathepsin B as the main mechanism by which NLRP3 is activated upon *L. monocytogenes* infection of human PBMCs (187). Similarly, *Streptococcus agalactiae* produces a β-hemolysin toxin which forms pores in the pathogen-containing vacuole and presumably releases RNA and lysosomal components into the cytoplasm for sensing by the NLRP3 inflammasome (178).

The lethal toxin produced by *B. anthracis* performs both pore-forming and enzymatic activities that lead to activation of the NLRP1 inflammasome. The lethal toxin is a two-component toxin comprising a pore-forming protective antigen and an enzymatically active lethal factor (188). The protective antigen facilitates lethal factor entry into the host cell cytoplasm, where the lethal factor cleaves mouse NLRP1b in the N-terminal region, leading to formation and activation of the NLRP1b inflammasome (61–64, 66). Mice carrying a cleavage-resistant variant of NLRP1b are unable to sense *B. anthracis* infection and succumb to infection faster than WT mice do (189, 190). Proteolytic cleavage therefore represents one mechanism by which the inflammasome can be activated by bacterial toxins.

Posttranslational modifications induced by enzymatically active toxins represent an additional mechanism by which the inflammasome can be activated. For instance, *Mycoplasma pneumoniae* encodes an ADP-ribosylating and vacuolating toxin, designated community-acquired respiratory distress syndrome (CARDS) toxin (191), which activates the NLRP3 inflammasome by direct ADP-ribosylation of NLRP3 (191). Mice lacking NLRP3 and infected with *M. pneumoniae* are unable to produce IL-1β and exhibit delayed bacterial clearance during acute pulmonary infection (192), clearly indicating a role for the NLRP3 inflammasome in bacterial clearance; however, whether activation of the NLRP3 inflammasome by the CARDS toxin directly relates to the observed *in vivo* protection from *M. pneumoniae* infection remains unclear. It would therefore be prudent to generate a mutant *M. pneumoniae* strain lacking the CARDS toxin to more clearly define the contribution of this toxin to bacterial clearance *in vivo*.

TABLE 4 DNA viruses produce PAMPs and DAMPs during infection that activate inflammasomes and other sensors

Virus (type of genome)	Inflammasome sensor(s) [activator(s)] [reference(s)]
Adenovirus (dsDNA)	NLRP3 (cathepsin B, ROS) (208, 210, 212, 213)
Bovine herpesvirus 1 (dsDNA)	IFI16 (viral DNA) (428), NLRP3 (unknown activator) (428)
Epstein-Barr virus (dsDNA)	AIM2 (viral DNA) (200, 204), IFI16 (viral DNA) (429)
Hepatitis B virus (circular, partially dsDNA)	AIM2 (viral DNA) (198, 203, 430, 431)
Herpes simplex virus (dsDNA)	NLRP3 (ROS) (201, 205–207), IFI16 (viral DNA) (205, 215)
Human bocavirus (ssDNA)	NLRP3 (viral noncoding RNA) (432)
Human cytomegalovirus (dsDNA)	AIM2 (viral DNA) (193)
Human papillomavirus 16 (dsDNA)	AIM2 (viral DNA) (199)
Kaposi's sarcoma-associated herpesvirus (dsDNA)	IFI16 (viral DNA) (433, 434)
Modified vaccinia virus Ankara (dsDNA)	AIM2 (viral DNA) (201), NLRP3 (unknown activator) (168, 209)
Mouse cytomegalovirus (dsDNA)	AIM2 (viral DNA) (162, 164)
Vaccinia virus (dsDNA)	AIM2 (viral DNA) (31, 164)
Varicella-zoster virus (dsDNA)	NLRP3 (unknown activator) (211)

Posttranslational modification and inactivation of Rho family GTPases by enzymatically active bacterial toxins can also indirectly activate the Pyrin inflammasome. Pyrin is normally phosphorylated by host RhoA serine-threonine kinases PKN1 and PKN2, promoting Pyrin inhibition by 14-3-3 proteins (68–70). Bacterial toxins posttranslationally modify Rho family GTPases in the I-switch region and inhibit RhoA-dependent kinase activity, thereby relieving inhibition of Pyrin and licensing activation of the Pyrin inflammasome (68, 71, 72). Specifically, the *Clostridium difficile* cytotoxins TcdA and TcdB monoglucosylate RhoA, the *Clostridium botulinum* toxin C3 ADP-ribosylates RhoA, and the *Vibrio parahaemolyticus* toxin VopS and the *Histophilus somni* toxin IbpA adenylate RhoA (71, 72, 74, 75). These studies highlight that diverse posttranslational modifications induced by bacterial toxins can be sensed by multiple inflammasome sensors.

VIRUSES

Viruses enter the host cell to hijack the machinery necessary for viral replication. Viral PAMPs can trigger innate immune responses either on the host cell surface, within the endosome, or in the cytoplasm. Emerging evidence also suggests that innate immune detection might occur in the nucleus. Inflammasome sensors are activated in response to both DNA and RNA viruses, ensuring efficient immunosurveillance and elimination of different families of viruses. In this section, we discuss the molecular mechanisms regulating virus-induced activation of the inflammasome.

DNA Viruses

DNA viruses replicate in either the cytoplasm or the nucleus, and the majority activate the inflammasome through innate immune recognition of viral DNA (Table 4). Cytoplasmic DNA is sensed by the inflammasome sensor AIM2; however, not all DNA viruses activate AIM2 (discussed further below). Murine cytomegalovirus (MCMV) and vaccinia virus trigger activation of the AIM2 inflammasome in mouse bone marrow-derived macrophages (BMDMs) or bone marrow-derived dendritic cells (BMDCs) (31, 162, 164), suggesting that their viral DNA activates the AIM2 inflammasome (Fig. 3). In addition, mice lacking AIM2 and infected with MCMV have lower levels of circulating IL-18 and higher viral titers after 36 h than those of infected WT mice (164). Similar to its murine counterpart, human cytomegalovirus (HCMV) also activates the AIM2 inflammasome in human THP-1 monocytic cells (193). Unlike the case in bacterium-induced activation of the AIM2 inflammasome, type I IFN signaling and IFN-inducible proteins are not required to facilitate sensing of MCMV by AIM2 (100, 162). Interestingly, HCMV expresses the tegument protein pUL83, which interacts with and inhibits AIM2 (194) and the related ALR member IFI16 (195–197), indicating the importance of DNA inflammasome sensors for detection of this viral pathogen.

Other DNA viruses, including hepatitis B virus (HBV), human papillomavirus 16 (HPV16), Epstein-Barr virus (EBV), and modified vaccinia virus Ankara (MVA), can activate
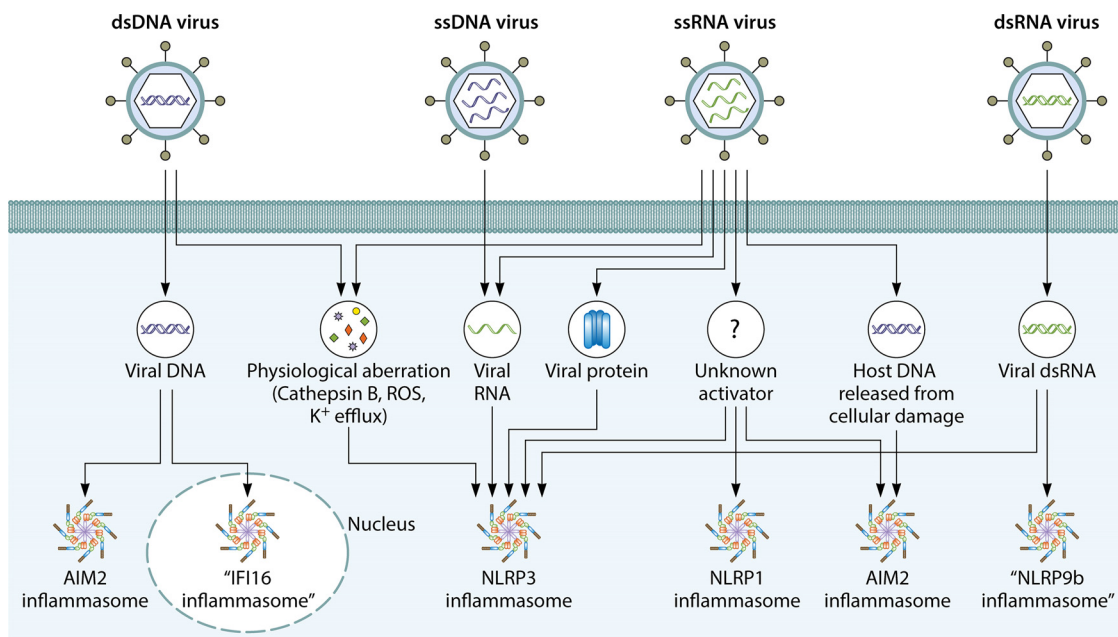
FIG 3 Viral activators of the inflammasome. DNA and RNA viruses carry viral PAMPs and induce physiological aberrations and host cell damage that can trigger activation of the inflammasome. DNA from double-stranded DNA (dsDNA) viruses can enter the cytoplasm and the nucleus to engage activation of the AIM2 inflammasome and the putative IFI16 inflammasome, respectively. Both DNA and RNA viruses can cause physiological aberrations in the form of cathepsin B release, production of ROS, and potassium efflux, which are signaling cues leading to activation of the NLRP3 inflammasome. RNA and viral proteins of single-stranded RNA (ssRNA) viruses and replication intermediaries of a single-stranded DNA (ssDNA) virus have been shown to trigger activation of the NLRP3 inflammasome. Host DNA release from virus-induced damage can lead to activation of the AIM2 inflammasome. There is some evidence to suggest that an ssRNA virus might activate the NLRP1 inflammasome. Double-stranded RNA (dsRNA) from a dsRNA virus has been shown to activate a putative NLRP9b inflammasome in mouse enterocytes.

the AIM2 inflammasome (198–201) (Table 4). HBV infection induces AIM2-mediated caspase-1 activation or IL-1β and IL-18 secretion in human glomerular mesangial cells, hepatocytes, and PBMCs (198, 202, 203). Similar observations have been made in human keratinocytes infected with HPV (199) and human THP-1 monocytes infected with EBV (200). Transfected EBV DNA induces IL-1β secretion in the human tumor cell line HK1 via the AIM2 inflammasome (204). Despite these observations, the molecular mechanism underpinning activation of the AIM2 inflammasome by DNA viruses has not completely emerged. The putative activator of AIM2 in these cases is presumably the genomic DNA and/or replication intermediaries of these viruses. However, biochemical and imaging studies are required to confirm whether viral DNA binds to AIM2 in the cytoplasm and/or the nucleus during viral infection.

Furthermore, not all DNA viruses activate the AIM2 inflammasome (Table 4). The DNA viruses adenovirus, herpes simplex virus 1 (HSV-1), MVA, varicella-zoster virus (VZV), and human bocavirus 1 all preferentially activate the NLRP3 inflammasome over AIM2 (164, 205–211). The main activator of the NLRP3 inflammasome induced by DNA viruses is unknown. However, adenovirus infection leads to disruption of lysosomal membranes, which results in the release of cathepsin B and activation of NLRP3 (210, 212, 213). In addition, adenovirus infection induces the production of ROS in THP-1 cells, which also contributes to NLRP3 inflammasome activation (208, 210, 213). Similarly, HSV-1 infection induces expression of NLRP3, cleavage of caspase-1, and maturation of IL-1β in human foreskin fibroblasts and human THP-1 cells (205, 208). Secretion of IL-1β in response to HSV-1 was also found to be independent of AIM2 in mouse thioglycolate-elicited macrophages (164). Together these examples highlight that although DNA viruses possess DNA, some preferentially activate the NLRP3 inflammasome over AIM2.

The reasons underlying why certain DNA viruses do not engage activation of the AIM2 inflammasome are unknown. Given that AIM2 binds DNA in a sequence-

independent manner (169), it is unlikely that DNA sequences from these viruses are not recognized by AIM2. A more plausible explanation is that these viruses encode inhibitory proteins similar to the host-derived AIM2-inhibiting PYD-containing proteins that can directly bind and inhibit AIM2 (169, 214). Viral DNA binding proteins may also prevent access of AIM2 to the DNA and thereby prevent inflammasome activation. Alternatively, it is possible that rapid shuttling of viral DNA into the host nucleus evades detection by AIM2 in the cytoplasm. In the latter case, other nuclear DNA sensors might be able to compensate the innate immune recognition of the virus. Indeed, the DNA of HSV-1 has been shown to activate IFI16 in the nucleus (Fig. 3) (205, 215). It is also possible that, as shown for human monocytes, the cGAS-STING axis may drive NLRP3 inflammasome activation in response to cytosolic DNA (168). This would support findings of past studies suggesting that DNA viruses activate the NLRP3 inflammasome rather than the AIM2 inflammasome in human monocyte-derived cells but cannot explain why AIM2 is not activated in other cell types (168, 205, 208, 210, 211). Taken together, the data show that DNA viruses can activate either the AIM2 or NLRP3 inflammasome (Fig. 3); however, the precise activators and regulatory mechanisms leading to activation of these inflammasomes are still not entirely clear.

RNA Viruses

RNA viruses can harbor either a single- or double-stranded RNA genome. An increasing number of RNA viruses have been found to activate the inflammasome (Table 5), including those which pose major threats to public health. Below, we focus our discussions primarily on influenza virus and human immunodeficiency virus (HIV) and on how infection by each of these viruses leads to activation of the inflammasome (Fig. 3).

Influenza A virus. Influenza A virus is an important human pathogen that has caused multiple pandemics in human history. The virus is subtyped based on its surface glycoproteins hemagglutinin (H) and neuraminidase (N) (216). There is strong evidence to demonstrate that multiple subtypes of influenza A virus trigger activation of the NLRP3 inflammasome in macrophages and dendritic cells (217–224). Several mechanisms have been proposed to explain how influenza virus infection leads to NLRP3 activation. Both RNA and protein components of influenza virus trigger activation of the NLRP3 inflammasome (Fig. 3) (219–221, 223, 225). Transfection of RNA derived from the A/H7N9 strain activates the NLRP3 inflammasome in BMDCs (219, 225), implying that viral RNA is sufficient to activate the NLRP3 inflammasome. However, the viral peptide PB1-F2, derived from strains A/H7N9 and A/H1N1, can also activate NLRP3 in BMDMs (220, 221). Further studies have identified additional mechanisms by which influenza virus can activate the NLRP3 inflammasome. For instance, influenza virus strain A/H3N2 encodes an ion channel, M2, causing ion imbalances during infection of mouse BMDMs and BMDCs and thereby activates NLRP3 (223). Mice lacking NLRP3 and administered the viral peptide PB1-F2 of strain A/H7N9 produce less IL-1β in the lungs than that in WT mice (221), suggesting that this viral peptide mediates activation of the NLRP3 inflammasome *in vivo*. Together these observations show that it is possible that both viral RNA and peptides are the PAMPs responsible for activating the NLRP3 inflammasome during influenza virus infection.

Studies have also suggested that an RNA-protein complex comprised of the influenza A viral RNA and viral proteins NP and PB1 is recognized by the innate immune sensor ZBP1 (also known as DAI or DLM-1) (226–228). Recognition of this RNA-protein complex by ZBP1 drives activation of the NLRP3 inflammasome and multiple forms of programmed cell death in a manner dependent on the kinases RIPK1 and RIPK3 and on caspase-8 (226). How the ZBP1–RIPK1–RIPK3–caspase-8 scaffold mediates activation of the NLRP3 inflammasome is unknown. Nevertheless, these studies suggest that activation of the NLRP3 inflammasome by influenza virus might require an upstream sensor that recognizes viral PAMPs. Together these studies indicate that in the context of infection of a host, multiple pathogen detection pathways and mechanisms of inflammasome activation are likely to be utilized.

TABLE 5 RNA viruses produce PAMPs and DAMPs during infection that activate inflammasomes and other sensors

Virus (type of genome)	Inflammasome sensor(s) [activator(s)] [reference(s)]
Chikungunya virus (positive-sense ssRNA)	AIM2 (unknown activator) (435)
Dengue virus (positive-sense ssRNA)	NLRP3 (K⁺ efflux, cathepsin B) (436)
Encephalomyocarditis virus (positive-sense ssRNA)	NLRP3 (viroporin 2B) (261, 437)
Enterovirus type 71 (positive-sense ssRNA)	NLRP3 (3D protein, viroporin 2B) (253, 254, 261), AIM2 (unknown activator) (255)
Hepatitis C virus (positive-sense ssRNA)	NLRP3 (viral RNA, protein P7) (239, 257–259, 438, 439)
Human immunodeficiency virus (positive-sense ssRNA)	NLRP3 (protein R, Tat protein) (239, 240, 243, 244)
Influenza A virus (negative-sense ssRNA)	NLRP3 (viral RNA, PB1-F2 peptide, M2) (217–223, 225, 232), AIM2 (host cell dsDNA) (233, 234)
Japanese encephalitis virus (positive-sense ssRNA)	NLRP3 (ROS, K⁺ efflux) (440)
Lymphocytic choriomeningitis virus (negative-sense ssRNA)	NLRP1 (unknown activator) (441)
Measles virus (negative-sense ssRNA)	NLRP3 (unknown activator) (442)
Newcastle disease virus (negative-sense ssRNA)	NLRP3 (unknown activator) (443)
Parainfluenza virus type 3 (negative-sense ssRNA)	NLRP3 (K⁺ efflux) (444)
Poliovirus (positive-sense ssRNA)	NLRP3 (viroporin 2B) (261)
Porcine reproductive and respiratory syndrome virus (positive-sense ssRNA)	NLRP3 (unknown activator) (445, 446)
Rabies virus (negative-sense ssRNA)	NLRP3 (unknown activator) (447)
Respiratory syncytial virus (negative-sense ssRNA)	NLRP3 (SH viroporin, viral RNA) (182, 260, 448, 449)
Reovirus (dsRNA)	NLRP3 (viral RNA) (182)
Rhinovirus (positive-sense ssRNA)	NLRP3 and NLRC5 (ion channel protein 2B) (262)
Rotavirus (dsRNA)	NLRP9b (dsRNA) (263)
Sendai virus (negative-sense ssRNA)	NLRP3 (viral RNA) (222, 450)
Vesicular stomatitis virus (negative-sense ssRNA)	NLRP3 (viral RNA) (225, 437, 451)
West Nile virus (positive-sense ssRNA)	NLRP3 (unknown activator) (452), AIM2 (unknown activator) (435)
Zika virus (positive-sense ssRNA)	NLRP3 (oxidative stress, NS5 protein) (256, 453, 454), AIM2 (unknown activator) (455)

Given the importance of NLRP3 in sensing infection, influenza virus encodes a nonstructural protein, NS1, that is capable of binding to and inhibiting activation of the NLRP3 inflammasome (229, 230). Specifically, mutating residues in the RNA- and TRIM25-binding domains of NS1 prevented immunoprecipitation of NS1 with NLRP3 and increased secretion of IL-1β relative to that with WT NS1 (229), indicating that these regions are important for mediating NLRP3 binding and inhibition.

While the NLRP3 inflammasome responds to influenza virus infection, it remains unclear whether this pathway confers protection against or susceptibility to the virus *in vivo*. A study has shown that mice lacking NLRP3 and infected with influenza virus strain A/H1N1 (also known as A/PR/8/34) harbor higher viral titers in their lungs and have a higher mortality rate than those of WT mice (217, 218). Contrastingly, another study found that mice lacking NLRP3 and infected with the highly pathogenic influenza virus strain A/H7N9 have increased survival and develop less pulmonary inflammation than that in WT mice (219). These differing results may be explained, in part, by studies which report that temporal inhibition of NLRP3 by use of the small-molecule compound MCC950 influences the survival rate of mice infected with the influenza virus strains A/WSN/1933 (231) and A/PR/8/34 (232). The latter study found that delayed treatment with MCC950 increases survival of mice, whereas treatment with MCC950 as early as 1 day after infection results in lethality (232). These results partially reconcile the earlier conflicting results and suggest that the NLRP3 inflammasome may contribute to antiviral host defense at the early stages of infection while driving overt inflammation and immunopathology at later stages.

Conflicting results also exist regarding the role of AIM2 in influenza virus infection. Influenza A virus infection of lung epithelial cells can cause substantial damage, resulting in the release of host DNA that can activate the AIM2 inflammasome (233, 234). Whether AIM2 inflammasome activation benefits the host during influenza virus infection remains uncertain. While a study reported that mice lacking AIM2 and infected with influenza virus strain A/H1N1 have less lung injury and a higher survival rate than those of infected WT mice (233), another study found that mice lacking AIM2 are more susceptible than infected WT mice to infection with A/H1N1 (234). These conflicting results may be due to differences in the source of the A/H1N1 virus or the infection dose used or to subtle differences in mouse genetic background, microbiota, or the vivarium used to house these animals (235). However, the exciting finding that both influenza virus-derived PAMPs and the DAMPs generated as a result of infection can trigger activation of two inflammasome complexes, NLRP3 and AIM2, clearly highlights the functional overlap between inflammasome sensors in host defense against this clinically important virus.

HIV. Since the discovery and initial isolation of HIV 30 years ago, approximately 75 million people have been infected, and more than 37 million currently live with the infection worldwide (236). Polymorphisms in the genes encoding NLRP3 and IL-1β are associated with susceptibility to HIV infection (237, 238). HIV infection triggers activation of the NLRP3 inflammasome in a variety of cell types, including human monocytes (237, 239–241), human and rodent microglia (242–244), and human podocytes (245). While the mechanism of NLRP3 inflammasome activation by HIV has yet to be fully defined, evidence suggests that ROS, cathepsin B, and virus-induced potassium efflux from the host cell might all contribute to activation of NLRP3 (240, 242, 245). Furthermore, transfection of HIV-derived single-stranded RNA (ssRNA) is sufficient to activate caspase-1 and induce secretion of IL-1β (240), implying that viral RNA may activate the NLRP3 inflammasome. There is also some evidence to suggest that the HIV proteins R and Tat can activate NLRP3 in human and rodent microglia, respectively (243, 244). However, further biochemical and mechanistic studies are required to more fully assess which viral PAMPs activate the NLRP3 inflammasome and whether direct or indirect sensing of PAMPs is involved.

Further studies have suggested that HIV infection can trigger pyroptosis in a manner that is independent of the NLRP3 inflammasome in tissue-derived CD4$^+$ T cells but not in blood-derived CD4$^+$ T cells (246–249). In this scenario, the incomplete reverse

transcripts of HIV are recognized by IFI16 in CD4$^+$ T cells of the lymphoid tissue, which subsequently drives the infected cells toward pyroptosis (246, 248, 249). The levels of IFI16 expression in tissue- and blood-derived CD4$^+$ T cells might provide an explanation for this observation; indeed, qPCR analysis revealed that tissue-derived CD4$^+$ T cells have three times the level of *IFI16* transcripts in blood-derived CD4$^+$ T cells (246). Further studies revealed that the virological synapse—an intercellular junction between an infected cell and an uninfected cell that is generated by HIV—mediates viral transmission and pyroptosis between neighboring lymphoid CD4$^+$ T cells, ultimately accelerating the demise of the CD4$^+$ T cell population and the progression to AIDS (248–250).

Although pyroptosis of CD4$^+$ T cells is detrimental to the host, there is some evidence that anti-HIV therapies are linked to inflammasome activation. For example, the nucleoside analog reverse transcriptase inhibitor abacavir, which is used as part of anti-HIV therapies, induces mitochondrial damage and subsequent activation of the NLRP3 inflammasome in human monocytes (251). Similarly, nelfinavir, an inhibitor of the HIV aspartyl protease, is used in the treatment of HIV infection and potentially activates the AIM2 inflammasome owing to the ability of the drug to rupture the nuclear envelope (252). In this way, activation of inflammasome pathways by anti-HIV therapies potentially contributes to their anti-HIV effects, although further research is needed to substantiate this hypothesis. Indeed, it has been suggested that inflammasome activation by abacavir contributes to severe delayed-type drug hypersensitivity (251), an off-target effect sometimes experienced by patients. The inflammasome pathway therefore may be beneficial in the detection of HIV infection but appears to also have detrimental outcomes in causing CD4$^+$ T cell pyroptosis and some of the side effects associated with anti-HIV therapies.

Other RNA viruses. Other RNA viruses, including enterovirus type 71 (EV71), hepatitis C virus (HCV), Japanese encephalitis virus (JEV), respiratory syncytial virus (RSV), rhinovirus, encephalomyocarditis virus (EMCV), measles virus, parainfluenza virus type 3, vesicular stomatitis virus (VSV), Newcastle disease virus (NDV), rabies virus, Sendai virus, dengue virus, and Zika virus, have been shown to trigger activation of the NLRP3 inflammasome (Table 5). EV71 has been reported to be recognized by both the NLRP3 and AIM2 inflammasomes, depending on the cell types studied (253–255). The RNA-dependent RNA polymerase (RdRp) 3D protein of EV71 has been suggested to directly bind and activate the NLRP3 inflammasome in human THP-1 cells, rhabdomyosarcoma cells, and HEK293T cells (254). In a similar manner, the RdRp NS5 protein produced by Zika virus directly binds and activates NLRP3 (256), implying that NLRP3 recognition of viral RdRp proteins may facilitate inflammasome activation in response to ssRNA viruses more generally. It will be interesting to assess whether RdRp proteins expressed by other ssRNA viral pathogens can likewise bind to and activate NLRP3. While EV71 infection also appears to induce activation of the AIM2 inflammasome in neuronal cells (255), the activator in this case is unknown. The EV71 proteases 2A and 3C specifically cleave NLRP3 and prevent it from forming an inflammasome complex in infected cells (253).

Viral RNA and the viral ion channel proteins of RNA viruses have been suggested to activate the inflammasome. For example, the viral RNA of reovirus (182), the viral RNA and viral protein viroporin P7 of HCV (257–259), the viral RNA and viroporin SH of RSV (182, 226, 260), and the viroporin 2B proteins of EMCV, EV71, poliovirus, and rhinovirus (261, 262) all result in activation of the NLRP3 inflammasome. A study reported that the RNA of rotavirus triggers a poorly characterized NLR, NLRP9b, in intestinal organoids (Fig. 3) (263). The rotavirus RNA interacts with the host RNA helicase DHX9, which then binds NLRP9b and licenses activation of the inflammasome (263). Moreover, mice lacking NLRP9b and infected with rotavirus have an increased viral load in enterocytes, increased fecal antigen shedding, the occurrence of diarrhea, and more severe pathology than that in WT mice (263). The discovery of a new putative inflammasome sensor in enterocytes argues that many more sensors might have inflammasome-forming capacity and are expressed in a cell-type-specific manner (264). It is possible that

TABLE 6 Fungi produce PAMPs and DAMPs during infection that activate inflammasomes and other sensors

Fungus	Inflammasome sensor(s) [activator(s)] [reference(s)]
Aspergillus fumigatus	NLRP3 (K^+ efflux, ROS) (265, 271, 272), AIM2 (presumably DNA) (265, 271, 272), caspase-11 (unknown activator) (110)
Candida albicans	NLRP3 (K^+ efflux, ROS) (275–277, 282), NLRC4 (unknown activator) (282)
Candida parapsilosis	NLRP3 (K^+ efflux) (276)
Cryptococcus neoformans	NLRP3 (K^+ efflux, ROS) (284, 285)
Histoplasma capsulatum	NLRP3 (K^+ efflux, cathepsin B) (289)
Malassezia furfur	NLRP3 (K^+ efflux) (456)
Microsporum canis	NLRP3 (K^+ efflux, ROS, cathepsin B) (286)
Paracoccidioides brasiliensis	NLRP3 (K^+ efflux, ROS, cathepsin B) (288, 457)
Saccharomyces cerevisiae	NLRP3 (zymosan and mannan) (266)
Sporothrix schenckii	NLRP3 (unknown activator) (458)
Trichophyton schoenleinii	NLRP3 (K^+ efflux, ROS) (287)

distinct inflammasome complexes are formed in different cell types in response to different viral factors generated by the same virus. An exciting avenue of research would be to investigate how these viral factors are liberated and presented to inflammasome sensors in immune and nonimmune cells to provide an integrated antiviral response in the host.

FUNGI

Fungi are eukaryotic organisms that represent some of the most important human pathogens. Evidence suggests that fungal DNA, spores, and cell wall-associated polysaccharides are recognized by inflammasome sensors (265–269) (Table 6). *Aspergillus fumigatus* is a major human pathogen which causes opportunistic infections and mortality in immunocompromised individuals. *A. fumigatus* produces an abundance of spores, known as conidia (270), which are able to activate multiple inflammasomes (265, 271). Germinating conidia induce activation of both the AIM2 and NLRP3 inflammasomes in BMDCs (265). Indeed, mice lacking both AIM2 and NLRP3 and infected with *A. fumigatus* suffer more damage and hemorrhage, harbor a higher fungal load, and produce less IL-1β and IL-18 in the lungs than those in WT mice or mice lacking either AIM2 or NLRP3 (265). Mechanistically, *A. fumigatus* infection induces potassium efflux and ROS production in mouse BMDCs and human THP-1 cells, which triggers activation of the NLRP3 inflammasome (265, 271). In addition, NLRP3 activation requires phagocytosis of *A. fumigatus* conidia by the host cell (265, 271, 272). However, the mechanism by which fungal DNA enters the cytoplasm for sensing by AIM2 remains unknown. It is possible that, similar to observations made in the context of bacterial infection (100, 162), fungal conidia phagocytosed by the host cells are subsequently attacked by IFN-inducible proteins, liberating fungal DNA into the cytoplasm. Mice lacking caspase-11 are also more susceptible than WT mice to infection by *A. fumigatus* (110). Although caspase-11 is a cytoplasmic sensor of bacterial LPS, caspase-11 has been shown to recognize the host-derived danger signal oxidized phospholipids (273), which may be liberated in the lungs over the course of *A. fumigatus* infection *in vivo*. However, the role of caspase-11 in sensing oxidized phospholipids is controversial and may vary depending on cell type (274); further studies are required to ascertain the function of caspase-11 in *A. fumigatus* infection.

The other major fungal pathogen, *Candida albicans*, has also been shown to activate the inflammasome. *C. albicans* infection of LPS-primed human and mouse monocytes or mouse peritoneal exudate cells activates the NLRP3 inflammasome (268, 275–280), with evidence of potassium efflux occurring in response to infection (276). Similarly, mice lacking NLRP3 are hypersusceptible to *C. albicans* infection and carry substantially higher fungal burdens in the kidneys than those in WT mice at 3 to 7 days postinfection (275, 281). The NLRC4 inflammasome also confers host protection in the oral cavity of mice in response to infection with *C. albicans* (282). Mice lacking NLRC4 have an elevated oral fungal burden and substantially increased susceptibility to the dissemination of the fungus compared to those of WT controls (282). The mechanism under-

pinning NLRC4-mediated protection is unknown; however, the protective effect of NLRC4 stems from the stromal compartments (282). Other than the bona fide NLRC4 activators bacterial flagellin and T3SS proteins, mitochondrial DNA has also been proposed to activate NLRC4 (283). Therefore, it is plausible that damage-induced release of mitochondrial DNA might activate the NLRC4 inflammasome to drive a protective response during *C. albicans* infection.

The cell wall components zymosan and mannan, derived from the yeast *Saccharomyces cerevisiae*, are able to activate the NLRP3 inflammasome in mouse BMDMs and BMDCs treated with ATP (266), suggesting that these cell wall components may serve as a priming signal (signal 1) via activation of CLRs rather than as inflammasome-activating agents (signal 2). Cell wall components of certain fungi often provide a protective mask to evade recognition by inflammasome sensors. *Cryptococcus neoformans* is an encapsulated human pathogen which can cause disease in both immunocompetent and immunocompromised hosts. This fungal pathogen activates the NLRP3 inflammasome in human and mouse macrophages only when it lacks the polysaccharide capsule (284, 285), strongly suggesting that encapsulation is a potential mechanism by which this fungus evades detection by the inflammasome.

Other fungi can also trigger activation of the NLRP3 inflammasome (Table 6). Similar to *Candida* species, the majority of these fungi induce potassium efflux and ROS production that culminate in activation of the NLRP3 inflammasome in infected host cells (286–289). Taken together, the data show that fungal infection appears to predominantly trigger activation of the NLRP3 inflammasome, with some fungal species eliciting an innate immune response via the AIM2 and NLRC4 inflammasomes.

PROTOZOA

Protozoa are unicellular eukaryotic organisms which have the potential to cause life-threatening conditions in higher animals, especially in tropical regions (290). The clinically relevant protozoa include the genera *Plasmodium*, *Leishmania*, *Trypanosoma*, *Toxoplasma*, and *Entamoeba*. In this section, we discuss emerging evidence of immunomodulatory effects of inflammasomes during protozoal infection (291).

Plasmodium spp.

Plasmodium spp. are the causative agents of malaria, a debilitating disease which places a heavy burden on public health, especially in Africa and South Asia. The WHO estimated that 212 million cases of malaria were reported in 2015 worldwide, resulting in 429,000 deaths (292). Malaria in humans is mainly caused by five species of the genus *Plasmodium*: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium knowlesi*. Polymorphisms in the genes encoding NLRP1 and IL-1β are associated with more severe *P. vivax* infection, whereas a polymorphism in the gene encoding IL-18 is associated with protection against *P. vivax*-induced anemia (293). Further, patients infected with *Plasmodium* have elevated levels of proinflammatory cytokines, including tumor necrosis factor (TNF) and IL-1β (294); the level of IL-1β in patients correlates with disease severity, particularly for cerebral malaria (295).

The replication cycle of *Plasmodium* spp. exists in two phases: the reproductive phase, which occurs in a vector (female mosquitoes of the *Anopheles* genus), and the infectious phase, which occurs in a mammalian host (296). During the infectious phase of its life cycle, the parasite digests host-derived hemoglobin in the blood. This process generates free heme, which is toxic to the parasite. *Plasmodium* spp. detoxify and convert free heme into a pathogen-derived metabolite, hemozoin, which is a major activator of the inflammasome.

Hemozoin and hemozoin-DNA complexes can both induce activation of the inflammasome. Hemozoin itself triggers activation of the NLRP3 inflammasome in mouse BMDMs and BMDCs and in the human monocytic THP-1 cell line (297–300). Hemozoin-mediated activation of NLRP3 in mouse BMDMs requires the tyrosine kinases SYK and LYN (299). In addition to hemozoin, the DAMP heme can also activate NLRP3 in mouse

macrophages, in a manner dependent on SYK, NADPH oxidase 2, mitochondrial ROS, and potassium efflux but independent of heme internalization, lysosomal damage, ATP release, the purinergic receptor P2X7R, and cell death (301).

Hemozoin might also transport plasmodial DNA into the lysosomal compartment, where the hemozoin-plasmodium-DNA complex interacts with the DNA-sensing receptor TLR9 (302). Indeed, the hemozoin-plasmodium-DNA complex triggers TLR9 translocation from the endoplasmic reticulum to the phagolysosome (303), where hemozoin-induced phagolysosomal instability triggers activation of NLRP3 (303). Further, the hemozoin-plasmodium-DNA complex induces neutrophil infiltration in mice, in a manner dependent on AIM2 and NLRP3 (303). Upon dissociation from hemozoin, plasmodial DNA can activate AIM2 (303). In humans, immunocomplexes containing both human and plasmodial DNAs are found at high levels in the blood of patients infected with *P. falciparum* or *P. vivax* (294). These immunocomplexes induce colocalization of NLRP3 and AIM2 in the inflammasome speck and activation of caspase-1 in human monocytes (294). In addition, NLRP3 and NLRP12 complexes have been observed in PBMCs of patients infected with *P. vivax* (304). These studies collectively demonstrate that pathogen-derived metabolites and DAMPs generated during *Plasmodium* infection can activate inflammasome responses in humans and mice.

Although studies have indicated the importance of inflammasomes in sensing *Plasmodium* infection, inflammasome-mediated responses can result in overt inflammation in the host (297, 301, 303). For instance, WT mice injected with hemozoin develop acute peritonitis, whereas mice lacking NLRP3, caspase-1, and IL-1 receptor (IL-1R) do not (297). Likewise, hemozoin was also found to mediate hemolysis-induced lethality in mice via activation of the NLRP3 inflammasome and production of IL-1β (301). These studies suggest that hemozoin-induced activation of the NLRP3 inflammasome pathway is a potent driver of acute inflammation *in vivo*, often to the detriment of the host.

More comprehensive studies are required to investigate the synergy between inflammasome complexes in the context of *Plasmodium* infection. For example, the relevance of NLRP1 and NLRP12 to *Plasmodium* infection is of particular interest. While no known ligand has been associated with NLRP12, NLRP1 is activated by any protease that can induce cleavage at the N-terminal domain of NLRP1 (61–67). These findings raise the question of whether certain *Plasmodium* spp. encode an NLRP1-targeting protease. Additional studies of the inflammasome by use of human cells and tissues would allow better extrapolation of the data for the design of therapy to treat patients affected by malaria.

Leishmania spp.

Twenty species of *Leishmania* have been reported to cause infection in humans, resulting in an estimated 1.5 million new cases of leishmaniasis worldwide every year (305, 306). Upon receiving a bite from an infected *Phlebotomus* sand fly, a motile and extracellular form of *Leishmania* called a promastigote is introduced into the host; promastigotes can be phagocytosed by macrophages, neutrophils, and dendritic cells (307). Genomic profiling has revealed that genes encoding NLRP3, AIM2, caspase-1, and IL-1β are highly expressed in human lesions caused by *Leishmania braziliensis* infection (308). Further, increased production of IL-1β by monocytes and of serum IL-1β has been observed in patients with *Leishmania mexicana* infection (309).

Infections caused by *Leishmania amazonensis*, *L. braziliensis*, and *Leishmania infantum chagasi* can induce activation of the NLRP3 inflammasome and restriction of parasite replication in both mouse macrophages and mice (310). Multiple species of *Leishmania* activate the NLRP3 inflammasome via potassium channels and cathepsin release (310) (Table 7). In response to *L. amazonensis* infection, IL-1β signaling upregulates nitric oxide (NO) synthase and thereby induces NO production and subsequent host protection (310). Infection caused by *Leishmania major* also induces activation of the NLRP3 inflammasome in mouse macrophages and mice (310–313); however, in-

TABLE 7 Protozoa produce PAMPs and DAMPs during infection that activate inflammasomes and other sensors

Protozoan	Inflammasome sensor(s) [activator(s)] [reference(s)]
Entamoeba histolytica	NLRP3 (ATP release by P2X7R, K^+ efflux) (340, 341)
Leishmania spp., including *L. major*, *L. amazonensis*, *L. braziliensis*, and *L. infantum chagasi*	NLRP3 (K^+ efflux, cathepsin B) (310–313)
Leishmania infantum	NLRP3 (unknown activator) (459)
Plasmodium spp., including *P. falciparum* and *P. berghei*	NLRP3 (hemozoin, ROS, K^+ efflux, lysosome rupture) (297–301, 303), AIM2 (plasmodial DNA) (303), NLRP12 (unknown activator) (304)
Toxoplasma gondii	NLRP1 (unknown activator) (320, 324, 325), NLRP3 (unknown activator) (323, 460)
Tritrichomonas musculis	ASC-dependent inflammasome (unknown activator) (461)
Trypanosoma cruzi	NLRP3 (K^+ efflux, ROS, cathepsin B, lysosomal rupture) (337, 338)

flammasome signaling is dispensable for the development of lesions or restriction of parasite burdens in mice (310).

Two other studies found that NLRP3 accentuates nonhealing *L. major* infections in mice on either the BALB/c or C57/BL6 background (311, 313). The first study found that, in BALB/c mice, IL-18 production as a result of NLRP3 inflammasome activation promotes T_H2 responses as signified by elevated IL-4 production (311). Furthermore, IL-18 production somehow inhibits T_H1 responses as signified by reduced IFN-γ production (311). The IL-18-mediated T_H2 response increases susceptibility to *L. major* infection, and neutralization of IL-18 in mice provides resistance to *L. major* infection (311). Another group found that when C57BL/6 mice are infected with the nonhealing *L. major* Seidman strain, the ensuing NLRP3-dependent response drives IL-1β production and severe immunopathology (313). Mechanistically, secretion of IL-1β leads to an influx of neutrophils at the site of infection and promotes the development of skin lesions (313). Although these studies collectively demonstrate that *Leishmania* spp. can induce activation of the NLRP3 inflammasome, the resultant outcomes in the host are very different. While the NLRP3 inflammasome and IL-1β provide protection against *L. amazonensis*, *L. braziliensis*, and *L. infantum chagasi* (310), NLRP3 contributes to driving host susceptibility in the case of *L. major* infection (310, 311, 313). The discrepancies observed in these studies may be multifactorial. First, the use of different *Leishmania* strains introduces species-specific differences among the studies. Second, the studies utilized different infection doses of *L. major*: specifically, one study infected C57BL/6 mice with 1×10^6 stationary-phase *L. major* promastigotes (310), whereas another infected C57BL/6 mice with 1,000 metacyclic promastigotes of *L. major* (313). Another possibility is the use of mouse strains on different genetic backgrounds: C57BL/6 mice tend to be relatively resistant to leishmaniasis compared to BALB/c mice, and the genetic background can dictate whether IL-18 drives a T_H1 or T_H2 response (314, 315). Further, *L. major* and *L. mexicana* encode a metalloprotease, GP63, which cleaves human NLRP3 at six putative sites and mouse NLRP3 at three putative sites, resulting in inhibition of the NLRP3 inflammasome (312). These virulence factors conferring evasion of the host immune surveillance might also be present in specific species or strains, suggesting that a more extensive investigation that controls for the aforementioned host and parasite factors is required to further assess the physiological role of inflammasomes in leishmaniasis.

A further study introduced an extra layer of complexity, showing that the gut microbiota of infected sand flies contributes to inflammasome signaling in *Leishmania donovani* infection (316). *L. donovani* and gut microbes induced activation of the NLRP3 inflammasome and production of IL-1β to levels higher than those induced by *L. donovani* infection alone (316). The authors suggested that the gut microbes provided a priming signal (signal 1), whereas the *L. donovani* infection provided the NLRP3 activation signal (signal 2) (316). This study therefore highlights an involvement of gut microbe-derived PAMPs in the complex interplay between inflammasome signaling and *Leishmania* infection (316).

Toxoplasma gondii

The obligate intracellular parasite *Toxoplasma gondii* is the causative agent of toxoplasmosis, which is transmitted to humans through ingestion of contaminated food, water, or dust, through vertical transmission *in utero*, and through contact with infected transplants (317, 318). *T. gondii* induces transcriptional upregulation of various inflammasome components, including NLRP1, NLRP3, NLRC4, AIM2, and NAIP, in human THP-1 macrophages (319). Genetic analysis of patients with congenital toxoplasmosis further revealed that polymorphisms in the gene encoding NLRP1 are associated with an increased risk of toxoplasmosis (320). Knockdown of NLRP1 by RNA interference in the human monocytic leukemia MonoMac6 cell line results in an increased parasitic burden in response to *T. gondii* infection (320). However, it was reported that these cells have reduced viability in response to *T. gondii* infection (320), which is unexpected given that knockdown of NLRP1 would lead to a reduced level of pyroptosis. However, it is possible that other cell death pathways, such as the pyronecrosis observed in mouse macrophages infected with *T. gondii* (321), compensate for the lack of pyroptosis. Further genetic evidence revealed that short hairpin RNA (shRNA)-mediated inhibition of ASC and caspase-1 leads to a substantial reduction in IL-1β production in primary human monocytes and THP-1 cells infected with *T. gondii* (322).

Both NLRP1b and NLRP3 have been found to provide protection against *T. gondii* infection in mice or rats (323–325); however, the activators triggering either type of inflammasome in response to *T. gondii* infection are unknown. It is thought that the granule protein GRA15, which is secreted by the parasite during invasion of monocytes, provides a priming signal for the NLRP3 inflammasome by inducing NF-κB-mediated upregulation of IL-1β (322, 326). While the NLRP3 inflammasome-activating signal has not been identified, it may be a secreted parasitic PAMP or a DAMP generated by dying neighboring cells (322). In this context, GBPs appear to have a role in releasing PAMPs from the *Toxoplasma*-containing vacuole into the cytoplasm for inflammasome sensing in certain cell types (101, 327–330). For example, GBP1 is recruited to the *T. gondii*-containing vacuole in human mesenchymal stromal cells (331) but not in human lung epithelial A549 cells (332). In addition, given that certain proteases can cleave and activate NLRP1 (61, 63, 65), future studies could investigate the protease(s) encoded by *T. gondii* that is capable of cleaving and activating NLRP1. The molecular pathway involved in NLRP3 inflammasome activation by *T. gondii* and how NLRP3 synergizes with NLRP1 to mediate the host defense against this parasite remain to be investigated.

Trypanosoma spp.

Trypanosomiasis is a parasitic disease caused by members of the *Trypanosoma* genus, which are transmitted to humans by a bite from an infected tsetse fly and infect 10 million people worldwide (333–335). The NLRP3 inflammasome confers host protection during *Trypanosoma cruzi* infection (336, 337); mice lacking NLRP3, ASC, and caspase-1 and infected with *T. cruzi* have an elevated parasite burden, mortality rate, and heart inflammation compared to those of WT mice (336, 337). Activation of the NLRP3 inflammasome in response to *T. cruzi* infection appears to be multifactorial, given that ROS production, potassium efflux, cathepsin B release, and lysosomal damage have all been implicated in NLRP3 activation in BMDMs (337, 338). Furthermore, splenocytes derived from mice lacking NLRP3 or caspase-1 exhibit defects in NO production (336), suggesting a possible interplay between the inflammasome and NO pathways in mediating host protection against *T. cruzi* infection. It is also possible that GBPs and IRGs disrupt the membrane of the trypanosome-containing vacuole and thereby release pathogens and/or PAMPs into the host cytoplasm, as has been observed for *T. gondii* (97). However, further biochemical and imaging studies are required to gain insight into the mechanisms by which *T. gondii* and/or its PAMPs are sensed by the NLRP3 inflammasome. Given the availability of mice lacking either IL-1β, IL-18, or gasdermin D, future studies can

also focus on revealing the relative contributions of IL-1β, IL-18, and pyroptosis to the host defense against *Trypanosoma* infection.

Entamoeba histolytica

Entamoeba histolytica is the causative agent of amebiasis, which affects more than 100 million people and causes 100,000 deaths worldwide every year (339). Cell surface interactions between *E. histolytica* and macrophages trigger NLRP3 inflammasome activation. Mechanistically, the *E. histolytica* surface protease EhCP5 activates macrophage $\alpha_5\beta_1$ integrin, subsequently leading to the release of ATP through the pannexin-1 channel (340). This extracellular burst of ATP opens the potassium channel P2X7R, leading to potassium efflux and activation of the NLRP3 inflammasome (341). Interestingly, activation of $\alpha_5\beta_1$ integrin has also been proposed to drive the recruitment of NLRP3 from the cytoplasm to regions of the macrophage membrane that are in association with the parasite (340); however, the significance of this recruitment has yet to be investigated fully. EhCP5 was also found to cleave and inactivate IL-1β and IL-18 (342, 343), which might be an important strategy used by the parasite to reduce inflammasome responses. In addition, *E. histolytica* produces a monocyte locomotion inhibitory factor which decreases expression of the gene encoding IL-1β in mouse macrophages (344). Further, two cysteine proteases of *E. histolytica*, EhCP1 and EhCP4, degrade immune components, including pro-IL-18, the complement component C3, and immunoglobulin G (IgG) (345, 346), contributing to the pathogenesis of *E. histolytica* infection. These studies demonstrate that *E. histolytica* encodes multiple virulence factors to counteract the effects of the inflammasome and other innate immune components, highlighting the importance of these host defense systems against *E. histolytica* infection. It would be worthwhile to investigate potential cross talk between inflammasome complexes, other innate immune components, and adaptive immune cells during infection by this pathogenic parasite.

CONCLUSIONS AND FUTURE PERSPECTIVES

Less than 2 decades into its discovery, the inflammasome has become one of the centerpieces of immunology and has continued to inspire research into pattern recognition and innate immunity. A central feature of the inflammasome is its ability to respond to pathogens and danger signals from within the host cytoplasm and to emanate a rapid inflammatory and cell death response. Inflammasomes can recognize the basic architecture and cellular composition of microbes, including nucleic acids and virulence factors, but also can recognize cellular perturbations caused by the infection process. In most cases, the inflammasome induces a protective response, either by induction of inflammation and cellular recruitment via IL-1β and IL-18 or by physical destruction or removal of the infected cell via pyroptosis. Emerging evidence suggests that gasdermin D pores can damage the bacterial cell membrane, but the role of gasdermin D in nonbacterial infections remains largely unknown. In addition, the relative contributions of gasdermin D and cytokine production to the overall inflammasome response against infectious disease has not been investigated thoroughly. This intriguing research area will be explored further with the availability of mice lacking gasdermin D, IL-1β, or IL-18.

Another important issue to address is the mechanisms by which microbial ligands are presented to inflammasome sensors. While mechanistic details have emerged describing the liberation of ligands from bacteria, how ligands from other pathogens are released remains a mystery. Further, how do inflammasomes cooperate with one another in response to pathogens that are capable of activating multiple inflammasome sensors? Recruitment of more than one inflammasome sensor to a single multimeric complex has been observed in BMDMs. Does this phenomenon also occur in a physiological setting? Furthermore, how does the inflammasome regulate other cell-autonomous and immunological processes, including the production of inflammatory lipids and antimicrobial mediators, autophagy, cell migration, and adaptive immunity? Of all inflammasome complexes, the NLRP3 inflammasome is functionally the

most versatile, in that it can respond to a plethora of microbial triggers and danger signals. Importantly, it is still unclear how NLRP3 is able to respond to such diverse stimuli or whether a unifying signal triggering activation of the NLRP3 inflammasome exists. Perhaps the compositional makeup of the NLRP3 inflammasome can differ to allow it to respond to structurally diverse activators. Finding answers to these scientific queries will require cross-disciplinary and collaborative approaches.

Uncontrolled inflammasome activity is detrimental to the host, leading to tissue damage and even death. Experimental therapies that are able to attenuate inflammasome hyperactivation have been successful in the treatment of endotoxemia and autoinflammatory disorders, suggesting that immunomodulators of the inflammasome are a versatile armamentarium that may be applied more widely in clinics. For example, inhibition of the inflammasome may be beneficial for curtailing overt inflammatory responses in sepsis that often lead to rapid lethality. In contrast, heightening the activity of the inflammasome may lead to enhanced immunity against certain infectious agents, as evidenced by the mechanistic actions of certain antiviral therapies. Further exploration of small-molecule activators and inhibitors of the inflammasome would provide new options for targeting specific inflammasomes in the treatment of diseases.

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