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INFLAMMASOME ACTIVATION AND EVASION BY BACTERIAL PATHOGENS

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Abstract

Innate immune system plays an essential role in combating infectious diseases by recognizing invading pathogens and activating host defense response. Inflammasomes complexes are a central component of the cytosolic innate immune surveillance and are vital in host defense against bacterial pathogens. Bacterial products or pathogen-induced modifications in the intracellular environment are sensed by the inflammasome receptors that form complexes that serve as a platform for caspase-1- or caspase-11-dependent induction of pyroptosis and secretion of cytokines, IL-1β and IL-18. However, several pathogenic bacteria have developed strategies to evade inflammasome activation. This review highlights the recent advances in the mechanism of inflammasome activation by bacterial pathogens and some of the bacterial evasion strategies of inflammasome activation.

Introduction

The innate immune system plays a crucial role in detecting pathogens and mounting host defense response. Germ-line encoded pattern recognition receptors (PRRs) sense pathogen associated molecular patterns (PAMPs) or damage associated molecular patterns (DAMPs) [1]. PRRs can either be membrane bound or cytosolic. The cytosolic multiprotein complexes, inflammasomes, have emerged as essential elements of innate immune defense [2]. The assembly of inflammasome complexes is initiated by a class of cytosolic receptors belonging to the nucleotide-binding domain and leucine rich repeat containing protein (NLR) family, AIM2 (absent in melanoma 2)-like receptor (ALR) family, or by a protein, pyrin. Upon sensing of pathogens or danger signals, these proteins recruit an adaptor protein ASC (apoptosis-associated speck like protein containing CARD), which links the binding of NLR/ALR/Pyrin to the proform of a protease, caspase-1 [3]. Alternatively, certain receptors could directly bind to caspase-1 [2]. Subsequently, the inflammasome complex undergoes oligomerization resulting in the autoproteolysis of caspase-1 into enzymatically active

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Declaration of interests

The authors have no competing financial interests.

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caspase-1, which cleaves proforms of the inflammatory cytokines IL-1β and IL-18 into their mature forms [3]. In addition, inflammasome associated caspases (caspase-1, caspase-11, human caspase-4/5) induce cleavage of gasdermin D (GSDMD), releasing its N-terminal fragment, which oligomerizes on the plasma membrane, resulting in pore formation and inflammatory cell death called pyroptosis (Figure 1) [4–7]. Inflammasome activation also requires an upstream 'first signal' that is initiated by recognition of ligands by toll-like receptors (TLRs) and the subsequent NF-κB- or IRF3-dependent transcription of certain inflammasome components and pro-IL-1β, and the sensor caspase-11, respectively [2].

The major inflammasome pathways involved in sensing bacterial infections include, NLRP1b, NLRP3, caspase-11/4, NLRC4, AIM2, Pyrin, and NLRP6 [8]. A wide range of bacterial products induce the formation of these inflammasome complexes and the downstream signaling cascades. However, it has also been well-established that numerous bacterial pathogens have developed strategies to evade inflammasome activation. This review highlights the inflammasome pathways that are activated by bacterial pathogens, the underlying mechanisms of activation, and the inflammasome evasion strategies employed by pathogenic bacteria.

NLRP1b inflammasome

NLRP1 is the first NLR protein reported to form an inflammasome complex [9]. Unlike other NLRs, NLRP1 is characterized by its distinct domain structure with a C-terminal function-to-find (FIIND) domain followed by a CARD domain (Figure 1) [10]. Humans only have one NLRP1 protein whereas mice have three paralogs of NLRP1 (NLRP1a-c) [9,11]. Among these, mouse NLRP1b is the most well characterized and is known to be activated by the lethal factor of anthrax toxin and by IpaH7.8, an E3 ubiquitin ligase effector secreted by *Shigella flexneri* [10]. Although the molecular mechanism of NLRP1b inflammasome activation remained unclear, multiple studies have now provided crucial insights into this [10,12–17]. During unstimulated conditions, the NLRP1b FIIND domain undergoes a constitutive autoproteolysis resulting in the generation of two polypeptides. Interestingly, these N-terminal and C-terminal peptides remain bound by a noncovalent interaction [10,17]. When cells are exposed to anthrax lethal toxin, the protective antigen enables translocation of lethal factor into the host cell cytoplasm. The enzymatically active lethal factor cleaves the N-terminal fragment of NLRP1b leading to its ubiquitination and proteasomal degradation resulting in the release of the C-terminal fragment. The CARD domain of C-terminal fragment then recruits caspase-1 and assembles into an inflammasome complex (Figure 1). Similarly, *Shigella* ligase, IpaH7.8, directly ubiquitinates NLRP1b, leading to the proteasomal degradation of N-terminal fragment and subsequent C-terminal-mediated inflammasome complex formation (Figure 1) [10,17]. These observations demonstrated that cleavage and functional degradation of N-terminal fragment is an essential initiating step in NLRP1b inflammasome activation. Notably, mice carrying a cleavage-resistant variant of NLRP1b fail to sense *B. anthracis* infection and are highly susceptible to the pathogen [18,19]. *Listeria monocytogenes* have also been reported to activate NLRP1 through metabolic stress but the exact mechanism is unknown [20].

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Canonical NLRP3 inflammasome

NLRP3 is the best-studied inflammasome and is activated by a broad range of triggers [9]. NLRP3 is not known to interact with these ligands directly, instead these stimuli induce certain downstream cellular perturbations such as the efflux of potassium ions (K^+), generation of mitochondrial reactive oxygen species (ROS), release of mitochondrial DNA into the cytosol, and cathepsin release due to lysosomal disruption that trigger the NLRP3 activation [8,21]. Additionally, certain NLRP3 activators trigger disassembly of the trans-Golgi network [22]. This dispersed trans-Golgi network interacts with the polybasic region of NLRP3 via its phosphatidylinositol-4-phosphate (PtdIns4P) and facilitates NLRP3 activation by serving as a platform for NLRP3 aggregation (Figure 1) [22]. Notably, interaction with a kinase, NIMA-related kinase 7 (NEK7), is also required for NLRP3 activation [23,24]. NLRP3 bound NEK7 interacts with a neighboring NLRP3 to mediate NLRP3 oligomerization (Figure 1) [25]. Several Gram-positive bacterial pathogens such as *Streptococcus pyogenes, Staphylococcus aureus,* and *Listeria monocytogenes* activate the NLRP3 inflammasome via pore-forming toxins such as streptolysin O, hemolysins, listeriolysin O, and pneumolysin [26]. ADP-ribosylating and vacuolating toxin of *Mycoplasma pneumoniae* mediates NLRP3 inflammasome activation by direct ADP-ribosylation of NLRP3 [27]. Interestingly, Yersinia type III secretion system effector protein, YopJ, activates NLRP3 via a novel mechanism; YopJ inhibits TAK1, which leads to a caspase-8-dependent cleavage of GSDMD and subsequent K^+ efflux-mediated NLRP3 activation (Figure 1) [28]. Additionally, purified bacterial RNA and bacterial RNA:DNA hybrids have been shown to trigger NLRP3 activation [29,30]. The NLRP3 inflammasome is crucial for protection against multiple bacterial infections. For example, mice lacking NLRP3 exhibit higher bacterial loads and increased mortality upon infection with *Streptococcus pneumonia* [31]. Similarly, Nlrp3$^{-/-}$ mice infected with *M. pneumoniae* fail to produce IL-1β and exhibit delayed bacterial clearance [32]. In contrast, NLRP3 inflammasome has a detrimental role during infection with *B. cereus* in vivo [26]. Nlrp3$^{-/-}$ mice and mice administered with pharmacological inhibitor of NLRP3 are protected from *B. cereus* induced lethality [26].

Noncanonical NLRP3 inflammasome or the cytosolic LPS sensing pathway

The non-canonical inflammasome, also known as the cytosolic LPS sensing pathway, is activated primarily by Gram-negative bacteria such as *Escherichia coli, Shigella flexneri, Citrobacter rodentium, Vibrio* cholerae, and *Burkholderia thailandensis* [33]. Unlike the canonical inflammasome pathways, the activation of the cytosolic LPS sensing pathway is mediated by a set of inflammatory caspases; caspase-11 in mice and caspase-4 or 5 in humans [34–37]. Caspase-11/4/5 directly binds to the lipid A moiety of cytosolic LPS via its CARD domain resulting in the self-oligomerization of these caspases [34]. This leads to a site-specific cleavage of caspase-11/4/5 generating an enzymatically active p10 form of the corresponding caspase [38]. The p10 fragment binds to the C-terminal domain of GSDMD with high affinity via an exosite mediated interaction, which results in a tetrapeptide-independent GSDMD cleavage, generation of N-terminal GSDMD fragment, and pyroptosis (Figure 1) [38]. Additionally, the formation of plasma membrane pores by N-terminal GSDMD leads to K^+ efflux-mediated activation of NLRP3 inflammasome and subsequent secretion of IL-1 cytokines [39].

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Several mechanisms have been described for cytosolic access of LPS, which is an important pre-requisite for caspase-11 activation. In the case of cytosolic bacteria and bacteria residing in the phagosomal vacuoles, members of the guanylate-binding protein (GBP) and immunity related GTPase (IRG) family such as IRGB10 enable the release of LPS [40–42]. Recent studies have shown that GBP1 functions as a cytosolic PRR that binds to LPS on the surface of cytosol-invading pathogens such as *Salmonella* and *Shigella*. Upon sensing of LPS, GBP1 initiates the assembly of a GBP2–4 platform on the bacterial surface, which recruits caspase-4 leading to its activation (Figure 1) [43–45]. On the other hand, during infections with extracellular bacteria, LPS delivery into the cytosol is mediated by outer membrane vesicles (OMVs) secreted by the bacteria. OMVs enter the cells via clathrin-mediated endocytosis and LPS is released into the cytosol from early endosome (Figure 1) [46]. Other proteins such as HMGB1 and SCGB3A2 have also been implicated in LPS delivery into the cytosol. Upon sensing of extracellular LPS by TLR4, hepatocytes release HMGB1, which directly binds to LPS and facilitates LPS entry into the cells via RAGE-receptor mediated endocytosis [47]. HMGB1 then permeabilizes the endosomal membrane leading to the release of LPS into cytoplasm [47].

The cytosolic LPS sensing pathway has been demonstrated to have a protective or detrimental role depending on the type of bacterial infection. Mice deficient in caspase-11 are highly susceptible to *Burkholderia thailandensis* or *B. pseudomallei* and display high bacterial burdens [48]. Caspase-11 is also required for effective bacterial clearance in lungs during *Acinetobacter baumannii* or *Klebsiella pneumoniae* infection, in intestine during *Salmonella* Typhimurium infection, in kidney during uropathogenic *Escherichia coli* (UPEC) infection, and in spleen during *Brucella abortus* infection [49–52]. In contrast to these, cytosolic LPS sensing by caspase-11 plays a detrimental role during sepsis. Here, the inflammasome responses go unchecked resulting in tissue damage and lethality in host [53,54]. Caspase-11 mediated cleavage of GSDMD and the resulting pyropotosis appears to be the primary mediator of sepsis pathogenesis. Consistent with this, mice deficient in caspase-11 or GSDMD are protected from sepsis induced by high dose LPS as well as cecal ligation and puncture [5,37].

NLRC4 inflammasome

The NLRC4 inflammasome detects bacterial pathogens like *S. flexneri, Salmonella* Typhimurium, *Pseudomonas aeruginosa, L. pnuemophila* and is triggered by flagellin and type III (T3SS) and IV (T4SS) secretion system components that enter the cytosol [55]. Interestingly, NLRC4 does not bind to the ligands directly, instead members of another NLR family of proteins namely neuronal apoptosis inhibitory proteins (NAIPs) act as sensors of the ligands and directly bind to them. NAIP-ligand binding is followed by NAIP-NLRC4 interaction which further leads to inflammasome assembly [55]. Phosphorylation of NLRC4 by protein kinase Cδ and/or leucine rich repeat-containing kinase-2 (LRRK2) at S533 residue is critical for its activation [56]. There are seven NAIP genes in mice whereas humans have a single NAIP gene encoding two functional isoforms [57]. Murine NAIP1 recognizes T3SS needle proteins whereas NAIP2 interacts with T3SS basal rod proteins. NAIP5 and 6 recognize flagellin [57] . Some bacteria like *L. monocytogenes* escape the pathogen-containing vacuole, in order to invade the cytoplasm and replicate, thereby directly

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introducing flagellin into the cytoplasm. On the other hand, in the case of bacteria that remain in a pathogen-containing vacuole such as *S.* Typhimurium, flagellin is injected into the cytoplasm via T3SS or T4SS apparatus [57]. One isoform of human NAIP binds to the T3SS needle subunit of *Chromobacterium violaceum* whereas the other isoform of recognizes flagellin and T3SS inner rod and needle proteins of *S.* Typhimurium, *S. flexneri*, and *Burkholderia* spp., resulting in NLRC4 inflammasome activation in macrophages [57]. NLRC4 inflammasome plays a crucial role in host defense against many bacterial pathogens. NLRC4-deficient mice exhibit increased susceptibility to oral infection with *Salmonella* Typhimurium [58]. Similarly, NLRC4 deficient mice also succumb to oral infection with *Citrobacter rodentium* and intratracheal infection with *K. pneumoniae* [55,59,60].

AIM2 inflammasome

AIM2 inflammasome detects double-stranded DNA (dsDNA) from intracellular pathogens like *Francisella tularensis, F.novicida,* and *L. monocytogenes* [9]. AIM2 directly binds to DNA via its HIN-200 DNA binding domain and induces caspase-1 activation in an ASC-dependent manner [9]. The mechanism by which the bacterial DNA is released into the cytoplasm of the host cells has been well studied in *F. novicida* infection. Shortly after phagocytosis by the host cell, *F. novicida* escape the pathogen containing vacuole utilizing its T6SS and invade the cytoplasm. Subsequently, the GBPs, GBP2, GBP5 and the interferon-inducible protein, IRGB10, bind to the cytosolic bacteria and promote bacterial lysis and DNA release into the cytoplasm [42]. The expression of GBPs and IRGB10 are controlled by type I interferon signaling cascade. Cytosolic dsDNA is also recognized by cGAS (cyclic GMP-AMP synthase), which in turn triggers STING-dependent activation of type I IFNs. Notably, AIM2-mediated cleavage of GSDMD and the resulting K^+ efflux suppresses this cGAS-mediated type I IFN activation during *Francisella* infection [61]. AIM2-deficient mice are highly susceptible to *Francisella* and *Mycobacterium tuberculosis* infection [42,61,62]. GBP and IRGB10 deficient mice are also highly susceptible to *Francisella* infection suggesting that they are critical for the protective role of AIM2 [42].

Pyrin inflammasome

Pyrin is a non-NLR inflammasome protein encoded by *MEFV* gene which has been associated with familial Mediterranean fever [63]. Pyrin does not directly bind to PAMPs but is activated in response to modifications of host proteins, Rho GTPases, by bacterial toxins and effector proteins [63]. During homeostatic conditions, GTPase, RhoA, activates the serine-threonine protein kinases, PKN1 and PKN2, that bind and phosphorylate pyrin at Ser208 and Ser242. This phosphorylated pyrin interacts with chaperone proteins 14–3-3ε and 14–3-3τ and remains in an inactive state [64]. Several bacterial proteins like TcdA/B of *Clostridium difficile*, C3 toxin of *C. botulinum*, TecA of *Burkholderia cenocepacia,* VopS of *Vibrio parahaemolyticus*, YopE and YopT of *Yersinia,* and pertussis toxin from *Bordetella pertussis* modify RhoA and prevent pyrin phosphorylation, thereby promoting pyrin inflammasome activation [63,65,66]. Pyrin has a host protective role in certain bacterial infections; it has been shown that TecA-mediated pyrin activation decreases bacterial loads and virulence of *B. cenocepacia* during systemic infection in mice [65].

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NLRP6 inflammasome

NLRP6 is a relatively new member of the NLR family involved in inflammasome activation. NLRP6 is highly expressed in the intestine and plays a crucial role in maintaining intestinal homeostasis by regulating the composition of microbiome [8]. A recent study identified lipoteichoic acid (LTA) from Gram-positive bacteria, *L. monocytogenes,* as a ligand for NLRP6. Binding of LTA to NLRP6 induced caspase-11 activation leading to processing of caspase-1 and IL-18 secretion (Figure 1) [67]. Interestingly, Nlrp6$^{-/-}$ mice upon *Listeria* infection, show reduced bacterial burdens and better survival, thus suggesting a detrimental role for NLRP6 in bacterial infection. Similarly, NLRP6 also acts as a negative regulator of host defense in mice infected with *Staphylococcus aureus,* or *S.* Typhimurium [68,69]. On the other hand, NLRP6 plays a protective role in murine model of *Citrobacter*-induced enteritis indicating that the role of NLRP6 vary depending on the type of bacterial infection [70].

Inflammasome evasion by bacterial pathogens

The mechanisms by which the pathogens evade inflammasome defense mechanisms can be broadly categorized into two strategies: a) escaping inflammasome sensing by modifying or suppressing the expression of ligands and b) active suppression of inflammasomes using inhibitory proteins. Pathogens can alter the structure of an inflammasome-activating ligand. *Heliobacter pylori, Yersinia pestis,* and *F. novicida* modify their LPS into a tetra-acylated form to avoid detection by both TLR4 and caspase-11 [71]. Another strategy adapted by pathogens is to minimize the expression of inflammasome ligand. For example, during gastrointestinal infection, *Salmonella* expresses high levels of flagellin and rod protein PrgJ, which are sensed by NLRC4, whereas during intracellular replication during a systemic infection, the expression of flagellin is suppressed and rod protein SsaI is expressed, which is not detected by NLRC4 [72,73]. When *Salmonella* are manipulated to maintain flagellin expression during systemic infection, it resulted in an effective NLRC4-dependent bacterial clearance. This explains why *Nlrc4*$^{-/-}$ mice exhibit increased susceptibility to infection with *Salmonella* introduced orally but not intraperitoneally [72].

Numerous Gram-negative bacterial pathogens are equipped with special secretion systems such as the T3SS that resemble a syringe that deliver bacterial effector proteins across the cell membrane into the cytosol. Many of these effectors efficiently interfere with inflammasome activation (Figure 2). A well-studied example is *Yersinia spp.* (*Y. pestis, Y. enterocolitica, Y. pseudotuberculosis)* T3SS effector proteins known as Yops (Yersinia outer proteins). YopM protein of *Yersinia* directly binds to caspase-1 and prevents its interaction with ASC [74]. YopM also inhibits activation of pyrin inflammasome by binding to host kinases, PRK1 and PRK2 [75,76] (Figure 2). Another effector YopK interacts with the T3SS translocon and blocks the leakage of flagellin or PAMPs into the host cell cytoplasm, thus evading NLRP3 and NLRC4 inflammasome activation [77]. *P. aeruginosa* secretes T3SS effector exoenzymes, ExoU and ExoS, that interfere with NLRC4 inflammasome activation [78]. The intracellular pathogenic bacterium *Edwardsiella tarda* inhibits NLRP3 inflammasome via a type VI secretion system effector EvpP. EvpP blocks elevated intracellular Ca^{2+}-mediated Jnk activation, which is essential for ASC phosphorylation and subsequent oligomerization [79]. An effector protein, OspC3, from *Shigella* binds to p19

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subunit of caspase-4 and interferes with caspase-4 p19/p10 heterodimerization and activation to delay epithelial cell death and promote infection [80]. *Legionella pneumophila* T4SS effector SdhA stabilizes the *Legionella*-containing vacuole membrane, prevents the release of bacterial DNA into the cytosol, and thereby blocks AIM2 inflammasome activation [81]. Similarly, *Salmonella* T3SS effector SifA maintains the stability of pathogen-containing vacuole to prevent the activation of caspase-11 [48]. T4SS effector IcaA of *Coxiella burnetii* hampers the interaction between LPS and caspase-11 and inhibits the activation of the cytosolic LPS sensing pathway [82]. Overall, it is becoming increasingly clear that bacterial pathogens have developed a diverse range of strategies to interfere with inflammasome activation.

Conclusions

Over the recent years, much progress has been made towards understanding the mechanisms of inflammasome activation by bacterial pathogens and their components and how this activation shapes up the host defense against these pathogens. Yet, detailed elucidation of molecular mechanism of inflammasome activation in some cases needs to be identified. We have highlighted a few of examples of how the bacterial pathogens counteract and escape the inflammasome activation. Further studies on how various bacterial pathogens subvert inflammasome activation is required. Similarly, studies that focus on the host regulatory mechanisms that keep inflammasome responses under control are limited. Uncovering the mechanisms of inflammasome regulation may lead to development of therapeutics for the treatment of diseases causes by unchecked inflammasome responses such as sepsis.

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Highlights

- Functional degradation is an essential step in NLRP1b inflammasome activation.
- Site-specific cleavage of caspase-11/4/5 generates an enzymatically active fragment that cleaves gasdermin D.
- Lipoteichoic acid of *Listeria monocytogenes* activates the NLRP6 inflammasome.
- Bacterial pathogens employ secretion system effectors to evade inflammasome activation.

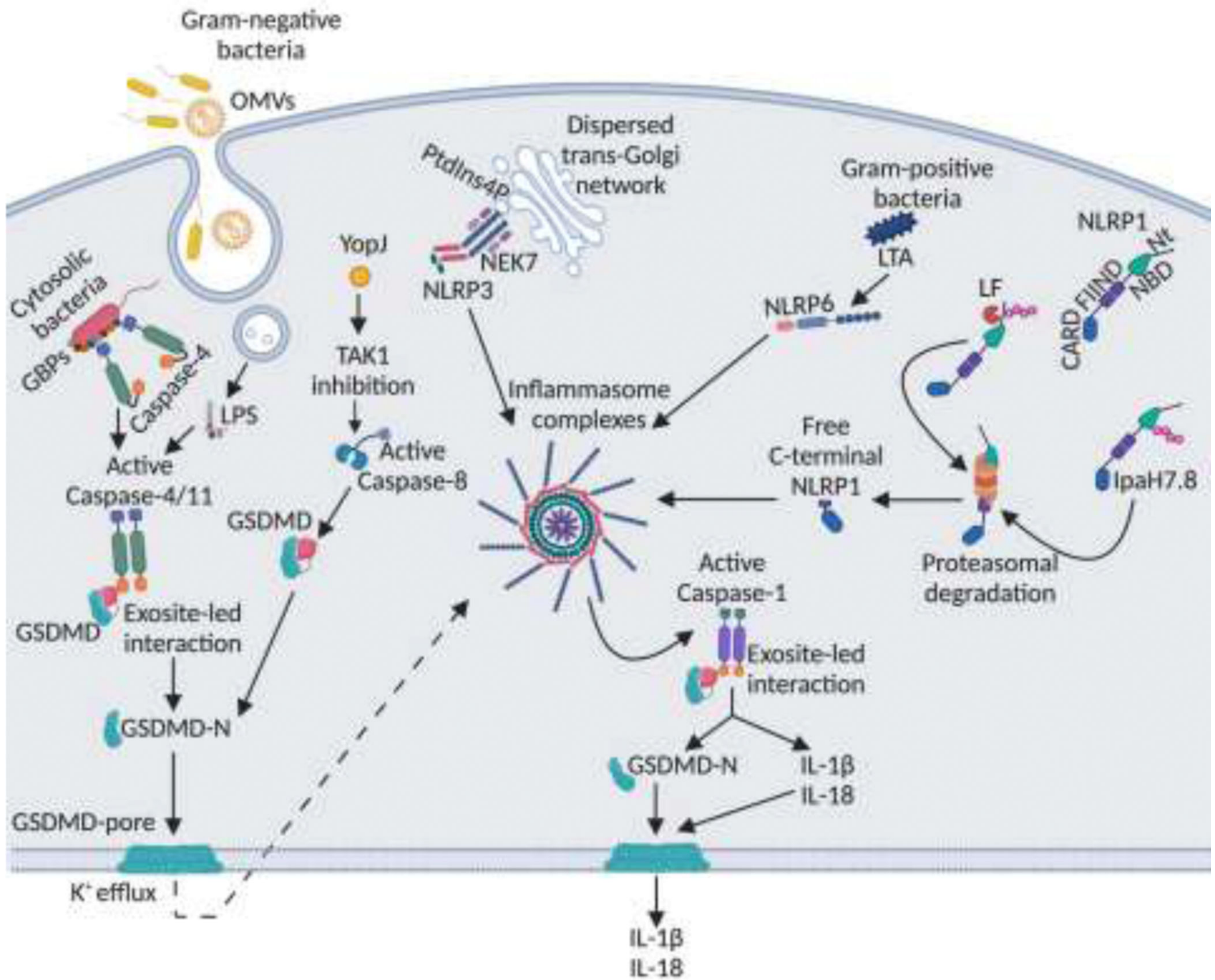

Figure 1. Recent advances in the mechanisms of inflammasome activation by bacterial pathogens.

LPS from Gram-negative bacteria enters the cytosol from OMV-containing endosomes or directly from cytosolic bacteria. GBPs coat cytosolic bacteria and serve as a platform for caspase-4 recruitment and activation. Active caspase-4/11 interacts with the C-terminus of GSDMD in an exosite-dependent manner leading to GSDMD cleavage into N-terminal fragment, which forms pores on the plasma membrane resulting in pyroptosis. K^+ efflux via GSDMD pores leads to NLRP3 activation. YopJ protein of *Yersinia* inhibits TAK1 leading to activation of caspase-8, which cleaves GSDMD leading to pyroptosis and NLRP3 activation. Certain NLRP3 activators trigger disassembly of trans-Golgi network exposing PtdIns4P, which recruits NLRP3 leading to its aggregation and activation. NEK7 also aids in the NLRP3 oligomerization. Lipoteichoic acid (LTA) of Gram-positive bacteria binds to NLRP6 leading to inflammasome activation. The FIIND domain of NLRP1 undergoes constitutive autoproteolysis during unstimulated conditions, however, the resulting C- and N-terminal polypeptides remain bound together. Anthrax lethal factor (LF) cleaves the N-terminal

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peptide leading to its ubiquitination. *Shigella* IpaH7.8 directly ubiquitinates the N-terminal peptide. Ubiquitinated N-terminal peptide undergoes proteasomal degradation releasing a free NLRP1 C-terminal fragment, which assembles into an inflammasome complex. Once the inflammasome complex is assembled, procaspase-1 is cleaved into active caspase-1, which cleaves pro-forms of IL-1 cytokines into their active forms. Active caspase-1 also interacts with the C-terminus of GSDMD in an exosite-dependent manner leading to GSDMD cleavage, pyroptosis, and release of IL-1 cytokines via GSDMD pores.

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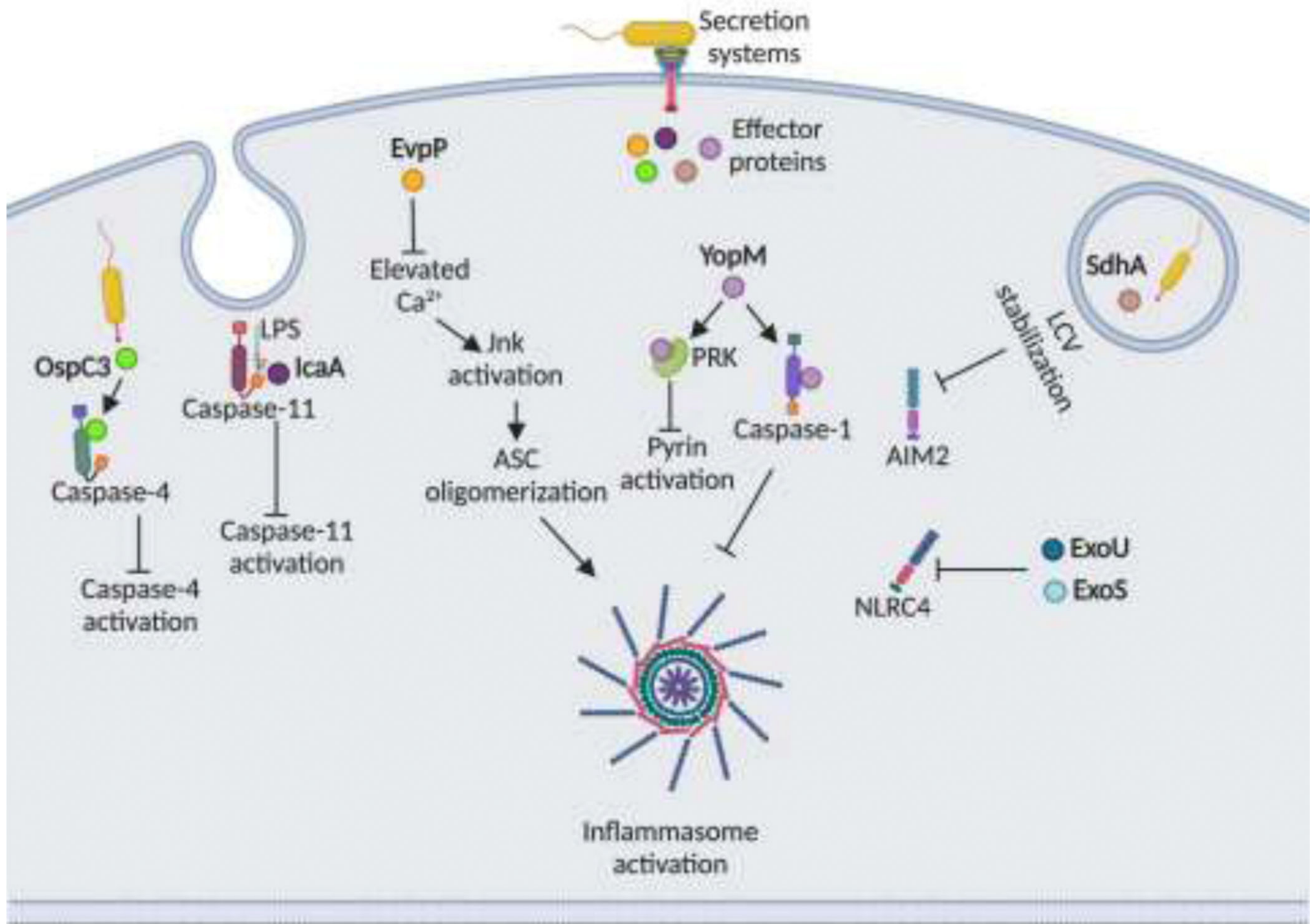

Figure 2. Inflammasome inhibition by effector proteins of bacterial secretion systems.
Effectors of T3SS/T4SS suppress inflammasome activation by varying mechanisms. OspC3 of *Shigella* binds to the p19 subunit of caspase-4 and inhibits its interaction with p10 subunit thereby suppressing caspase-4 activation. IcaA of *C. burnetti* interferes with LPS-caspase-11 interaction to inhibit caspase-11 activation. EvpP of *E. tarda* blocks elevation of intracellular Ca^{2+} levels, which is required for JnK activation and ASC oligomerization. *Yersinia* YopM protein directly binds to caspase-1 and prevents caspase-1-ASC interaction. YopM also inhibits pyrin inflammasome by binding to host PRK kinases, which are required for pyrin activation. SdhA of *L. pneumophila* maintains the integrity of *Legionella*-containing vacuole (LCV) to block the escape of dsDNA into the cytosol and subsequent AIM2 activation. ExoU and ExoS exoenzymes of *P. aeruginosa* inhibits NLRC4 inflammasome activation.