The intricate interactions between inflammasomes and bacterial pathogens: Roles, mechanisms, and therapeutic potentials

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ABSTRACT

Inflammasomes are intracellular multiprotein complexes that consist of a sensor, an adaptor, and a caspase enzyme to cleave interleukin (IL)-1β and IL-18 into their mature forms. In addition, caspase-1 and -11 activation results in the cleavage of gasdermin D to form pores, thereby inducing pyroptosis. Activation of the inflammasome and pyroptosis promotes host defense against pathogens, whereas dysregulation of the inflammasome can result in various pathologies. Inflammasomes exhibit versatile microbial signal detection, directly or indirectly, through cellular processes, such as ion fluctuations, reactive oxygen species generation, and the disruption of intracellular organelle function; however, bacteria have adaptive strategies to manipulate the inflammasome by altering microbe-associated molecular patterns, intercepting innate pathways with secreted effectors, and attenuating inflammatory and cell death responses. In this review, we summarize recent advances in the diverse roles of the inflammasome during bacterial infections and discuss how bacteria exploit inflammasome pathways to establish infections or persistence. In addition, we highlight the therapeutic potential of harnessing bacterial immune subversion strategies against acute and chronic bacterial infections. A more comprehensive understanding of the significance of inflammasomes in immunity and their intricate roles in the battle between bacterial pathogens and hosts will lead to the development of innovative strategies to address emerging threats posed by the expansion of drug-resistant bacterial infections.

Contents

1. Introduction

Bacterial infections are a significant threat to human health, despite continuing efforts to develop new antibiotics. Issues related to the increase of drug-resistant bacteria underscores the need to identify new therapeutic approaches based on a deeper understanding of the intricate immune defense mechanisms against intracellular bacterial pathogens (Antimicrobial Resistance, 2022; Collaborators, 2022; Jernigan et al., 2020). A promising direction for developing new therapies to overcome antibiotic resistance involves gaining a deeper understanding of the host immune defense against pathogens. Among the array of innate immune defense systems, inflammasomes are important players in orchestrating host defense and inflammation during bacterial infections.

The inflammasome, an innate arsenal during infection, is a cytoplasmic protein complex consisting of a sensor, an adaptor, and a caspase (Mariathasan et al., 2004; Martinon, Burns, & Tschopp, 2002). The recognition of endogenous and microbial stimuli is facilitated by both nucleotide-binding oligomerization domain-like receptors (NLRPs) and nucleotide-binding oligomerization domain-like receptor C proteins (NLRCs) (Allen et al., 2009; Broz et al., 2010; Matico et al., 2024; Rauch et al., 2017; Tenthorey, Kofoed, Daugherty, Malik, & Vance, 2014; Wang et al., 2016; Zhou, Yazdi, Menu, & Tschopp, 2011). The NLRP3 inflammasome, one of the best characterized inflammasomes, undergoes a two-step activation process: Signal 1 for "priming" and Signal 2 for "assembly and activation". Signal 2 of the NLRP3 inflammasome requires a variety of stimuli, including potassium ion (K^+) efflux, lysosomal destabilization, and mitochondrial dysfunction (Gross et al., 2016; Lin et al., 2023; Ouyang et al., 2013). A growing body of research has uncovered the complex molecular processes controlling the transcriptional and post-translational priming of the NLRP3 inflammasome (Bertheloot, Latz, & Franklin, 2021; Burgener et al., 2019; Kayagaki et al., 2015; Shi et al., 2015). Given the key function of the NLRP3 inflammasome in pyroptotic cell death, it represents a valuable target for developing therapeutics against bacterial infections by disrupting infectious niches. This review provides a comprehensive discussion on the mechanisms of its activation or suppression by bacterial pathogens and their effectors, while also highlighting the existing knowledge gap in understanding the regulatory mechanisms of the NLRP3 inflammasome and its potential application to therapeutics for bacterial infections.

Other inflammasomes, including NLRP1, NLRP6, NLRP7, NLRC4, and absent in melanoma 2 (AIM2) (Khare et al., 2012; Lee et al., 2021; Mukherjee et al., 2020; Tran et al., 2023; Zhao et al., 2011), have various roles during bacterial infections. Advances in understanding these complex mechanisms include the initiation and enhancement of the inflammasome and pyroptotic activation during infection. In this review, we highlight the complexity and diversity of inflammasome responses across different bacterial infections, aiming to broaden the scope of inflammasome research beyond the NLRP3 inflammasome. This approach

underscores the intricate interplay between bacterial pathogens and the host inflammasome machineries, which may play distinct or overlapping roles in detecting and responding to bacterial threats. In addition, various bacteria and their effectors can also trigger or suppress the inflammasomes and pyroptosis pathways (Beckwith et al., 2020; Deng et al., 2022; Li et al., 2021; Xiong et al., 2022). The dysregulated activation of inflammasomes attenuates host cell death and pathological inflammation during bacterial infections (Li, Liu, et al., 2021; Tourlomousis et al., 2020; Yang et al., 2021). Additionally, we provided insight into artificial or natural substances that have the ability to alter the activity of inflammasomes as possible treatments for bacterial infections.

In this review, we summarize recent advances regarding the roles and mechanisms underlying inflammasome activation during bacterial infections. We also discuss the strategies used by bacteria to subvert or activate inflammasomes for their benefit during the battle between host and pathogen. In addition, we explore natural or synthesized substances that might influence inflammasome activity as future antibacterial therapies. These insights might pave the way for new strategies based on elucidating the regulation of NLRP3-mediated inflammatory responses and the modulation of pyroptosis to remove infected cells, presenting a potentially effective host-directed strategy to combat intracellular bacterial infections.

2. Overview of inflammasome and pyroptosis

2.1. Canonical, noncanonical, and alternative inflammasome

There are three types of inflammasome pathways: the canonical, noncanonical, and alternative pathways, based on the mechanisms. The major sensors of the canonical inflammasome complex are the nucleotide oligomerization domain (NOD)-like receptors (NLRs), including NLRP1, NLRP3, NLRC4, and HIN-200 protein AIM2. In addition, NLRP2, NLRP6, NLRP7, NLRP11, NLRP12, and interferon gamma inducible protein 16 have been identified (Salami, Bettadapura, & Wang, 2023). The adaptor is an apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC) that links NLRP1, NLRP3, AIM2, and Pyrin, to pro-caspase-1, which is activated to cleave and release mature forms of IL-1β and IL-18 (Salami et al., 2023). The appropriate production of both IL-1β and IL-18 are important for boosting host protection during infections. These cytokines are essential for the production of interferon-γ (IFN-γ), which functions in the T helper (Th)1 immune responses and activates macrophages infected with intracellular bacteria (Landy, Carol, Ring, & Canna, 2024; Mayer-Barber & Yan, 2017).

During noncanonical inflammasome activation, cytosolic lipopolysaccharide (LPS) is recognized by human caspase-4/5 and murine caspase-11. Guanylate-binding proteins (GBPs), including GBP1–4, are crucial for assembly of the protein platforms on the surface of bacteria and recruiting human caspase-4 (murine caspase-11)

for antibacterial host defense (Wandel et al., 2020). These actions subsequently trigger the cleavage of gasdermin D (GSDMD) to release GSDMD-N and induce pyroptosis of host cells (Feng et al., 2022). In particular, GBP1 or GBP2 can enhance LPS-induced caspase-4 activation to further activate the noncanonical inflammasome in host cells during Gram-negative bacterial infections (Dickinson et al., 2023). Another study revealed that noncanonical NLRP3 inflammasome assembly and activation depends on the bacterial viability and are mediated through the recognition of both bacterial mRNA and LPS (Moretti et al., 2022). In this setting, LPS binding to pro-caspase-11 augments bacterial mRNA-mediated NLRP3 inflammasome activation, which is required for the activation of LPS-bound pro-caspase-11, suggesting interdependent activating mechanisms (Moretti et al., 2022). Moreover, the orphan nuclear receptor Nur77 can bind to cytoplasmic LPS and NLRP3, thereby activating the noncanonical NLRP3 inflammasome. Nur77-deficient mice exhibit a significantly reduced host response to LPS (Zhu et al., 2023).

An alternative inflammasome pathway requires only one stimulus, rather than the two signals typically associated with inflammasome activation. Interestingly, an alternative NLRP3 inflammasome has been observed in human monocytes, but not in murine monocytes (Gaidt et al., 2016). Yuhui et al. showed that alternative NLRP3 inflammasome activation triggered by heat-killed Gram-negative bacteria is regulated by cellular FADD-like IL-1β-converting enzyme-inhibitory protein, which are also regulated by nuclear factor-κB (NF-κB) signaling, in human primary monocytes (Gao et al., 2023). In particular, toll-like receptor (TLR)4- TIR domain-containing adapter molecule (TRIF)-receptor-interacting serine/threonine-protein kinase 1 (RIPK1)-Fas-associated death domain-CASP8 signaling triggers the caspase-8-dependent activation of the NLRP3 inflammasome (Gaidt et al., 2016); however, the alternative pathway is unique in terms of inflammasome activation, as it operates independently of K⁺ efflux, GSDMD, and cell death (Gaidt et al., 2016).

Figs. 1 and 2 show an overview of our current understanding of the canonical, noncanonical, and alternative inflammasome pathways; however, the detailed mechanisms and interconnected pathways are beyond the scope of this review. In the following section, we focus solely
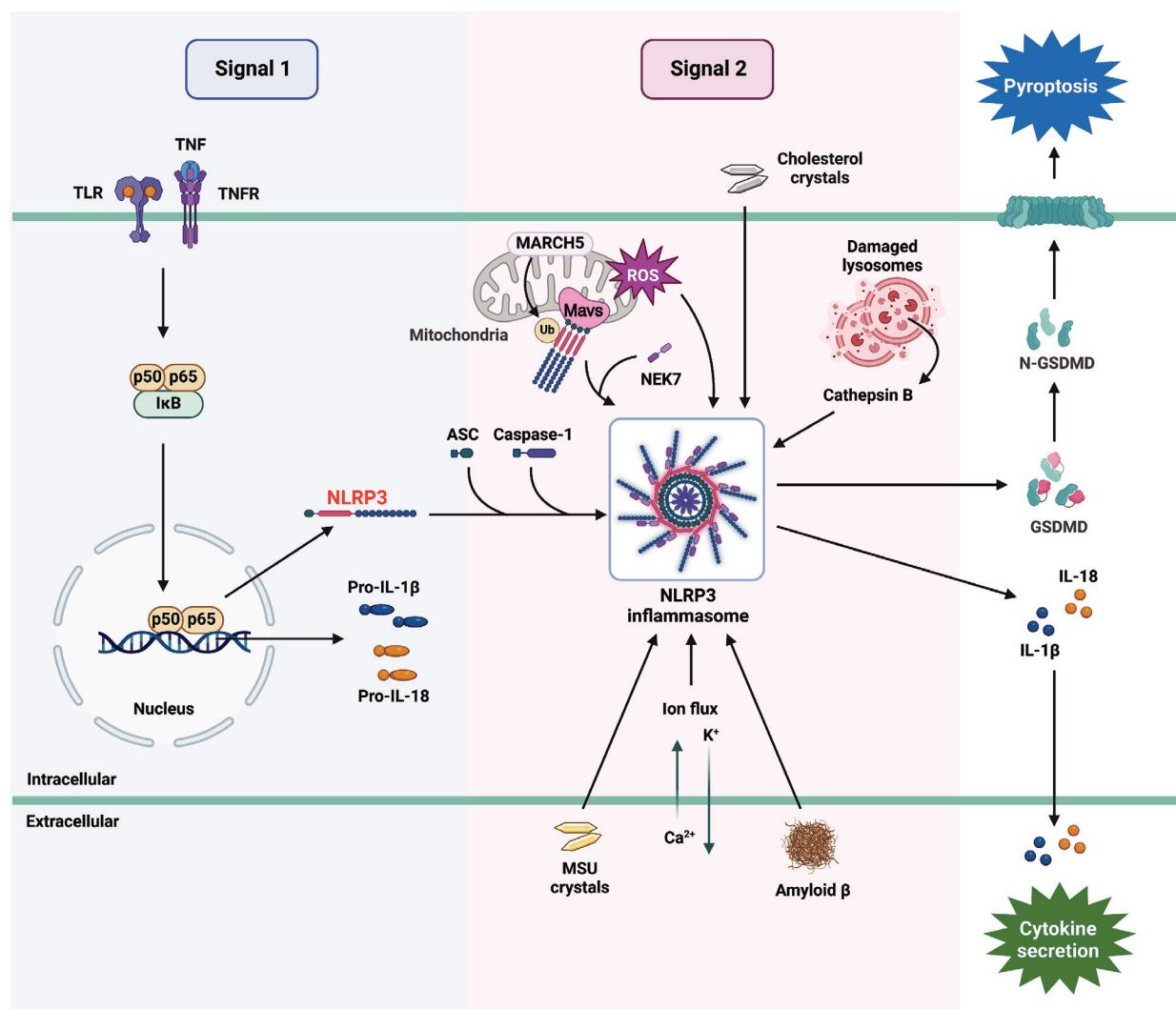
Fig. 1. Overview of NLRP3 inflammasome activation.
To activate NLRP3 inflammasome, both signal 1 and signal 2 are required. Signal 1 involves the activation of NF-κB via cytokines such as TNF or TLR signaling pathways, leading to increased transcription of NLRP3, pro-IL-1β, and pro-IL-18. Signal 2 is a signal necessary for the assembly of the NLRP3 inflammasome complex. Numerous stimuli (mitochondrial ROS, cholesterol crystals, MSU crystals, amyloid β, ion flux, and cathepsin B from damaged lysosomes) provide the signal 2 of the NLRP3 inflammasome activation. MARCH5, an E3 ligase of mitochondria, polyubiquitinates NLRP3, inducing NLRP3 inflammasome activation. Figure created with BioRender.com.
MSU, monosodium urate; ROS, reactive oxygen species; TLR, toll-like receptor; TNFR, tumor necrosis factor receptor; Ub, ubiquitin.
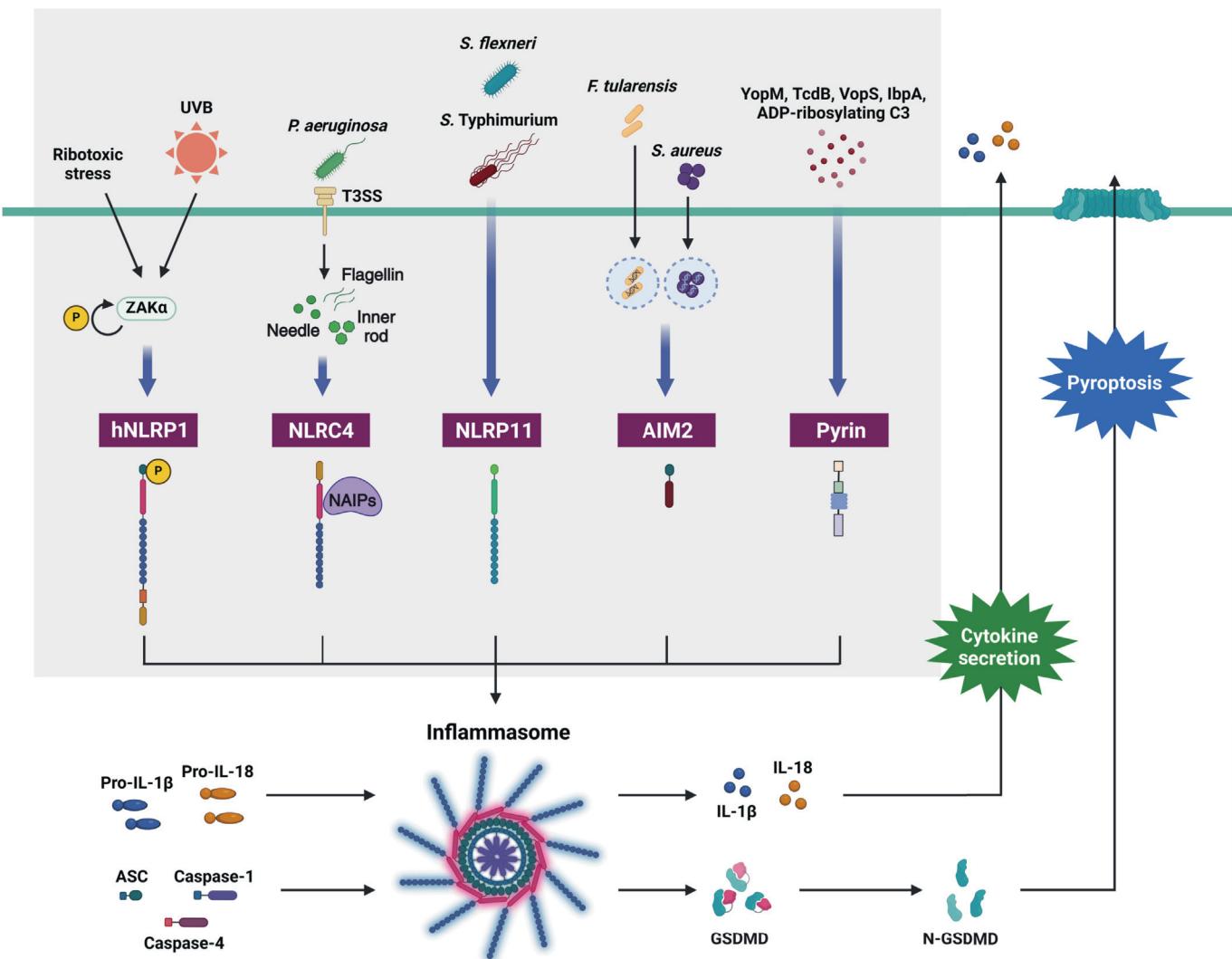
Fig. 2. Inflammasomes activation during infection.
UVB and ribotoxic stress excessively phosphorylate NLRP1 to activate inflammasome. NLRP11 activates the inflammasome via caspase-4 during infections with Gram-negative bacteria such as *S.* Typhimurium and *S. flexneri*. AIM2 binds to bacterial DNA to activate the inflammasome, while NLRC4 forms oligomerization with NAIP proteins that sense pathogens. The pyrin inflammasome is activated in response to various bacterial toxins (YopM, TcdB, VopS, IbpA, and ADP-riboxylating C3). These various inflammasome activations trigger pyroptosis and induce cytokine secretion. Figure created with BioRender.com.
UVB, ultraviolet B.

on the major innate receptors involved in the activation of inflammasomes in the context of bacterial infections.

2.2. Bacterial infection-associated inflammasomes: NLRP1, NLRP3, NLRP6, NLRP11, NLRC4, and AIM2

In this section, we briefly summarize the major types of inflammasomes containing NLRs and AIM2-like receptors, which are associated with bacterial infections. Members of the NLR family, including NLRP1, NLRP3, NLRP6, and NLRC4, sense pathogen-associated (PAMPs) and damage-associated molecular patterns. AIM2 is responsible for detecting cytosolic DNA originating from either the host or bacteria (Dai, Zhou, & Shi, 2023). The activation of each inflammasome is intertwined with the innate immune and inflammatory responses during bacterial infections and other infectious diseases (Fig. 1, Fig. 2). Because each inflammasome triggers a distinct immune response, understanding its mechanisms is paramount for establishing the host defense and pathogenic responses.

2.2.1. NLRP3 inflammasome

NLRP3, among the NLR inflammasomes, has been studied extensively because of its broad responsiveness to various stimuli and its role in numerous human diseases (Paik, Kim, Silwal, Sasakawa, & Jo, 2021). The NLRP3 inflammasome consists of three major components: a sensor molecule (NLRP3), which is composed of three domains (pyrin domain [PYD], NACHT, and the leucine-rich repeat [LRR]), an adapter molecule (ASC), featuring a PYD at the N-terminus and caspase recruitment domain (CARD) at the C-terminus, and an effector (caspase-1), which includes a CARD domain (Moretti & Blander, 2021). Upon activation, ASC binds to NLRP3, initiating the assembly of the ASC dimers into a speck-like structure. Subsequently, ASC links with pro-caspase-1 through its CARD domain, which results in the conversion of inactive pro-caspase-1 into its active form (Moretti & Blander, 2021). Notably, the LRR domain serves as a sensor that regulate NLRP3 activity in two states: auto-inhibited state and open/active state, which is dependent on adenosine 5'-O-(3-thio) adenosine triphosphate (ATP) hydrolysis (Brinkschulte et al., 2022). Sharif et al. revealed critical

residues on NIMA-related kinase 7 (NEK7) that interact with NLRP3, particularly at the LRR domain and HD2 interface. Site-directed mutagenesis revealed that mutations in these residues, particularly Q129, R131, and R136, significantly impaired NLRP3 binding and activation (Sharif et al., 2019). Furthermore, the E280 residue in NEK7's C-lobe, which is opposite the NLRP3-interacting surface, interacts with the surrounding NLRP3 residues S794, Q796, and K797. NEK7 binding induces a significant rotation (about 85°) in the subdomains of the NACHT domain, which is required for transforming NLRP3 into its active form (Sharif et al., 2019). The same research group revealed the cryo-electron microscopy (cryo-EM) structures of the disc-shaped NLRP3 inflammasome complex, which includes NLRP3 with ATP, NEK7, and the adaptor protein ASC (Xiao, Magupalli, & Wu, 2023). The active NACHT domain of NLRP3 mediates most interactions in the disc, whereas the C-terminal LRR domain is not involved in the disc interfaces. This study proposed that NEK7 plays an important role in converting inactive NLRP3 into the active NLRP3 inflammasome disc (Xiao et al., 2023).

The canonical pathway for NLRP3 inflammasome activation requires two or three distinct steps, including: 1) transcriptional priming, 2) posttranslational modifications (PTMs) for licensing, and 3) NLRP3 inflammasome assembly triggered by Signal 2 (Barnett, Li, Liang, & Ting, 2023; Moretti & Blander, 2021; Paik et al., 2021; Qin & Zhao, 2023). The priming signal (Signal 1) is triggered by cytokine stimulation and TLR signaling, which results in the transcriptional upregulation of NLRP3, pro-IL-1β, and pro-IL-18 via NF-κB activation. TLR ligands and tumor necrosis factor (TNF) trigger a priming signal through TLR-dependent signaling pathways, such as Tak1 and NF-κB, to enhance the transcriptional activation of NLRP3 inflammasome components, such as NLRP3 and pro-IL-1β (Paik et al., 2021).

Recent studies have elucidated the intricate mechanisms underlying the mediation of NLRP3 inflammasome licensing through diverse PTMs, including ubiquitylation (Palazon-Riquelme et al., 2018; Py, Kim, Vakifahmetoglu-Norberg, & Yuan, 2013; Song et al., 2016), SUMOylation (Barry et al., 2018; Qin et al., 2021), acetylation (He et al., 2020), and phosphorylation (Stutz et al., 2017). Because of the through coverage in recent reviews on the activation mechanisms of the NLRP3 inflammasome (Barnett et al., 2023; Moretti & Blander, 2021; Paik et al., 2021; Qin & Zhao, 2023), this review does not include these details. Instead, it focuses on bacterial manipulation of the licensing process, which is discussed in the subsequent bacteria section. Recent studies have provided insight on host factors involved in regulating the PTMs of NLRP3 inflammasome components. A recent study, for example, emphasized the role of the mitochondria-associated E3 ligase, MARCH5, in NLRP3 inflammasome activation via its interaction with NLRP3 and K27-linked polyubiquitination on residues K324 and K430 of NLRP3. March5 deletion in myeloid cells reduced IL-1β and IL-18 production and reduced mortality rates following exposure to LPS or Pseudomonas aeruginosa (Park et al., 2023). In addition, deubiquitinases, specifically USP7 and USP47, regulate inflammasome activation in macrophages. Inhibition of USP7 and USP47 blocks inflammasome formation by preventing ASC oligomerization and speck formation, independent of transcription (Palazon-Riquelme et al., 2018). The E3 small ubiquitin-like modifier (SUMO) ligase tripartite motif-containing protein 28 (TRIM28) is a key enhancer of NLRP3 inflammasome activation by increasing NLRP3 protein levels. TRIM28 binds to NLRP3 and promotes its modification by SUMO1, SUMO2, and SUMO3, which in turn inhibits NLRP3 ubiquitination and proteasomal degradation. As a result, TRIM28 deficiency reduces NLRP3 inflammasome activation both in vitro and in vivo (Qin, Li, et al., 2021). Additionally, NLRP3 is acetylated in macrophages and deacetylated by sirtuin (SIRT)2, an NAD+-dependent deacetylase. Using cell-based models, co-culture systems, and aging mouse models, it has been shown that SIRT2-mediated deacetylation of NLRP3 can prevent and even reverse aging-associated inflammation and insulin resistance (He et al., 2020).

The activation signal (Signal 2) is triggered by various PAMPs of bacterial pathogens, which promotes the oligomerization of the NLRP3

inflammasome complex. As a second signal, cathepsin B released from damaged lysosomes, mitochondrial reactive oxygen species (mtROS) production, and ion flux (K+/Cl− efflux and Ca2+ influx) activate the NLRP3 inflammasome (Chevriaux et al., 2020; He, Zeng, Yang, Motro, & Nunez, 2016; Lin et al., 2019; Murakami et al., 2012; Tang et al., 2017). Many bacterial pathogens attempt to survive within host cells by resisting phagolysosomal fusion, inhibiting autophagic flux, and disrupting lysosomal function (Cano et al., 2015; Geng et al., 2020; Sachdeva & Sundaramurthy, 2020). Both extracellular and intracellular particulates, such as cholesterol crystals, amyloid β, and monosodium urate crystals, also trigger NLRP3 inflammasome activation through multiple receptor signaling pathways (Paik et al., 2021). The production of cellular and mtROS, which consist of oxygen-reduced molecules, is important not only for their lethal effects on microorganisms, but also for their potential inflammatory and metabolic regulatory activities. The pro-inflammatory properties of mtROS are associated with Signal 2 for inflammasome activation, which results in the cleavage of pro-IL-1β and pro-IL-18 before their secretion, as well as GSDMD, leading to pyroptosis. Therefore, some microorganisms can modulate NLRP3 and AIM2 inflammasomes through ROS production (Rosa et al., 2023).

The pivotal roles of the NLRP3 inflammasome in the pathogenesis of various human diseases have been elucidated and are extensively discussed in numerous review articles (Fusco, Siracusa, Genovese, Cuzzocrea, & Di Paola, 2020; Li, Guo, & Bi, 2020; Sharma & Kanneganti, 2021; Yao, Sterling, Wang, Zhang, & Song, 2024); however, studies characterizing bacterial effectors that inhibit NLRP3 inflammasome activation and elucidating their underlying mechanisms are still at an early stage. Future comprehensive studies are needed to identify the role and mechanisms of host-pathogen interactions in regulating the NLRP3 inflammasome during pathogenesis or implementing defensive mechanisms against diverse bacterial infections.

2.2.2. NLRP1, NLRP6, NLRP11, and AIM2 inflammasomes

NLRP1, which was the first inflammasome sensor identified, is associated with autoinflammatory diseases and cancer (Calabrese et al., 2024; Grandemange et al., 2017; Tye et al., 2018; Zhai et al., 2017). Humans express only one NLRP1 protein, whereas mice have three homologs (NLRP1a, NLRP1b, and NLRP1c) (Gai et al., 2019; Rathinam, Vanaja, & Fitzgerald, 2012). Various stimuli have been identified as being associated with NLRP1 activation. Anthrax lethal toxin (LT) and Shigella flexneri activate only specific NLRP1 allele subsets by directly modifying and degrading the NLRP1 N-terminal fragment (Hellmich et al., 2012; Sandstrom et al., 2019). Indirect activators, including Toxoplasma gondii (T pathogen) and cytosolic ATP, regulate NLRP1 inflammasome activation (Cirelli et al., 2014; Liao & Mogridge, 2013). Additionally, inhibitors of the serine proteases dipeptidyl peptidases 8 and 9 activate all functional rodent NLRP1 alleles (Gai et al., 2019). NLRP1 is predominantly expressed in the skin and airway, where it is involved in the ultraviolet B- and toxin-mediated ribotoxic stress response (Robinson et al., 2022). Mechanistically, the ribotoxic stress response triggers the direct hyperphosphorylation of the human-specific disordered linker region of NLRP1 through MAP3K20/leucin-zipper and sterile-α motif (ZAKα) kinase and p38, leading to the induction of pyroptosis (Robinson et al., 2022). A recent cryo-EM revealed that the naturally occurring oxidized form of thioredoxin binds to human NLRP1 and acts as a suppressor for the NLRP1 inflammasome (Zhang et al., 2023).

Studies have firmly established a connection between NLRP6 and the maintenance of intestinal homeostasis through microbiome regulation (Vanaja, Rathinam, & Fitzgerald, 2015). The NLRP6 inflammasome is activated during bacterial infections. NLRP6 knockout (KO) mice showed higher survival rates and lower Staphylococcus aureus burdens compared to wild-type (WT) mice, due to increased neutrophil recruitment and enhanced bacterial killing. This indicates that NLRP6 negatively regulates neutrophil-mediated defense during S. aureus infection, and targeting NLRP6 could enhance bacterial clearance in

pneumonia (Ghimire et al., 2018). Lipoteichoic acid, generated by Gram-positive bacteria, activates NLRP6 and recruits caspase-11 and caspase-1 via the adaptor ASC. This leads to IL-1β and IL-18 maturation in macrophages. Mice lacking NLRP6 or caspase-11 showed reduced susceptibility to *Listeria monocytogenes* infection, with lower pathogen loads and impaired IL-18 production (Hara et al., 2018). In this comprehensive review, delineating the roles of the NLRP6 inflammasome in the context of bacterial infections is addressed.

NLRP11 acts as a pattern-recognition receptor for bacterial LPS in the cytosol or intracellular Gram-negative bacteria, particularly in human macrophages and other primates. NLRP11 activates the inflammasome through caspase-4 during intracellular Gram-negative bacteria infection (Rojas-Lopez et al., 2023). Although studies of these inflammasomes are somewhat limited compared with those of NLRP3, a more comprehensive understanding is important for the development of innovative treatments that target multiple inflammasome pathways during diverse bacterial infections.

As a cytosolic DNA sensor, AIM2 is essential for the assembly of inflammasome complexes, which in turn produces IL-1β and IL-18 (Hornung et al., 2009; Oh et al., 2023). AIM2 inflammasome is activated by double-stranded DNA derived from DNA viruses, bacteria, or dead cells. For examples, *Franciella novicida* infection induces type I IFN (IFN-I) signaling and IFN-inducible proteins, which attack the bacterial membrane of *F. novicida*. As a result, DNA is released into the cytoplasm, leading to the activation of the AIM2 inflammasome (Belhocine & Monack, 2012; Man et al., 2016). Mounting evidence underscores the importance of AIM2 in host defense against bacterial infections, even if we still don't fully understand how it interacts bacterial DNA and how AIM2 modulators work. In subsequent sections of this review, we discuss the roles of AIM2 inflammasome in various bacterial infections, which offer insight into AIM2-targeted therapy for treating infections.

2.2.3. NLRC4 inflammasome

In contrast to other inflammasomes, NLRC4 requires the involvement of neuronal apoptosis inhibitory proteins (NAIPs), which act as receptors for NLRC4 activation. Thus far, all NLRC4 and NAIP studies have been based on mouse NLRC4 and NAIP, as human cells only encode one NAIP protein type (Romanish, Nakamura, Lai, Wang, & Mager, 2009). Activation of the NAIP/NLRC4 inflammasome involves NAIP family members serving as pathogen-sensing proteins (Matusiak et al., 2015). Gram-negative bacteria, including *Salmonella* Typhimurium, *Legionella pneumophila*, and *P. aeruginosa*, activate the NLRC4 inflammasome (Amer et al., 2006; Franchi et al., 2006; Sutterwala et al., 2007; Suzuki et al., 2007). In mice, the needle and inner rod proteins are detected by NAIP1 and NAIP2, while flagellin is recognized by NAIP5 or NAIP6. In humans, NAIP detects both the needle and inner rod proteins, as well as flagellin (Wen et al., 2021). Once activated, NAIP proteins interact with and induce the oligomerization of NLRC4, further activating the inflammasome complex through the direct recruitment of procaspase-1 with the CARD domain of NLRC4 (Matusiak et al., 2015). Despite the inability of NLRC4 to recognize type 3 secretion system (T3SS) or flagellin directly, NAIP proteins have a pivotal role in the NLRC4-mediated response to pathogens.

Besides the NLRP3 inflammasome, the NAIP/NLRC4 inflammasome has been examined in the context of host-bacterial interactions. Certain bacteria, such as *Salmonella*, can evade the immune system by downregulating the expression of flagellin and avoid detection by NAIPs/NLRC4 inflammasomes (Akhade et al., 2020). In this review, we discuss the roles of NLRC4 inflammasome in various Gram-negative bacterial infections; however, the precise mechanisms governing the modulation of NLRC4 inflammasome by bacterial factors remain unclear.

2.2.4. Pyrin inflammasome

Pyrin, also known as tripartite motif-containing 20, is an intracellular receptor that is encoded by *MEFV* on chromosome 16 and primarily expressed in innate immune cells (Schnappauf, Chae, Kastner, & Aksentijevich, 2019). *MEFV* mutations are linked to the onset of the autoinflammatory disease called Familial Mediterranean fever (FMF) (Schnappauf et al., 2019). The unique structure of pyrin consists of the PYD, B-box domain, coiled-coil domain, and a B30.2 domain (Malik & Bliska, 2020). The PYD domain at the N-terminus binds to ASC to activate inflammasome assembly and induce IL-1β maturation (Malik & Bliska, 2020). Pyrin functions to activate inflammasomes in response to various bacterial toxins or effectors by inactivating the small GTPase RhoA (Loeven, Medici, & Bliska, 2020; Xu et al., 2014). Several bacterial factors, including YopM of *Yersinia pestis*, TcdB of *Clostridium difficile*, VopS of *Vibrio parahaemolyticus*, lbpA of *Histophilus somni*, and the ADP-ribosylating C3 toxin of *C. botulinum*, are all activating factors of the pyrin inflammasome, which affects innate immunity (Chung et al., 2016; Xu et al., 2014). To avoid unwanted dysregulated inflammasome activation, pyrin is maintained in an inactive conformation and negatively regulated through multiple mechanisms involving RhoA-protein kinase C-like kinase (PRK; also known as PKN) and 14–3-3 proteins (Gao, Yang, Liu, Wang, & Shao, 2016; Loeven et al., 2020; Malik & Bliska, 2020; Masters et al., 2016; Park, Wood, Kastner, & Chae, 2016). Further understanding of the regulatory mechanisms by which the pyrin inflammasome is activated during pathogenic infections will lead to new strategies for treating infectious and autoimmune inflammatory diseases.

2.3. Inflammasome regulation in terms of immunobiological processes

Several immune components, molecules, and pathways have been identified that regulate inflammasome assembly and activation. These include GBPs, cytokines, autophagy pathways, immunometabolism, and noncoding RNA. In this section, we briefly introduce the recent progress involving several factors and pathways that influence inflammasome activation during bacterial infections (Fig. 3, Fig. 4).

2.3.1. GBPs

GBPs are dynamin-related large GTPases that recognize pathogen- or damage-associated molecular patterns and are induced by the IFN-γ. They have an important role in cell-intrinsic defense against intracellular pathogens through sensing, triggering inflammasome responses, and inducing host cell death (Rivera-Cuevas, Clough, & Frickel, 2023). GBPs functions are associated with to inflammasome activation through multilayered processes. For example, GBPs mediate the activation of the caspase-1-associated inflammasome during Gram-negative bacterial infections, including *Salmonella*, *Francisella*, *Chlamydia*, *Legionella*, and *Vibrio* (Man, Place, Kuriakose, & Kanneganti, 2017). GBPs target and lyse pathogenic membranes to destroy protozoal and bacterial pathogens (Man et al., 2017; Ngo & Man, 2017). GBP-mediated disruption of the vacuolar membrane of bacteria results in the release of LPS into the cytosol, thereby triggering the activation of caspase-4/5 and caspase-11, as well as noncanonical NLRP3 inflammasome assembly (Man et al., 2017; Santos et al., 2020). GBP1 and GBP2 play a role in sensing, binding, and aggregating LPS to promote caspase-4 activation and pyroptosis (Dickinson et al., 2023). Furthermore, human GBP1 (hGBP1) binds directly to LPS on the bacterial outer membrane, causing LPS clustering through protein polymerization. This disrupts the O-antigen barrier, exposing lipid A, which leads to caspase-4 activation, enhances the antibacterial effects of polymyxin B, and blocks the actin-driven motility of *Shigella* (Kutsch et al., 2020). GBP5 promotes inflammasome activation triggered by bacterial DNA of *Brucella abortus* infection (Marinho, Brito, de Araujo, & Oliveira, 2024). The detection of bacteria within pathogen-containing vacuoles by GBPs involves the participation of galectins and the ubiquitin system. Galectins can sense vesicular damage by binding to sugars (glycans) that become exposed in the cytosol when intracellular vesicles rupture. The recognition of such damage by galectins was observed with the pathogens *Shigella flexneri*, where galectin-3 binds to exposed sugars on ruptured vacuoles (Paz et al., 2010). These galectin-3-decorated
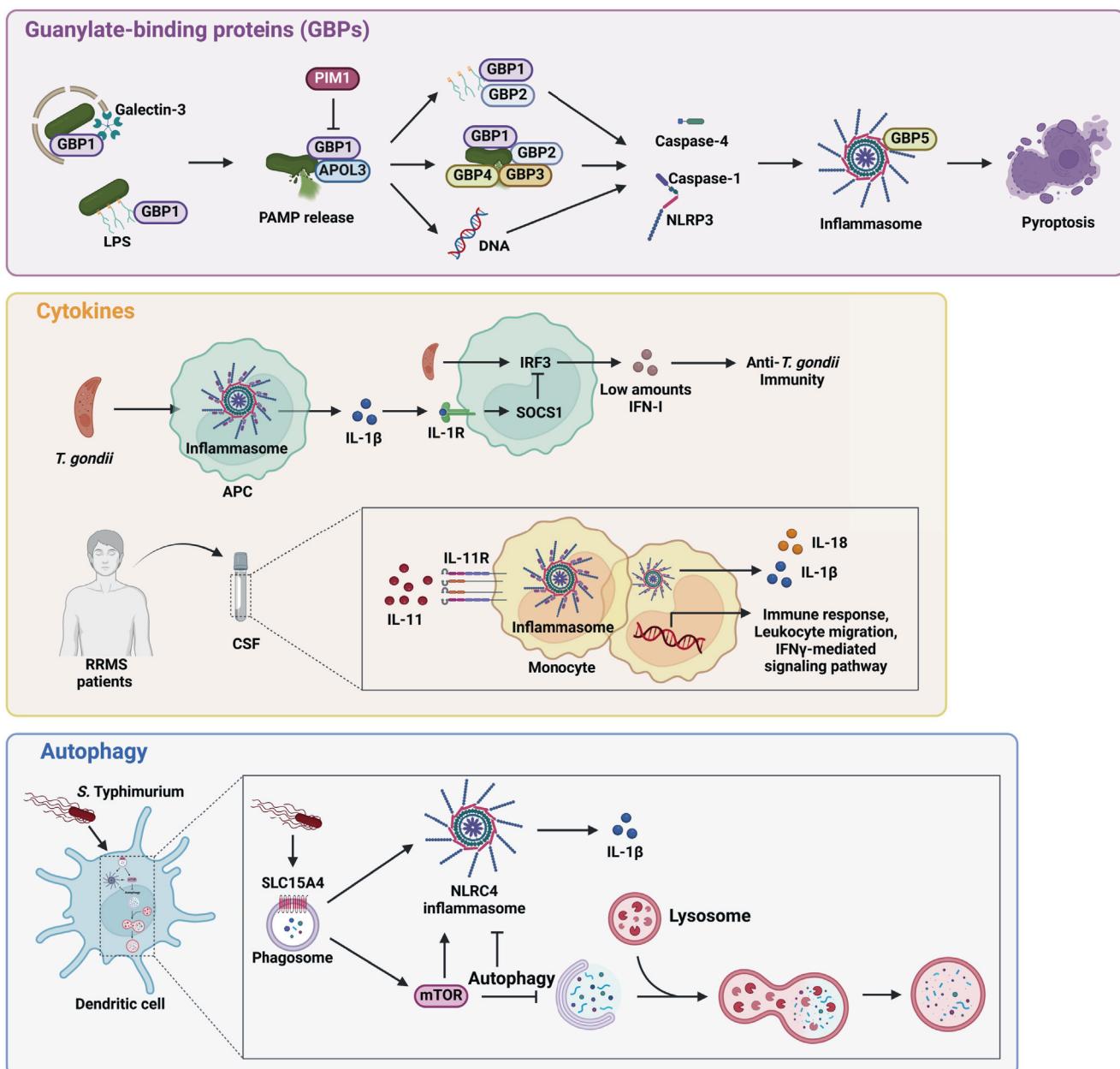
Fig. 3. GBPs, cytokines, and autophagy regulate inflammasome assembly and activation.
GBP-mediated disruption of the vacuolar membrane of bacteria leads to the release of PAMP into the cytosol, thereby triggering the activation of inflammasome and pyroptosis. PIM1 acts as negative regulator of GBP1. During *T. gondii* infection, SOCS1 inhibits IRF3 via IL-1β signaling-mediated inflammasome activation in APC, leading to reduced levels of IFN-I induction and anti-toxoplasmal immunity. The IL-11-IL-11R signaling in monocytes obtained from RRMS patients' CSF activates the inflammasome, contributing to various immune responses. SLC15A4 is recruited to phagosomes to enhance inflammasome activity in dendritic cells infected with *S.* Typhimurium. In addition, mTOR, a negative regulator of autophagy, is required for the promotion of IL-1β. Figure created with BioRender.com.
APC, antigen presenting cell; CSF, cerebrospinal fluid; IFN, interferon; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharide; PAMP, pathogen-associated molecular pattern; RRMS, relapsing-remitting multiple sclerosis; SLC15A4, solute carrier family 15 member 4; SOCS1, suppressor of cytokine signaling 1.

membranes colocalize with ubiquitin and related proteins, potentially serving as signaling hubs. Additionally, upon priming by IFN-γ, immunity-related GTPases help associate vacuoles containing *Toxoplasma* and *Chlamydia* with ubiquitin via the E3 ubiquitin ligase TRAF6. This ubiquitination triggers the recruitment of GBPs to the vacuoles through the p62 protein, enabling the destruction of pathogen-containing vacuoles and providing cell-autonomous immunity (Haldar et al., 2015). Importantly, hGBP1 contributes to co-localization with and rupture of *Legionella*-containing vacuoles in a T4SS-dependent manner and induces the IFN-γ-mediated inflammasome responses (Bass et al., 2023). Furthermore, hGBP1 induces caspase-4-mediated

pyroptosis; however, it inhibits IFN-γ-primed human epithelial cells from forming multinucleated giant cells (Dilucca, Ramos, Shkarina, Santos, & Broz, 2021). GBP-induced bacterial DNA release activates the AIM2 inflammasome complex (Man et al., 2017; Praefcke, 2018).

The kinase PIM1 is a negative regulator of GBP1. PIM1 phosphorylates GBP1 for sequestration by 14–3-3σ, thereby preventing GBP1 membrane association. The *Toxoplasma* protein TgIST suppresses PIM1, which further increases GBP1 activity, thereby enhancing host protection against *T. gondii* infection (Fisch et al., 2023). Moreover, the *Shigella* effector IpaH9.8 prevents caspase-4-mediated pyroptosis through the degradation of GBPs (Goers et al., 2023).
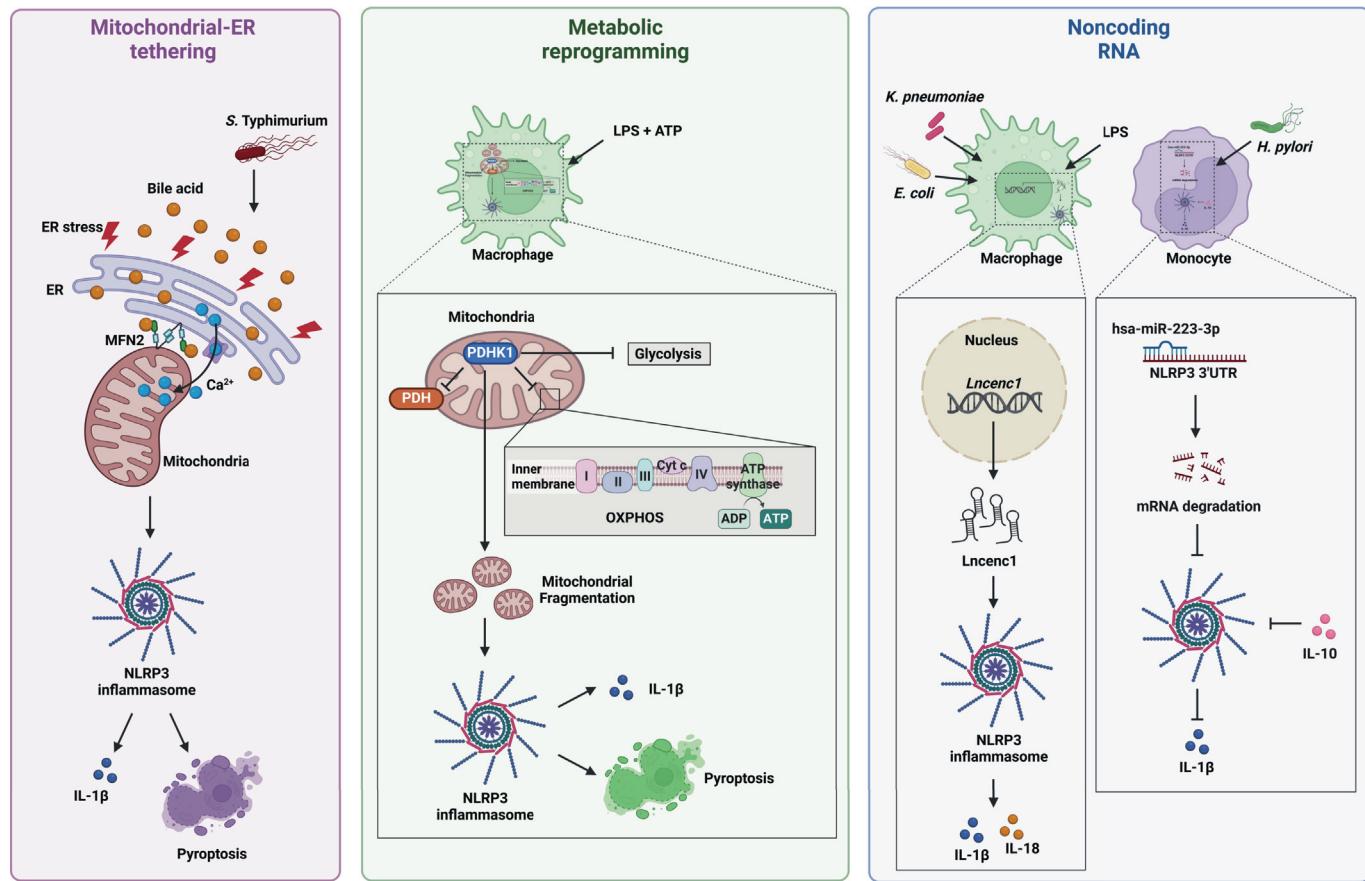
Fig. 4. Mitochondrial-ER tethering, metabolic reprogramming, and noncoding RNA regulate inflammasome assembly and activation.
During *S.* Typhimurium infection, bile acids induce intracellular Ca^{2+} redistribution and activate inflammasome through MFN2. Mitochondrial PDHK participates in mitochondrial fragmentation and NLRP3 inflammasome activation. In addition, activation of PDHK inhibits PDH and OXPHOS. In Gram-negative bacteria-infected macrophages, Lncenc1 induces activation of inflammasome and release of IL-1β and IL-18. Moreover, hsa-miR-223–3p and IL-10 regulate expression of NLRP3 during. *H. pylori* infection. Figure created with BioRender.com.
ATP, adenosine triphosphate; ER, endoplasmic reticulum; Lncenc1, long non-coding RNA, embryonic stem cells expressed 1; LPS, lipopolysaccharide; MFN2, mitofusin 2; mRNA, messenger RNA; OXPHOS; oxidative phosphorylation; UTR, untranslated region.

Future research is needed to identify negative regulators, originating from bacteria or hosts, that act upon GBPs in order to unravel the molecular mechanisms underlying the individual GBP-induced host defense against infections.

Recent studies indicated selectivity for mouse GBP1 and GBP3 in recognizing, binding, and killing intracellular *F. novicida* and *Neisseria meningitidis* and activating the inflammasome (Feng, Enosi Tuipulotu, et al., 2022). Moreover, hGBP1 promotes the lysis of *T. gondii*-containing vacuoles to release parasite DNA, whereas GBP1 targets cytosolic *S.* Typhimurium and recruits caspase-4 to induce pyroptosis (Fisch et al., 2020). Further studies are needed to understand the GBPs species- and pathogen-specific differences and their functions during inflammasome activation.

2.3.2. Cytokines

Although inflammasome activation plays an important role in IL-1β and IL-18 secretion, numerous other cytokines participate in regulating and interacting with the inflammasome. As mentioned above, IFN-γ plays a critical role in initiating the GBP-mediated host defense mechanism against cytosolic bacteria by means of pyroptosis and inflammasome activation. In addition, several other cytokines regulate inflammasome activation. In obesity-induced asthma, NLRP3 inflammasome activation is associated with increased type 2 immunological responses, marked by elevated levels of IL-5 and IL-13. Depletion of IL-5 and IL-13 in experimental asthma models reduced obesity-induced NLRP3 inflammasome activation and alleviated steroid-resistant airway

hyperresponsiveness. These findings indicate that targeting type 2 cytokines may be a promising therapeutic strategy for controlling inflammasome-related pathologies (Pinkerton et al., 2022). Consistent with these findings, the IL-5 receptor antagonist YM-90709 suppresses NLRP3 inflammasome activation, in which results in the amelioration of intestinal inflammation in an inflammatory bowel disease model (Ou et al., 2024).

IFN-I and their signaling cascade are well known for being crucial in antiviral responses. Several studies have shown the involvement of IFN-I in the regulation of inflammasome activation. Similarly, for SARS-CoV-2 infection, blockade of the IFN-I responses by mutated IFN-α2 results in the attenuation of inflammasome activation and stress responses (Viox et al., 2023). However, human metapneumovirus-induced IFN-β has been shown to reduce IL-1β transcription in response to LPS or heat-killed *P. aeruginosa* and *Streptococcus pneumoniae* (Loevenich et al., 2023). In addition, anti-toxoplasmal immunity mediated by inflammasome activation requires the suppression of IFN-I production. Inflammasome-mediated IL-1β signaling induces the negative regulator suppressor of cytokine signaling 1 to inhibit IFN-I secretion through interferon regulatory factor 3 binding (Hu et al., 2022). While the precise mechanisms linking IFN-I and inflammasome responses remain unclear, these findings suggest a relationship between the two pathways. Recent research, however, indicates that these pathways might be uncoupled in terms of stimulator of interferon genes (STING). Although STING is essential for IFN-I signaling, its role in proton channel activity appears to be separate from its involvement in inflammasome

activation and microtubule-associated protein 1A/1B-light chain 3B lipidation (Liu et al., 2023).

Autoinflammatory disorders are characterized by overproduction of IL-1β and IL-18 due to aberrant inflammasome activation. This overproduction not only initiates a vicious cycle of inflammatory responses by inducing other pro-inflammatory cytokines, such as IL-6, but also exacerbates dysregulated thrombogenic processes. As a result, this prolonged immunological activation contributes to the pathogenesis of autoinflammatory, autoimmune, and cardiovascular diseases (Koga & Kawakami, 2018; Ridker & Rane, 2021). From a therapeutic perspective, IL-6 suppression is emerging as a promising strategy to counteract dysregulated inflammasome-related pathologies (Koga & Kawakami, 2022). Furthermore, IL-11, a pleiotropic cytokine of the IL-6 family, is known for its ability to induce fibrosis and chronic inflammation in multiple tissues (Ng, Cook, & Schafer, 2020; Schafer et al., 2017). Of particular interest, IL-11 has recently been reported to be involved in NLRP3 inflammasome activation in monocytes and the migration of inflammatory cells to the central nervous system in patients and mouse models of relapsing-remitting multiple sclerosis. Inhibiting IL-11/IL-11R signaling, likely mediated through the inhibition of NLRP3 inflammasome activity, helps mitigate the pathologies associated with central nervous system inflammatory infiltrates in autoimmune encephalomyelitis (Seyedsadr et al., 2023).

Thus, cytokine signaling pathways involving IL-5, IFN-I, IL-6, and IL-11 are linked with inflammasome signaling during infection and inflammation. However, further research regarding other cytokine pathways in relation to inflammasome activation is warranted. These efforts provide opportunities for developing therapeutic strategies that target specific cytokine signaling pathways involved in inflammasome regulation during infections.

2.3.3. Autophagy

Autophagy is an important intracellular catabolic process for maintaining homeostasis against various stressors, including pathogenic infections (Mao & Klionsky, 2017). Although earlier studies have emphasized the role of macroautophagy in the bulk degradation of intracellular cargos, the significance of selective autophagy, particularly xenophagy, in targeting individual pathogens to combat infections has become evident (Li et al., 2021; Vargas, Hamasaki, Kawabata, Youle, & Yoshimori, 2023). However, bacteria have evolved mechanisms to evade autophagosomal degradation, often exploiting the autophagy process to their advantage (Xiong, Yang, Li, & Wu, 2019). Moreover, autophagy is necessary for preserving mitochondrial homeostasis, thereby playing an important role in regulating NLRP3 inflammasome activation by maintaining mitochondrial function(Mishra et al., 2021; Yuk, Silwal, & Jo, 2020).

The relationship between autophagy and the inflammasome has been studied in various ways. Previous studies revealed autophagy negatively regulates inflammasomes and excessive inflammation during bacterial infection. Recent studies indicate that the loss of autophagy-related gene 5 in lung resident macrophages and dendritic cells induces an early Th17 responses without changing the *Mycobacterium tuberculosis* (Mtb) burden in macrophages. In particular, autophagy-related gene 5 in lung resident macrophages and dendritic cells has an inhibitory effect in the regulation of inflammatory responses and inflammasome activation during Mtb infection (Kinsella et al., 2023). Earlier studies indicated that autophagy induction triggered by *S. flexneri*-induced membrane particles is required to alleviate the inflammatory response (Dupont et al., 2009). Autophagy also has a negative role in the regulation of NLRP3 inflammasome activation by improving mitochondrial homeostasis (Zhong et al., 2016). Activated macrophage cause mitochondrial damage and the production of mtROS and mitochondrial DNA (mtDNA), resulting in NLRP3 and Parkin activation as well as p62 recruitment to mitochondria. To eliminate damaged mitochondria, it is translocated by p62 to the autophagosome, thus blocking NLRP3 signaling from the mitochondria (Zhong, Sanchez-Lopez, & Karin, 2016). Moreover, the histidine/peptide solute carrier transporter SLC15A4 is recruited to phagosomes to enhance inflammasome activity in dendritic cells infected with *S.* Typhimurium. Interestingly, mechanistic target of rapamycin complex 1 signaling, which negatively affects autophagy, is required for the promotion of IL-1β levels and caspase-1 cleavage, accompanied by inflammasome perinuclear assembly (Lopez-Haber et al., 2022). Further evidence regarding the molecular mechanisms underlying the interconnection between autophagy and inflammasome pathways will be useful for elucidating the NLRP3 network during pathogenic infections.

2.3.4. Mitochondrial-ER tethering

Mitochondria-associated membranes (MAMs) are specialized regions of endoplasmic reticulum (ER) membranes linked with mitochondria through tethering proteins in mammalian cells (Degechisa, Dabi, & Gizaw, 2022). These sites are represented by protein- and lipid-enriched hubs, i.e., mitochondria and ER contact sites, and exhibit various biological functions, such as lipid and Ca^{2+} transport, ER stress signaling, mitochondrial dynamics, autophagosome formation, apoptosis, and NLRP3 inflammasome activation (Degechisa et al., 2022; Garofalo et al., 2016; Kumar & Maity, 2021; Pereira et al., 2022; Zhou et al., 2023).

A recent study showed that bile acids, as endogenous ligands for mitofusin-2, activate the NLRP3 inflammasome and pyroptosis during infection. Mechanistically, bile acids promote mitochondrial tethering to the ER, thereby increasing the mitochondrial calcium required to activate the NLRP3 inflammasome activation. Bile acids increase mitochondrial oxidative phosphorylation to promote bacterial clearance by macrophages (Che et al., 2023). Various pathogenic bacteria may target MAMs, thereby subverting and disrupting multiple physiological pathways to establish their infections (Escoll, Rolando, & Buchrieser, 2017); however, this is unclear in terms of bacterial effectors and their regulation of structures and functions in MAMs. L. *pneumophila* effector protein sphingosine 1-phosphate lyase can target host sphingosine biosynthesis and inhibit autophagy (Rolando et al., 2016), although its direct regulatory role is unclear in the context of MAMs.

2.3.5. Metabolic reprogramming

Metabolism in immune cells plays an important role in the regulation of inflammation, the effector immune responses against infections, and the tissue damage and repair responses, to confer organismal homeostasis (Chi, 2022; Willmann & Moita, 2024). Inflammasomes activation induces a metabolic shift from oxidative phosphorylation to glycolysis (Yu et al., 2023). Recent findings indicate that NLRP3 inflammasome activation is regulated by metabolic signals, specific enzymes, and metabolites involved in immunometabolism (Hughes & O'Neill, 2018; Olona, Leishman, & Anand, 2022). An early study showed that LPS stimulation markedly increases the tricarboxylic acid cycle metabolite succinate, which stabilizes hypoxia-inducible factor-1α to enhance IL-1β production (Tannahill et al., 2013). Moreover, pyruvate kinase M2, of the glycolytic pathway, is involved in the activation of NLRP3 and AIM2 inflammasomes in murine macrophages (Xie et al., 2016).

Pharmacological or genetic inhibition of pyruvate dehydrogenase kinase (PDHK) suppresses NLRP3 inflammasome activation in murine and human macrophages, as well as septic mice (Meyers et al., 2023). Mechanistically, suppressing PDHK results in NLRP3 inflammasome-induced metabolic reprogramming and promotes autophagy and mitochondrial fusion, thereby inhibiting excessive mtROS generation. Thus, mitochondrial PDHK unexpectedly participates in NLRP3 inflammasome activation through increased mitochondrial stress during inflammation (Meyers et al., 2023). Lactate, a byproduct of aerobic glycolysis, reduces TNF and IL-1β levels in human macrophages, thus enhancing Mtb clearance, at least in part, through autophagy (Maoldomhnaigh et al., 2021). Immunometabolic reprogramming profiles may vary across different tissues and cells in response to invading pathogens and infection stimuli. Consequently, localized or targeted modulation of immunometabolism may serve as an attractive and

broadly applicable treatment for various bacterial infections. Furthermore, elucidating the detailed mechanisms underlying immunometabolic remodeling and inflammasome activation is essential.

2.3.6. Noncoding RNA

Noncoding RNAs do not encode proteins and may be divided into small RNAs, such as microRNAs, tRNA, Piwi-interacting RNA, short interfering RNAs, and long noncoding RNAs (e.g., lncRNA). LncRNA are >200 nucleotides in length (Agliano, Rathinam, Medvedev, Vanaja, & Vella, 2019). Numerous small and lncRNAs regulate inflammasome activation directly or indirectly in the context of bacterial infections. Importantly, a lncRNA, embryonic stem cells expressed 1 (Lncenc1), is highly upregulated in mouse lungs following Gram-negative bacterial infection or in response to LPS or ATP-induced inflammasome activation. Overexpression of Lncenc1 increases caspase-1 activity and releases IL-1β and IL-18 in macrophages, whereas inhibiting Lncenc1 ameliorates LPS-induced lung inflammation and protects mice from bacteria-induced lung injury (Han et al., 2023). In addition, the lncRNA LNCGM1082 promotes the binding between protein kinase C-delta (PKCδ) and NLRC4 to activate the NLRC4 inflammasome, thereby conferring resistance to S. Typhimurium infection (Gao et al., 2023). Deng et al. found that the expression of lncRNA Gm28309 was decreased in Brucella-infected macrophages in a bioinformatic analysis. Furthermore, it regulates the production of the NLRP3 inflammasome and pro-inflammatory interleukins through the miR-3068-5p-NF-κB regulatory axis (Deng et al., 2020). Interestingly, the expression of lncRNA X inactivate-specific transcript (XIST) is upregulated following Escherichia coli and S. aureus infection in bovine mammary alveolar cell-T. XIST knockdown increases E. coli and S. aureus-induced NLRP3 inflammasome and NF-κB signal pathway. Furthermore, cell viability is decreased and apoptosis is increased in XIST knockdown cells, suggesting that it controls cell and tissue damage under uncontrolled inflammatory conditions (Ma et al., 2019). The lungs from P. aeruginosa strain PAO1-infected mice showed decreased maternally expressed gene 3 transcript 4 (MEG3–4) lncRNA expression. Li et al. found that MEG3–4 sponged miR-138 regulates IL-1β abundance. Consequently, miR-138 binds to the 3′ untranslated region of the IL-1β, resulting in the modulation of inflammatory responses (Li et al., 2018).

Studies have shown that microRNAs (miRNAs) regulate inflammasome activation during bacterial infections. NLRP3 expression induced by Helicobacter pylori is regulated not by pathogenicity-associated factors, but rather by hsa-miR-223–3p and IL-10. Specifically, hsa-miR-223–3p directly targets the NLRP3–3′ untranslated region to regulate its expression during H. pylori infection (Pachathundikandi & Backert, 2018). In addition, the expression of miR-223–3p is reduced in blood from syphilis patients infected with Treponema pallidum, whereas the levels of IL-1β and caspase-1 are increased. Treatment with recombinant Tp17, a membrane immunogen, also reduces the levels of miR-223–3p levels in human umbilical vein endothelial cells. MiR-223–3p regulates recombinant Tp17-induced inflammasome activation and pyroptosis by targeting NLRP3 (Long, Kou, Li, Wu, & Wang, 2020). On the other hand, as miR-21 targets A20, NLRP3 inflammasome activation is suppressed in macrophages from miR-21 KO mice. Furthermore, miR-21-deficient mice have lower mortality rates and inflammatory cell infiltration into organs following LPS injection. These results suggest that miR-21 represents a therapeutic target for the treatment of septic shock. Indeed, the expression of miR-21 is upregulated in septic shock patients in the clinical miRNA expression profile data (Xue et al., 2019). Additionally, miR-155 modulates suppressor of cytokine signaling 1, caspase-1/11, and NLRP3 expression in Porphyromonas gingivalis-infected U937 cells, which attenuates pyroptosis and GSDMD cleavage (Li et al., 2019).

In an acute lung injury (ALI) model, decreased miR-223 attenuated NLRP3 and TLR4 signaling pathways by targeting NLRP3 and

the rho-related GTP-binding protein RhoB. Thus, miR-223 may be a regulator of inflammation and a prognostic marker in ALI (Yan, Lu, Ye, & Zhang, 2019). In addition, miR-16 levels were downregulated in lung tissues and A549 cell lines after LPS treatment. MiR-16 regulates the mRNA and protein expression levels of NLRP3, ASC, caspase-1, IL-1β, IL-18, and NF-κB by targeting TLR4 (Yang et al., 2019). The implication that noncoding RNA can regulate not only bacterial infection, but also inflammatory diseases, warrants further study.

2.3.7. Others: Triggering receptors expressed on myeloid cells 2 (TREM2), transcriptional coactivators, and neuropeptides

TREM2 is required for the amelioration of macrophage pyroptosis against several pyogenic bacteria (S. aureus, P. aeruginosa, S. pneumoniae, and E. coli), thereby enhancing its protective effects during infections. TREM2 triggers β-catenin phosphorylation at Ser675 to further inhibit the NLRP3 inflammasome and macrophage pyroptosis, thereby promoting macrophage-mediated pyogenic bacterial clearance (Wang et al., 2022).

Nuclear receptor coactivator 6 (NCOA6) integrates into the NLRP3 inflammasome, to facilitate the activation of NLRP3-ASC oligomerization by interacting with the NACHT domain of NLRP3 (Lee et al., 2024). Interestingly, NCOA6 expression is notably elevated in macrophages from patients with gout, and NCOA6 deletion improves the severity of acute tubular necrosis in crystal-induced arthritis models (Lee et al., 2024). The neuropeptide calcitonin gene-related peptide (CGRP) binds to NLRP3 and negatively regulates the antibacterial responses through suppression of NLRP3 inflammasome activation and IL-1β secretion. Notably, CGRP administration is detrimental, whereas CGRP antagonists are beneficial against bacterial infection (Zhu et al., 2023). Thus far, the roles of these regulatory molecules in bacterial infections remain poorly understood. Further research is required to elucidate the specific contribution of various transcriptional coactivators and neuropeptides to host defense mediated by inflammasomes during bacterial infections.

3. Overview of pyroptosis in bacterial infections

3.1. Canonical and noncanonical pyroptosis

Pyroptosis is a type of an immunologic cell death that is characterized by cell swelling, membrane rupture, and the release of proinflammatory cytokines (Broz, Pelegrin, & Shao, 2020; Kroemer, Galluzzi, Kepp, & Zitvogel, 2013). The pathways involved in pyroptosis activation include the canonical and noncanonical pathways. Canonical pyroptosis involves the activation of caspase-1, which is primarily activated by the NLR family, AIM2, and pyrin inflammasomes (Li et al., 2024). Activated caspase-1 cleaves GSDMD into its C-terminal and N-terminal fragments and converts IL-1β and IL-18 to their mature forms. The N-terminal fragment forms membrane pores through binding to the cell membranes, thereby releasing cellular contents (Li et al., 2024) The cyclic GMP-AMP synthase-STING signaling pathway is closely related to the activation of GSDMD and pyroptosis (Zhang et al., 2022).

Noncanonical pyroptotic activation involves caspase-4/5/11, through the non-inflammasome-mediated pathway, in response to cytosolic LPS (Wang, Ding, & Shao, 2023). Caspase-4/5 and −11 are required in humans and mice, respectively, for the activation of noncanonical pyroptosis. Cleavage by caspase-4/5 liberates N-terminal GSDMD through cleavage of GSDMD. The N-terminal GSDMD domain binds to membrane lipids and forms a pore to activate pyroptosis. In addition, caspase-4/5/11 activates caspase-1 (Wang, Ding, & Shao, 2023). While emerging studies indicate both positive and negative roles of pyroptosis during infections, a complete understanding of pyroptosis is lacking with respect to the antimicrobial response during bacterial infections.

3.2. GSDM family

There are six paralogs of GSDM family proteins in humans and 10 in mice (Burdette, Esparza, Zhu, & Wang, 2021; Ouyang et al., 2023). The GSDM family includes GSDMA, GSDMB, GSDMC, GSDMD, GSDME, and deafness autosomal recessive 59. All GSDM family members, except deafness autosomal recessive 59, have two domains: a pore-forming N-terminal domain and a C-terminal domain, which function in autoinhibition (Burdette et al., 2021). Of all GSDM family members, the most studied in the context of pyroptosis are GSDMD and GSDME (Ouyang et al., 2023).

GSDMD is a mediator of pyroptosis through the rupture of the cell membrane after swelling. It plays an essential role in host defense against a variety of pathogenic infections, including *E. coli* and *Mycobacterium smegmatis* (Kuang et al., 2017; Shi, Gao, & Shao, 2017); however, some studies have indicated detrimental role of GSDMD in the provocation of infection through pathogen escape from host immunity (Ding et al., 2021). In both macrophages and non-macrophage cells, the activation of inflammatory caspases (1, 4, 5, and 11) results in the cleavage of human and mouse GSDMD at Asp276 and Asp 275, respectively (Kuang et al., 2017; Liu et al., 2016). The N-terminal region of GSDMD (GSDMD-N) forms high-order oligomers through a charge-charge interaction, translocates to the plasma membrane to lyse lipids, and forms a pore in the membrane, a typical morphological feature in pyroptosis (Kuang et al., 2017). As a result of membrane pore formation, host cell pyroptosis results in the release of various danger signals and pro-inflammatory cytokines into the extracellular environment. Pyroptosis of infected host cells contributes to the elimination of the infection sources; however, impaired or exacerbated cell death responses are linked to pathological inflammatory reactions in various disease settings (Newton, Strasser, Kayagaki, & Dixit, 2024; Tang et al., 2022).

Several host factors participate in the regulation of host cell pyroptosis to affect host protection or immune escape. For example, TREM2/β-catenin regulate macrophage pyroptosis by inhibiting NLRP3 inflammasome activation during pyogenic bacterial infection, including *S. aureus*, *P. aeruginosa*, *S. pneumoniae*, and *E. coli* (Wang et al., 2022). In addition, *S. pneumoniae* infection induces anaplastic lymphoma kinase/Jun N-terminal kinase (JNK)/NEK7-NLRP3-mediated pyroptosis, resulting in host protection (Wang et al., 2023).

In the absence of caspase-1 and GSDMD, caspase-3 activation can trigger GSDME-mediated pyroptosis through the extrinsic or intrinsic apoptotic pathways (Wang et al., 2017). Recent studies indicate that GSDME enhances its anticancer effects by inducing a pro-inflammatory state in the cold tumor immunological microenvironment (Hu et al., 2023; Wang et al., 2017). However, emerging evidence sheds light on the functions and molecular mechanisms of the caspase-3/GSDME pathway in a number of pathogenic processes, including infectious and inflammatory diseases, such as sepsis (Jiao et al., 2023). GSDME-mediated pyroptosis has been implicated in the death of aged neutrophils, triggering reactive inflammatory responses at the disease site (Ma et al., 2024). Furthermore, neurons in the brain tissues of patients with human immunodeficiency virus-associated neurocognitive disorder exhibit increased cleaved GSDME and the expression of Nijurin-1, both linked to neuronal damage and death (Fernandes et al., 2024). Additionally, a recent study found that herpes simplex virus types 1 and 2 cause GSDME-mediated cell death. This process is facilitated by ER stress driven by inositol-requiring kinase 1α and mitochondria-dependent activation of caspase-3, which results in inflammatory activation and death in neurons (Ren et al., 2023). These findings highlight the potential significance of GSDME activation as an important pathway in inducing pyroptotic cell death across various pathological settings.

The pyroptotic process eliminates the intracellular bacterial niche, making the pathogen vulnerable to phagocytosis by neighboring phagocytes, ultimately leading to the destruction of the pathogen; however, excessive and dysregulated pyroptosis may have detrimental effects on the host (Jorgensen & Miao, 2015). Various pathogens developed their unique tactics to subvert pyroptosis. The molecular characteristics of different forms of pyroptosis, including their distinct stages and the specific pathogens involved in infections, require further investigation to be fully understood. Although prior studies have proposed the use of pyroptotic executors, such as GSDM family members, as universal biomarkers in various diseases, particularly cancers (Ouyang et al., 2023; Wan et al., 2023), assessing GSDMD and GSDME levels as biomarkers in various infectious diseases may present a considerable challenge. Our understanding of the biological and pathological functions of GSDM family members in diverse infections is just beginning. Future studies are needed to decipher the novel functions of each GSDM family member under specific infection conditions.

4. Overview: Bacterial modulation of inflammasome activation and pyroptosis

Bacteria have several strategies to regulate inflammasome activation and pyroptosis, notably through three key mechanisms (Cunha & Zamboni, 2013; Ta & Vanaja, 2021). First, bacteria can modify or suppress the expression of inflammasome-activating ligands, preventing inflammasome activation. Second, certain bacterial effectors can overactivate the inflammasome and pyroptosis, resulting in pathological inflammation that accelerates disease progression. Third, bacteria actively inhibit or disassemble the inflammasome and pyroptotic machinery by utilizing bacterial inhibitory effectors or proteins. These strategies enable bacteria to survive and persist within host cells (Fig. 5). This section discusses bacterial evasion and escape from inflammasome activation and pyroptosis (Higa et al., 2013; Ta & Vanaja, 2021).

One common bacterial evasion strategy involves altering the structure of inflammasome-activating ligands, allowing bacteria to effectively "hide" from inflammasome responses and subsequent pyroptosis. For instance, *P. gingivalis* modifies its LPS to include an atypical lipid A structure, which helps it evade immune detection by TLR4, facilitating inflammation and caspase-11 activation (Slocum et al., 2014). Similarly, *S.* Typhimurium suppresses flagellin expression during intracellular replication, preventing caspase-1-induced pyroptosis and subsequent bacterial clearance. The *Salmonella* pathogenicity island 1 (SPI-1)-encoded rod protein SsaI also evades detection by NLRC4, contributing to virulence caused by *S. t*Typhimurium (Miao et al., 2010).

In addition to evasion, some bacterial toxins and effectors overactivate the inflammasome and induce cell death. For example, anthrax LT, a protease that activates the NLRP1b inflammasome sensor, triggers an inflammatory response involving neutrophils and the formation of neutrophil extracellular traps (Greaney et al., 2020). Likewise, *L. monocytogenes* uses listeriolysin O (LLO) to activate the NLRP3/cryopyrin inflammasome, enhancing its virulence (Mariathasan et al., 2006; Meixenberger et al., 2010).

Bacteria also employ the third strategy of actively inhibiting inflammasome components. Many Gram-negative pathogens have developed specialized secretion systems, such as the T3SS, to inject effector proteins directly into host cells, disrupting inflammasome activation. For example, *Yersinia* uses the YopM protein to bind caspase-1, preventing its interaction with ASC (LaRock & Cookson, 2012), while YopK blocks PAMP leakage, inhibiting the activation of NLRP3 and NLRC4 inflammasomes (Brodsky et al., 2010). The specific ways in which different bacteria use effectors and toxins to interfere with inflammasome pathways are discussed in detail in the following sections.

5. Roles of inflammasomes in the different contexts of bacterial pathogens

The activation of inflammasomes is essential for host defense against bacterial infections, by initiating inflammatory responses, recruiting immune cells, and enhancing the immune defense (Brewer, Brubaker, & Monack, 2019; Krakauer, 2019). Thus, it is not surprising that numerous
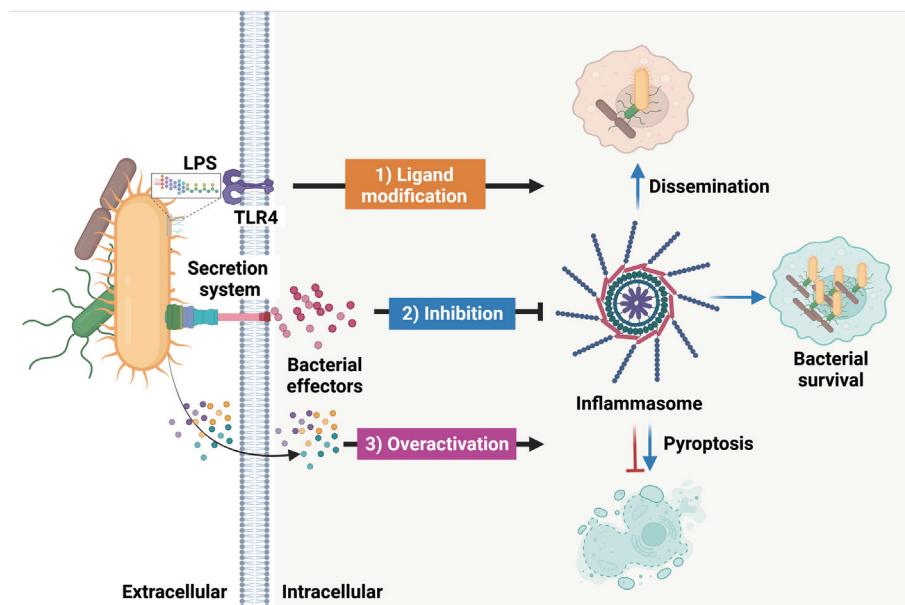
Fig. 5. Bacteria modulates inflammasome activation and pyroptosis.
Bacteria can modify inflammasome-activating ligands to modulate inflammasome activation. Moreover, bacterial effectors secreted through the secretion system and toxins can inhibit or overactivate the inflammasome. As a result, bacteria regulate the increase in bacterial survival and dissemination, as well as the activation and inhibition of pyroptosis. Figure created with BioRender.com. LPS, lipopolysaccharide; TLR4, toll-like receptor 4.

pathogens have developed strategies to evade and control inflammasome activation and pyroptosis (Brewer et al., 2019). In this section, we present a detailed summary of inflammasome activation during bacterial infection by highlighting recent advances in the field. We also discuss the current literature in terms of known bacterial evasion strategies and countermeasures that impact pathogenesis (Tables 1–3). Indeed, a variety of bacterial effectors attenuate host pyroptosis to evade immune clearance to establish progressive infection (Brewer et al., 2019; Chai, Lei, & Liu, 2023).

5.1. Gram-positive bacteria

5.1.1. Bacillus anthracis

B. anthracis is the etiological agent responsible for anthrax, a zoonotic ailment predominantly affecting livestock and, to a lesser extent, humans. This pathogen exists in the form of endospores within the soil (Mondange, Tessier, & Tournier, 2022). *B. anthracis* is recognized as a potential biological weapon and is categorized by the Centers for Disease Control and Prevention as a class A threat (Mondange et al., 2022). Previous studies have concentrated focused on the role of NLRP1 in the response to anthrax LT, as it becomes activated by the LTs produced by *B. anthracis*. The IL-1β response in hematopoietic cells exposed to anthrax LT requires NLRP1b. Notably, neutrophils play a significant role in LT-mediated IL-1β release in response to toxin, whereas platelets do not participate (Greaney et al., 2020). Interestingly, human and C57BL/6 J mouse macrophages do not activate the NLRP1 inflammasome, while macrophages from BALB/c and 129S mice have an LT-sensitive Nlrp1b allele (Boyden & Dietrich, 2006; Van Opdenbosch et al., 2014). These findings highlight the multifaceted nature of anthrax LT during the activation of the NLRP1 inflammasome, which is contingent upon the species involved. The complexity of the anthrax LT interaction with the NLRP1 inflammasome underscores the need for further studies. Unraveling the specific inflammasome activated by anthrax LT in human cells is a challenging yet imperative endeavor as it is essential for developing targeted interventions aimed at preventing and treating anthrax by modulating the inflammasome response.

5.1.2. Corynebacterium diphtheriae

C. diphtheriae is a Gram-positive and highly pleomorphic bacteria that causes diphtheria. It has arised a clinical awareness and surveillance because of the continuous and recurrent outbreaks that have occurred (Balakrishnan, 2024; O'Boyle et al., 2023). Thus far, it has not been widely determined whether *C. diphtheriae* directly induces inflammasome activation in host cells or *in vivo* models.

A recent study demonstrated that diphtheria toxin, the primary causative agent of human diphtheria, induces ZAKα/p38-mediated phosphorylation of NLRP1 in primary human keratinocytes. The activation of NLRP1 subsequently results in the secretion of pro-inflammatory cytokines, namely IL-1β and IL-18, by diphtheria toxin-exposed keratinocytes. The inhibition of ZAKα not only curtails pyroptotic cell death, but also prevents inflammasome-independent, non-pyroptotic cell death. These results underscore the pivotal role of the ZAKα-driven ribotoxic stress response and the NLRP1 inflammasome in the antibacterial immune responses and the pathogenesis of diphtheria (Robinson et al., 2023). However, it remains to be determined whether other inflammasomes are involved in host defense or the pathological responses to *C. diphtheriae* infection.

5.1.3. Lactobacillus plantarum

The probiotic bacteria, *L. plantarum* NC8, and the metabolite acetate inhibit NLRP3 expression and inflammasome activation to ameliorate pathologies, Th1/Th17 cells in the spleen, and pancreatic lymph nodes in type 1 diabetic mice (Zhang et al., 2023). Mechanistically, *L. plantarum*-derived post-biotics significantly increase autophagy through the activation of the AMP-activated protein kinase (AMPK) pathway. Autophagy activation results in the restriction of intracellular *S. enterica* Typhimurium and suppresses the expression of inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-18) during *S. enterica* Typhimurium infection (Wu et al., 2023). Defective autophagy increases the inflammatory response and inflammasome activation in porcine intestinal epithelial cells (Wu et al., 2023). It will be important to determine whether other probiotic bacteria can modulate inflammasome pathways to influence pathological responses in autoimmune and inflammatory diseases.

Table 1
The roles of inflammasome during Gram-positive infections.

Pathogen	Effector	Inflammasome	Mechanisms	Effect	Ref.
B. anthracis	Anthrax LT	NLRP1, Caspase-1	Neutrophil and PAD4 activity	IL-1β production	(Greaney et al., 2020)
		Nalp1b, Caspase-1	Activation of caspase-1	Induction of macrophage necrosis	(Boyden & Dietrich, 2006)
C. diphtheriae	DT	NLRP1	ZAKα/p38-mediated phosphorylation of NLRP1	Pyroptosis, Epidermal damage	(Robinson et al., 2023)
L. plantarum		NLRP3	*L. plantarum* NC8 and its metabolite acetate inhibit NLRP3 expression	Reduction the damage of T1D in the model mice	(Zhang et al., 2023)
		NLRP3	Activation of autophagy through AMPK pathway	Restriction of intracellular *Salmonella enterica* Typhimurium	(Wu et al., 2023)
L. monocytogenes	LLO T223	NLRP3, AIM2	LLO T223-dependent ASC phosphorylation through Lyn-Syk signaling	Exacerbation of the pathogenesis	(Tanishita et al., 2022)
		NLRC5	NLRC5-induced MHC class I gene upregulation and CD8$^+$ T cell responses	Control intracellular pathogen infection	(Yao et al., 2012)
		NLRP6	Negative regulation of the MAPK and NF-κB pathway	Resistant to *Listeria* infection in $Nlrp6^{-/-}$ mice	(Anand et al., 2012)
E. faecalis	LTA/butyrate	NLRP3	K$^+$ efflux, HDAC inhibition, TLR2/GPCR activation	Exacerbation of pulp necrosis, Pathogenesis of apical periodontitis	(Park et al., 2023)
The genus *Staphylococcus*					
S. aureus		NLRP1	Enhanced expression of the NLRP1, PYCARD proteins Increased caspase-1 activity	Contribution to the pathogenesis of atopic dermatitis	(Vaher et al., 2023)
	OatA	AIM2	Intracellular bacteriolysis	Induction of host cell necroptosis and *S. aureus* dissemination	(Feng et al., 2022)
	SAK	NLRP3	Activation of the priming step of NLRP3 inflammasome, Increased of K$^+$ efflux and ROS generation, Activation of NF-κB signaling	Potentiation the pathogenesis of highly virulent *S. aureus* infection	(Wang et al., 2022)
	PGN, LTA, α-toxin	NLRP3	Infiltration of neutrophils and retinal microglia	Regulation of innate immune responses in bacterial endophthalmitis	(Kumar et al., 2022)
		NLRP3	Butyrate activates AMPK signaling and antibacterial autophagy, Butyrate inhibits NLRP3 inflammasome	Amelioration bacterial endophthalmitis in mice	(Singh et al., 2023)
S. epidermidis		Caspase-1	Increased caspase-1 level	Peripheral immune cells infiltration and blood–brain barrier alteration	(Gravina et al., 2023)
	Esp	IL-1β	Proteolytic maturation of active IL-1β in keratinocytes	Contribution to host innate defense	(Rademacher et al., 2022)
The genus *Streptococcus*					
S. pyogenes	SLO, SLS	NLRP3	LTA acts as a priming signal, Induction of IL-1β release	Streptolysins are an attractive target for therapeutic intervention	(Richter et al., 2021)
	SpeB	IL-18	Maturation of IL-18	T cell activation, Secretion of IFN-γ	(Johnson et al., 2023)
S. pneumoniae		NLRP3	Phosphorylation of ALK and JNK	Regulation of pyroptosis and IL-1β secretion	(Wang et al., 2023)
S. suis		NLRP3	Activation of MAPK signaling pathways	Pyroptosis, Lymphocyte disruption, Pathogenesis of *S. suis*, Induction of splenomegaly	(Wang et al., 2022)
S. gordonii		NLRP6	Activation of macrophages	Evasion of host immune responses	(Metcalfe et al., 2023)
C. perfringens	Beta-1 toxin	NLRP3, Caspase-1	Caspase-1-dependent pathway	Induction of pyroptosis	(Zhang et al., 2023)
	PFO	NLRP3	Secretion of lecithinase	Cytokine release, Cell death	(Mathur et al., 2023)
		NLRP3	MLKL-K$^+$ efflux-dependent NLRP3 inflammasome signaling	Extracellular trap formation	(Liu et al., 2022)
C. septicum	α-toxin	NLRP3	α-toxin-induced ion fluxes	Induction of pyroptosis	(Jing et al., 2022)

ALK, anaplastic lymphoma kinase; DT, diphtheria toxin; GPCR, G-protein coupled receptor; HDAC, histone deacetylases; LLO, listeriolysin O; LT, lethal toxin; LTA, lipoteichoic acid; MAPK, mitogen-activated protein kinase; MLKL, mixed lineage kinase-like; OatA, O-acetyltransferase A; PAD4, peptidyl arginine deiminiase-4; PFO, perfringolysin O; PGN, peptidoglycan; SAK, staphylokinase; SLO, streptolysin O; SLS, streptolysin S; T1D, Type 1 diabetes.

5.1.4. Listeria monocytogenes

L. monocytogenes (LM) is a Gram-positive bacterium and intracellular pathogen that causes outbreaks of foodborne illnesses (Farber & Peterkin, 1991). Both NLRP3/cryopyrin and ASC are required for the secretion of IL-1β in macrophages and peripheral blood mononuclear cells infected with LM, particularly depending on the secretion of LLO (Mariathasan et al., 2006; Meixenberger et al., 2010). A recent study showed that T223 of LLO results in the ASC phosphorylation at amino acid residue Y144, which is required for ASC oligomerization. A *Listeria* mutant expressing LLO T223A fails to activate the inflammasomes, thereby attenuating the virulence of LM *in vivo* (Tanishita et al., 2022).

Thus, LLO is critically involved in ASC phosphorylation to activate inflammasomes that exacerbate LM pathogenesis.

In addition, AIM2 inflammasome activation contributes, in part, to the maturation of IL-1β and IL-18 in macrophages in response to LM infection (Rathinam et al., 2010). Moreover, NLRC5 is essential for host defense against LM infection *in vivo*. Importantly, NLRC5-mediated antimicrobial activities against LM depend on NLRC5-induced major histocompatibility complex class I gene upregulation, CD8$^+$ T cell activation, and cytotoxicity. NLRC5 also partially regulates NLRP3 inflammasome activation (Yao et al., 2012). In contrast, NLRP6 has a negative role in the protection against bacterial infection including

Table 2
The roles of inflammasome during Gram-negative infections.

Pathogen	Effector	Inflammasome	Mechanisms	Effect	Ref.
Achromobacter	T3SS	NLRC4, NLRP3	T3SS activates either NLRC4 or NLRP3 sensors	Pyroptosis, Lung damage	(Turton et al., 2023)
A. baumannii		NLRP3	Extracellular ATP, K^+ efflux, ROS generation, and lysosomal destabilization	IL-1β production, Increased lung pathology	(Kang et al., 2017)
		NLRP3	TRIF-IFN-I axis, IFNAR-mediated histone modification	GSDMD-mediated pyroptosis, MLKL-dependent necroptosis	(Li et al., 2018)
A. muciniphila		NLRP3	Increased the expression of NLRP3, caspase-1 p20, and IL-1β p17	Alleviation of DSS-induced acute colitis	(Qu et al., 2021)
		NLRP3	Pgam5 alters the gut microbiota	Amelioration of neuroinflammation and nerve injury	(Chen et al., 2023)
		NLRP3	Stimulation of antimicrobial activity, ROS production	Modulation of *S.* Typhimurium infection	(Liu et al., 2023)
B. abortus		NLRP3, AIM2	TLR2 and MyD88 adapter-like/TIRAP	Infiltration of neutrophils, Activation of the blood-brain barrier in neurobrucellosis	(Miraglia et al., 2016)
	c-di-GMP	AIM2	STING-dependent type I IFN pathway	Regulation of *B. abortus* replication	(Costa Franco et al., 2018)
	T4SS	NLRP12	Suppression of NF-κB and MAPK signaling	Regulation of host defense	(Silveira et al., 2017)
		NLRP6	Altered the intestinal microbiota composition	Resistance to *B. abortus* infection, Regulation of IgA secretion	(Rungue et al., 2021)
B. thailandensis	VgrG5	Caspase-1/11	Caspase-8/Ripk3/Caspase-1/Casaspe-11	Pyroptotic and apoptotic cell death, Restriction of *B. thailandensis* replication	(Place et al., 2021)
		Caspase-11	Oligomerization of E-Syt1 and its interaction with caspase-11	Pyroptosis	(Ma et al., 2023)
		Caspase-4	GBP1, IFN-γ-dependent signaling	Restriction of MNGCs formation and *B. thailandensis* spread	(Dilucca et al., 2023)
		NLRC4, Caspase-1	Caspase-1	Pyroptosis, Bacterial clearance	(Miao et al., 2010)
B. cenocepacia	TecA	Pyrin		Increased lung inflammation, weight loss, and lethality in mice	(Loeven et al., 2021)
B. pseudomallei	BsaL	Caspase-1, GSDMD	Activation of inflammasome by BsaL	Pyroptosis	(Lichtenegger et al., 2020)
	BsaK	NLRC4	Activation of inflammasome by BsaK	Activation of innate immune response	(Miao et al., 2010)
C. rodentium		NLRC4		Protection from severe intestinal inflammation	(Nordlander et al., 2014)
		Caspase-1/8/11	GSDMD-independent canonical inflammasome responses	Intestinal and systemic host defense	(Eeckhout et al., 2023)
		NLRP3	NLRP3 and ASC activation	Protection from intestinal inflammation	(Song-Zhao et al., 2014)
		NLRP6	Deubiquitination of NLRP6 inflammasome by Cyld	Prevention of excessive IL-18 production	(Mukherjee et al., 2020)
		NLRP3, Caspase-11	TRIF-IFN-Caspase-11 pathway	Caspase-1-independent cell death	(Rathinam et al., 2012)
C. difficile	TcdA, TcdB	Caspase-1, ASC	Activation of toxin-mediated ASC-containing inflammasome	Toxin-induced inflammation and damage *in vivo*, Pyroptosis	(Ng et al., 2010)
	Toxin B		LPS enhances the ability of toxin B	Production of IL-1β	(Htwe et al., 2021)
	TcdB	Pyrin	Switch-I modification of the Rho subfamily	Immune defense	(Xu et al., 2014)
	Flagellin	NLRC4	Induction of inflammasome-related cytokines gene expression	Induction of IL-18 synthesis	(Chebly et al., 2022)
E. coli, STEC, UPEC	CNF1	NLRP3	Pak-NLRP3 signaling	Regulation of the *E. coli* burden	(Dufies et al., 2021)
	SubAB	NLRP3, Caspase-1	IRE1α/PERK-dependent pathway	STEC survival, Infectious disease pathogenicity	(Tsutsuki et al., 2022)
		NLRP3, Caspase-1	Neutrophil serine proteases activation	IL-1β secretion	(Sabbione et al., 2023)
	OMVs HlyF	Noncanonical inflammasome	OMVs from HlyF-expressing *E. coli*	Regulation of inflammatory condition	(David et al., 2022)
		NLRP3, Caspase-1, GSDMD	ROS activation	Pyroptosis	(Zhang et al., 2022)
		Caspase-11, GSDMD	Extracellular peroxiredoxin 1	Development of bacterial infections and inflammatory bone disease	(Kang et al., 2023)
		NLRP3, Caspase-11	Catalytic activity of caspase-6	Pyroptosis	(Zheng et al., 2021)
F. tularensis	Cytoplasmic DNA	AIM2	Depletion of intracellular potassium, Bacterial internalization, Lysosomal acidification, IRF3 signaling	Innate immunity against *F. tularensis* infection	(Fernandes-Alnemri et al., 2010)
F. novicida		AIM2, Pyrin	AIM2-mediated Pyrin and ZBP1 expression	Induction of inflammatory cell death	(Lee et al., 2021)
		AIM2	GBP1 and GBP3-mediated inflammasome activation	Restriction of intracellular growth, Pathogen membrane rupture	(Feng et al., 2022)
Non-encapsulated *H. influenzae*		NLR, Caspase-1	Activation of TLR2/4, NOD1/2 and NLRP inflammasome pathway	Cytokine induction	(Brown et al., 2023)
H. influenzae,			TAC2 linked to inflammasome	Neutrophil activation	(Versi et al., 2023)

Table 2 (*continued*)

Pathogen	Effector	Inflammasome	Mechanisms	Effect	Ref.
M. catarrhalis					
M. catarrhalis	LOS	NLRP3, Caspase-11	Type I interferon signaling and GBPs	Pyroptosis	(Enosi Tuipulotu et al., 2023)
H. pylori		Caspase-1	NOD1-mediated IL-18 processing and maturation	Maintenance of epithelial homeostasis, Protection against pre-neoplastic changes	(Tran et al., 2023)
		NLRP3	Downregulation of TRIM31	Regulation of mtROS production and autophagy	(Yu et al., 2023)
H. pylori, H. felis		AIM2		Promotion of gastric epithelial and immune cell proliferation, and apoptosis	(Dawson et al., 2023)
K. pneumoniae		Caspase-11	Casaspe-11-mediated inflammasome activation	Protective immunity by activation of blood coagulation	(Perlee et al., 2020)
		Caspase-1/11	A28006 strain: Caspase-1/11-mediated activation A54970 strain: IL-10 production	Induction of pyroptosis, Resolution of infection Inhibition of pyroptosis, Non-resolution of infection	(Codo et al., 2018)
		NLRP3, Caspase-1, GSDMD	Induction of cathepsin B activation	Induction of caspase-1-dependent pyroptosis	(Kim et al., 2023)
		NLRP3, ASC	ADSC-derived exosomal miR-181a-5p targets STAT3 signaling	Repression of *K. pneumoniae*-induced lung injury	(Hu et al., 2022)
		NLRP6	Upregulation of NLRP6 expression	Regulation of neutrophil recruitment, generation and function	(Cai et al., 2021)
		AIM2	SARM1 inhibits AIM2 inflammasome Activation of caspase-8	Regulation of bacterial growth Induction of cell death	(Feriotti et al., 2022) (Mascarenhas et al., 2017)
L. pneumophila	Flagellin	Naip5/NLRC4/ASC NAIP5/NLRC4	Activation of caspase-1/7/8 and GSDMD	Restriction of *L. pneumophila* replication	(Goncalves et al., 2019)
		NLRC4	Interplay with CCR2 signaling through distinct pathways	Restriction of pulmonary bacterial infection	(Ataide et al., 2023)
	T4SS	Caspase-1/4	IFN-γ priming, Upregulation of GBP1	Increased bacterial exposure to the host cell cytosol	(Bass et al., 2023)
	T4SS	Caspase-1/8/11	TNF signaling	Control of pulmonary *Legionella* infection, Activation of rapid cell death	(Pollock et al., 2023)
L. interrogans		NLRP3	ROS-and cathepsin B-dependent NLRP3 inflammasome activation	IL-1β and IL-18 release	(Li et al., 2018)
	LPS	Caspase-11, GSDMD	LPS of *L. interrogans* prevents caspase-11 dimerization	Inhibition of cell death	(Bonhomme et al., 2023)
P. multocida	PmCQ6	NLRP3	K$^+$ efflux and Nek7 activation	Activation of caspase-1, Induction of IL-1β secretion	(Wang et al., 2022)
	PmCQ2, PmCQ6	NLRP3	Capsular thickness-dependent NLRP3 inflammasome activation	IL-1β release	(Fang et al., 2020)
		NLRP3, NLRP6	Synergic effect of NLRP6 and NLRP3	Protection against *P. multocida* infection, Formation of NET	(Wu et al., 2022)
P. aeruginosa	Exo S, Exo T	NLRP3, Caspase-1	Requirement for ADPRT activity of ExoS in neutrophils	Bacterial killing, Prevention of corneal perforation in *P. aeruginosa* keratitis	(Minns et al., 2023)
	MifR	NLRP3, Caspase-1, ASC	MifR-mediated NLRP3 activation	Contribution to the virulence of *P. aeruginosa* PAO1	(Xiong, Perna, Jacob, Lundgren and Wang, 2022)
	MucA	Caspase-1	Downregulation of the expression of T3SS and inflammasome ligands	Escape from host inflammasome defense	(Liu et al., 2022)
	EXOA	NLRP1	EEF2 inactivation, RSR-dependent ZAKα and p38 MAPK activation	Promotion of NLRP1-dependent epithelial damage	(Pinilla et al., 2023)
	ExoT	NLRC4	ExoT blocks the CrkII/Abl phosphorylation cascade	ExoT inhibits NLRC4-dependent inflammatory responses	(Mohamed et al., 2022)
	ExoU	NLRC4	ExoU-mediated oxidative stress and induction of autophagy at the mitochondria	Downregulation of NLRC4 inflammasome activation	(Hardy et al., 2022)
	T3SS, Flagellin	NLRC4, Caspase-1	PAD4-dependent histone citrullination	Neutrophil pyroptosis, DNA decondensation, *P. aeruginosa* spread	(Santoni et al., 2022)
	T3SS mutant	Caspase-4	Activation of NF-κB and TNF-α transcription and secretion	Induction of host cell lysis	(Kroken et al., 2023)
		NLRP3	CB2R activation reduces NF-κB activation	Reduction of *P. aeruginosa*-induced acute lung injury	(Nagre et al., 2022)
		NLRP3	CS induces mitochondrial damage	Increased acute lung injury and mortality	(White et al., 2022)
Salmonella enterica serovar Typhimurium	T3SS needle proteins	NLRC4	hNAIP- and mouse NAIP1-mediated recognition of bacterial T3SS needle protein	Inflammasome activation	(Yang et al., 2013)
	Flagellin	NLRC4	IFNAR regulates NLRC4/caspase-1/LPC axis, Repression of iPLA2 expression	Regulation of flagellin expression	(Akhade et al., 2020)
	SPI-1	Caspase-4	Caspase-4 and GSDMD pore-forming activity	Human IECS do not rely on NAIP/NLRC4 or NLRP3/ASC inflammasomes	(Naseer et al., 2022)

Table 2 (continued)

Pathogen	Effector	Inflammasome	Mechanisms	Effect	Ref.
	SpvC	Caspase-1/11	*SpvC* inhibits caspase-1/-11-dependent canonical and noncanonical pathways	Suppression of pyroptosis	(Zhou et al., 2024)
	T3SS, Flagellin	NAIP/NLRC4, NLRP3, Caspase-11	Caspase-1 activation	Pyroptosis, Induction of *Salmonella*-induced coagulopathy	(Pandeya et al., 2023)
	O-antigen ligase	Caspase-1, IL-18	Galectin-4-mediated caspase-1 activation and mature IL-18 production	Reduction of bacterial dissemination	(Li et al., 2023)
		NLRC4	TLR5-mediated LNCGM1082 activity promotes the binding of PKCδ with NLRC4	Resistance to bacterial infection	(Gao et al., 2023)
S. Enteritidis	SiiD	NLRP3	SiiD suppresses mtROS generation	Promotion of virulence and colonization *in vivo*	(Guo et al., 2023)
Shigella	OspC3, IpaH9.8	Caspase-4	IpaH9.8 degrades GBPs	Inhibition of caspase-44-mediated pyroptosis	(Goers et al., 2023)
	OspC3	NLRC4, Caspase-1/8/11	OspC3-dependent inhibition of caspase-11, TNFα activates caspase-8-dependent apoptosis	OspC3 counteracts the protective activity	(Roncaioli et al., 2023)
V. cholerae	Cholera toxin	NLRP3, ASC	El Tor: Secreted pore-forming toxin hemolysin Classical: cholera toxin and dependent of ASC	Activation of NLRP3-dependent and -independent pathway	(Queen et al., 2015)
	Hemolysin, MARTX	NLRP3, Pyrin, Caspase-11	Hemolysin/Nlrp3-independent inflammasome	Activation of pyrin inflammasome activation	(Mamantopoulos et al., 2019)
	OmpU	NLRP3	OmpU-mediated calcium flux and mtROS generation, OmpU-mediated TLR2 activation	NLRP3 inflammasome activation	(Dhar et al., 2023)
	T6SS	NLRP3	T6SS-induced pathway	Pyroptosis	(Cohen et al., 2022)
Yersinia	YopJ	NLRP3, NLRC4, Caspase-8	Rag GTPase activity, Lysosomal tethering of Rag-Ragulator	Pyroptosis	(Zheng et al., 2021)
Y. pseudotuberculosis	T3SS	Caspase-4	T3SS-mediated evasion of caspase-4 inflammasome	Regulation of inflammasome responses	(Zhang, Brodsky, & Shin, 2023)
Y. pestis	YspE1/2	Caspase-1, IL-1β	YspE2 ubiquitinates hGBP1 and leads to its proteasomal degradation	Promotion of survival of *Y. pestis*	(Cao et al., 2022)

ADPRT, ADP ribosyl transferase; ADSC, adipose-derived mesenchymal stem cell; CB2R, cannabinoid-2 receptor; CCR2, chemokine receptor 2; cGAS, cyclic GMP-AMP synthase; CNF1, cytotoxic necrotizing factor-1; CS, cigarette smoke; DSS, dextran sulfate sodium; EEF2, eukaryotic elongation factor 2; E-Syt1, extended synaptotagmin 1; EXOA, exotoxin A; ExoT, exotoxin T; HlyF, hemolysin F; IFNAR, interferon-α/β receptor; IgA, immunoglobulin A; iPLA2, calcium-independent phospholipase A2; LOS, lipooligosaccharide; LPC, lysophosphatidylcholine; MARTX, multifunctional auto-processing repeat-in-toxin; MifR, regulator of α-ketoglutarate transport; MLKL, mixed lineage kinase-like; MNGCs, multinucleated giant cells; mtROS, mitochondrial reactive oxygen species; NET, neutrophil extracellular trap; PAD4, protein arginine deaminase 4; Pak, P21 activated kinases, Pgam5, phosphoglycerate mutase 5; PKCδ, protein kinase C-delta; PmCQ2, *Pasteurella multocida* A strain CQ2; ROS, reactive oxygen species; RSR, ribotoxic stress response; SARM1, sterile α and HEAT armadillo motif-containing protein; SPI-1, *Salmonella* pathogenicity island 1; Sub AB, subtilase cytotoxin; TAC2, transcriptome-associated cluster 2; TecA, T6SS effector protein affecting cytoskeletal architecture; TLR5, toll-like receptor 5; TRIM31, tripartite motif 31; UPEC, uropathogenic *Escherichia coli*; YspE1, Yersinia secreted E3 ligase 1.

Table 3
The roles of inflammasome during mycobacteria and others infections.

Pathogen	Effector	Inflammasome	Mechanisms	Effect	Ref.
Mtb		Caspase-1/11	Cybb- and caspase1/11-dependent IL-1β production	Regulation of Mtb growth	(Thomas & Olive, 2023)
	ESX-1	NLRP3	ESX-1-mediated plasma membrane damage	Pyroptosis, Release of infectious particles	(Beckwith et al., 2020)
	PPE13	NLRP3	Interaction with the LRR and NATCH domains of NLRP3	Induction of IL-1β secretion	(Yang et al., 2020)
		Caspase-1	MDA5 activation	Promotion of intracellular bacillary growth in primed macrophages	(Bullen et al., 2023)
		AIM2, NLRP3, NLRC4	Release of mtROS in *Lrrk2*^G2019S^ macrophages	RIPK1/RIPK3/MLKL-dependent necroptosis	(Weindel et al., 2022)
	PtpB	NLRP3	PtpB alters host membrane composition	Inhibition of pyroptosis and host immunity	(Van Hauwermeiren & Lamkanfi, 2023), (Chai et al., 2022)
		NLRP3	DHOB suppresses deacetylase activities of HDAC1 and HDAC2	Increased IL-1β and NLRP3 expression	(Moreira et al., 2022)
		NLRP3, AIM2	Baicalein suppresses the assembly of AIM2 and NLRP3 inflammasome, Autophagy induction	Inhibition of pyroptosis	(Ning et al., 2023)
BCG		Caspase-1/11, NLRP3	BCG training increases NLRP3 expression during *B. abortus* infection	Reduction of *B. abortus* burden	(de Araujo et al., 2023)
M. pneumoniae		NLRP3	Upregulation of MyD88/NF-κB pathway	Regulation of IL-1β secretion, Inhibition of *M. pneumoniae* growth *in vivo*	(Segovia et al., 2018)
	CARDS toxin	NLRP3	Interaction of CARDS toxin with NLRP3, ADP-ribosylation of NLRP3 by CARDS toxin	Toxin-mediated inflammasome activation	(Bose et al., 2014)
R. typhi, R. rickettsii		Caspase-11, GSDMD	Inhibition of IL-1 cytokine secretion	Controlling the survival and colonization of *Rickettsia* species	(Voss et al., 2021)

B. abortus, Brucella abortus; BCG, *Mycobacterium bovis* bacille Calmette-Guérin; CARDS, comminity-acquired respiratory distress syndrome; DHOB, 4-(dimethylamino)-N-[6-(hydroxyamino)-6-oxohexyl]-benzamide; Esx-1, type VII secretion system; Lrrk2, leucin-rich repeat kinase 2; MDA5, melanoma differentiation factor 5; Mtb, *Mycobacterium tuberculosis*; mtROS, mitochondrial reactive oxygen species; PPE, Pro-Pro-Gl.

LM, *S.* Typhimurium, and *E. coli* (Anand et al., 2012). These data suggest that several inflammasome sensors play a distinct role in host protection against LM infection. The balanced activation of numerous inflammasomes may contribute to the prevention and control of LM infection *in vivo*.

5.1.5. The genus Staphylococcus

S. aureus, a Gram-positive coccus, activates the NLRP1 inflammasome in keratinocytes, increases IL-1β and IL-18 production, and contributes to the pathogenesis of atopic dermatitis (Vaher et al., 2023). Intracellular bacteriolysis of *S. aureus* promotes host cell necroptosis through AIM2 inflammasome activation (Feng et al., 2022). Increased bacteriolysis followed by cell death is associated with the pathogenesis of *S. aureus* dissemination into the kidneys and the inflammatory cytokine storm *in vivo* (Feng, Yang, et al., 2022). In addition, staphylokinase of *S. aureus* induces community-associated *S. aureus*-mediated pneumonia in WT and cathelicidin-related antimicrobial peptide KO mice. Mechanistically, staphylokinase activates the priming of the NLRP3 inflammasome, and the increase of K^+ efflux, ROS generation, and upregulated NF-κB signaling, which potentiates the pathogenesis of highly virulent *S. aureus* infection (Wang et al., 2022). Furthermore, *S. aureus* endophthalmitis is mediated by bacterial cell wall components and toxins through activation of the NLRP3 inflammasome complex in murine eyes (Kumar, Singh, Ahmed, Singh, & Kumar, 2022).

In terms of controlling strategies for NLRP3 inflammasome activation, butyrate derivatives, sodium butyrate, or phenylbutyrate suppress intraocular bacterial growth, retinal inflammation, and NLRP3 inflammasome activation. Mechanistically, butyrate treatment increases AMPK signaling, the colocalization of cathelicidin-related antimicrobial peptide into autophagosomes and antibacterial autophagy, which ameliorates intraocular *S. aureus* endophthalmitis (Singh, Singh, & Kumar, 2023).

S. epidermidis, the most common nosocomial pathogen in preterm infants with an increased risk of cognitive delay, can activate NOD-receptor signaling and transendothelial leukocyte trafficking, in the immature hippocampus following infection. These data suggest that the activation of the microglia inflammasome results in neuroinflammation following *S. epidermidis* infection (Gravina et al., 2023). Additionally, *S. epidermidis* infection results in the production of mature IL-1β in keratinocytes in a caspase-1–independent manner, which contributes to host innate defense in the skin (Rademacher et al., 2022). These data suggest that NLRP3 inflammasome activation contributes to the pathogenesis of *Staphylococcus* infection.

5.1.6. The genus Streptococcus

S. pyogenes (Group A *Streptococcus*; GAS), a Gram-positive pathogen that causes pharyngitis, impetigo, septicemia, streptococcal toxic shock-like syndrome, and necrotizing fasciitis, is a major pathogen in humans (Brouwer et al., 2023). Streptolysin O, a pore-forming toxin of GAS, can trigger inflammasome activation in murine and THP-1 macrophages (Richter et al., 2021). Mechanistically, GAS-derived lipoteichoic acid provides a priming signal for NLRP3 inflammasome activation. Both streptolysin O and streptolysin S, the major toxins of GAS, activate the NLRP3 inflammasome and induce IL-1β release in macrophages (Richter et al., 2021). In keratinocytes, pro-IL-18 is constitutively secreted, and the SpeB, a GAS protease, can activate the maturation of IL-18 upon GAS infection. Processed IL-18 activates T cell secretion of IFN-γ, promoting protective functions against GAS infection (Johnson et al., 2023). These data suggest that GAS- or their specific virulence factor-mediated maturation of IL-1β and IL-18 may play distinct roles depending on the cell types.

S. pneumoniae is a Gram-positive pathogen that causes severe infectious diseases, such as pneumonia and meningitis. The NEK7-NLRP3 complex and JNK phosphorylation are associated with *S. pneumoniae* infection. Together, these factors regulate IL-1β maturation, inhibit bactericidal effects, and inflammatory responses (Wang, Zhao, et al., 2023).

Xu et al. revealed that NLRP6$^{-/-}$ mice show improved survival rates and a reduced burden of *S. pneumoniae*. These findings emphasize the function of the NLRP6 inflammasome as a negative regulator that affects the development of NF-κB, IL-1β, and the extracellular signal-regulated kinase signaling pathway (Xu et al., 2021). Therefore, both NLRP3 and NLRP6 appear to play detrimental roles in the host defense against *S. pneumoniae* infection.

S. suis infection triggers early inflammatory responses with upregulated NLRP3 inflammasome activation and pyroptosis, which contributes to splenomegaly with lymphocyte disruption during the early stage of infection. This may contribute to the pathogenesis of *S. suis* infection (Wang et al., 2022). Furthermore, commensal oral bacterium *S. gordonii* uses NLRP6-dependent IL-1β production to enhance inflammation and avoid host immune responses after infection (Metcalfe, Panasiewicz, & Kay, 2023). Considering that different species of *Streptococcus* elicit specific types of inflammasomes leading to their respective pathologies, it is important to examine the regulatory mechanisms governing how each bacterium triggers distinct inflammasome complexes.

5.1.7. Enterococcus faecalis

E. faecalis is typically a commensal bacterium that causes infections at surgical sites, the urinary tract, and the bloodstream (Nappi, Avtaar Singh, Jitendra, & Fiore, 2023). Recently, it was revealed that butyrate, a short-chain fatty acid, enhances the activation of canonical and noncanonical inflammasomes in macrophages stimulated by *E. faecalis* lipoteichoic acid. This heightened response is associated with the inhibition of histone deacetylases (HDACs) (Park et al., 2023). Moreover, costimulation of *E. faecalis* lipoteichoic acid and butyrate not only triggered inflammasome activation, but exacerbated pulp necrosis and increased IL-1β expression in a rat experimental model of apical periodontitis (Park, Ha, et al., 2023). A thorough investigation is needed to identify the specific inflammasomes involved and elucidate their contributions to the pathogenesis of *E. faecalis*. Such insights are crucial for effectively managing severe *E. faecalis* infections, particularly those frequently observed in immunocompromised patients.

5.1.8. Porphyromonas gingivalis

P. gingivalis, a prominent periodontal pathogen, can evade the host's autophagic machinery by activating lysosome efflux and inhibiting autophagic maturation. It thrives within host cells, triggering mitochondrial damage and the inflammatory responses. The resulting increase in mitochondrial and lysosomal dysfunction associated with the activation of the NLRP3 inflammasome and subsequent release of IL-1β contributes to the pathology of *P. gingivalis* infection (Liu, Shao, Zhao, Ma, & Ge, 2023).

Notably, *P. gingivalis* outer membrane vesicles (OMVs) activate astrocytes and microglia, resulting in neuroinflammation, which is characterized by the production of IL-1β, tau phosphorylation at the Thr231 site, and the expression of NLRP3 inflammasome-associated proteins in the hippocampus (Gong et al., 2022). OMVs generated by P. gingivalis (W83) during its stationary phase activate the NLRP3 inflammasome, enhancing the pathogenicity and virulence of the bacteria (Mao et al., 2023). Additional studies are needed to address and alleviate inflammasome-related pathologies induced by *P. gingivalis* infection.

5.1.9. Clostridium perfringens

C. perfringens, a Gram-positive, anaerobic, spore-forming pathogen found widely in nature, is recognized as the causative agent of both foodborne illnesses and gas gangrene. An important issue associated with *C. perfringens* is the increasing prevalence of antibiotic resistance, which highlights the need for the development of innovative therapeutics (Grenda et al., 2023). *C. perfringens* beta-1 toxin, which is responsible for necrotizing enteritis and enterotoxemia, induces macrophage pyroptosis through the expression of the pyroptosis regulatory molecules and upregulation of the NLRP3 inflammasome assembly, which

leads to increased IL-18 and IL-1β release (Zhang et al., 2023). In addition, *C. perfringens* lecithinase (also known as phospholipase C) induces inflammasome activation to release IL-1β and IL-18; however, lecithinase-mediated induction of cell death is independent of GSDMD, MLKL, and the cell death effector protein ninjurin-1 (Mathur et al., 2023). The NLRP3 inflammasome blocker MCC950 partially inhibits lecithinase-induced lethality, indicating that lecithinase-induced pathologies are mediated through multiple inflammasomes, not just the NLRP3 inflammasome (Mathur et al., 2023). Notably, the MLKL plays an important role in protection against *C. perfringens* infection through K$^+$ efflux-dependent NLRP3 inflammasome activation and classical extracellular trap formation (Liu et al., 2022). Moreover, α-toxin of *C. septicum*, another *Clostridium* bacterial pathogen of sepsis and gas gangrene, activates the NLRP3 inflammasome and GSDMD-mediated pyroptosis by binding to glycosylphosphatidylinositol-anchored proteins (Jing et al., 2022). Although *Clostridium* species can activate various inflammasome complexes and induce pyroptosis, there is still a significant gap in our understanding of the molecular mechanisms through which their toxins trigger inflammasome activation and initiate diseases.

5.2. Gram-negative bacteria

5.2.1. Achromobacter

The genus *Achromobacter* consists of opportunistic Gram-negative pathogens that induce host cell death in human macrophages through the T3SS, which results in inflammasome-dependent pyroptosis. Bacteria-triggered pyroptotic cell death and inflammation require the presence of either NLRC4 or NLRP3. Furthermore, these bacteria can inhabit late phagolysosomes within host cells, causing lung damage and severe illness in a mouse infection model. These findings suggest that both NLRC4 and NLRP3 play significant roles in the pathogenesis of *Achromobacter* infection (Turton et al., 2023).

5.2.2. Acinetobacter baumannii

A. baumannii is an opportunistic and multidrug-resistant (MDR) Gram-negative bacterium that contributes to mortality in intensive care units (Itani et al., 2023). *A. baumannii* can induce NLRP3 inflammasome activation, enhancing lung pathology by triggering IL-1β production (Kang, Jo, Kim, & Park, 2017). *A. baumannii* initiates TRIF-dependent IFN-I production, leading to the upregulation of the Z-DNA-binding protein 1 (Zbp1), mixed lineage kinase-like (MLKL), caspase-11, and GSDMD genes. This intricate cascade ultimately results in NLRP3 inflammasome activation, which potentially contributes to MLKL-dependent necroptosis and GSDMD-mediated pyroptosis (Li et al., 2018).

The activation of the NLRP3 inflammasome and cleavage of GSDMD by *A. baumannii* are counteracted by short-chain fatty acids, such as sodium butyrate and sodium propionate, in THP-1 cells. These responses are mechanistically linked to upstream signaling through the TLR2/NF-κB/ROS pathway (Shu et al., 2022). Diverse clinical strains of *A. baumannii* exhibit varying levels of activation of the NLRP3 inflammasome, the non-canonical caspase-11 pathway, IL-1β production, and pyroptosis (Dikshit et al., 2018; Li et al., 2022). These observations underscore the strain-dependent nature of the inflammasome responses during *A. baumannii* infection. Further studies are warranted to elucidate the mechanisms underlying *A. baumannii*-triggered inflammasome activation and cell death, which will lead to the development of therapeutic strategies against MDR *A. baumannii* infections.

5.2.3. Akkermansia muciniphila

A. muciniphila, a well-known gut microbe, plays a beneficial role in colitis progression (Jian, Liu, Wang, Dong, & Zou, 2023). Strain BAA-835 significantly alleviates dextran sodium sulfate-induced acute colitis by reducing proinflammatory cytokines and increasing NLRP3, caspase-1 p20, and IL-1β p17 *in vivo*. The protective effects induced by *A. muciniphila* involve NLRP3 inflammasome activation, offering insights

for probiotic-based colitis treatment (Qu et al., 2021). In addition, *A. muciniphila* treatment mitigates neuroinflammation and nerve injury by modulating NLRP3 inflammasome during post-traumatic brain injury (Chen et al., 2023). Both live and pasteurized *A. muciniphila* exhibit protective effects against *S.* Typhimurium infection. This promotes NLRP3 expression and macrophage antimicrobial activity through ROS and nitric oxide generation (Liu et al., 2023). Diverse infection and inflammation models highlight the varied benefits of *A. muciniphila* through the distinct modulation of NLRP3 inflammasome activation. A deeper understanding is needed to elucidate the mechanisms of *A. muciniphila*-mediated regulation of NLRP3 inflammasome activation in different disease settings.

5.2.4. Brucella

Brucellosis is caused by the Gram-negative bacterium *Brucella* and remains a prominent global zoonotic infection (Soares, da Silva, & Lima, 2023). Previous studies have elucidated its ability to activate both AIM2 and NLRP3 inflammasomes, which are important for regulating *Brucella*'s intracellular survival during infection (Liu et al., 2015). This activation also plays a role in blood-brain barrier activation in cases of neurobrucellosis (Miraglia et al., 2016). The cyclic GMP-AMP synthase-independent STING pathway activation triggered by *B. abortus* is indispensable for intracellular control. It promotes host defense through GBPs and inflammasome activation (Costa Franco et al., 2018). Interestingly, NLRP12 is a suppressor of inflammatory cytokine generation and inflammasome activation in macrophages during *B. abortus* infection. NLRP12 deficiency correlates with enhanced resistance to *B. abortus* infection *in vivo*, influencing the protective function of inflammasome activation during early infection (Silveira et al., 2017). When exposed to *B. abortus* infection, *Nlrp6*$^{-/-}$ mice exhibit an altered colonic microbiota composition that is associated with increased permeability and *B. abortus* dissemination (Rungue et al., 2021). These findings indicate the involvement of multiple inflammasomes in protecting against *Brucella* infection.

A comprehensive understanding of inflammasome activation is necessary to prevent and treat brucellosis. Strategies aimed at enhancing combined inflammasome activation may be an approach to address this complex infection. Numerous effectors produced by *Brucella* modulate inflammasome activation and pyroptosis. For example, *Brucella* TcpB induces the ubiquitination and degradation of inflammatory caspases-1, 4, and 11, thereby inhibiting LPS-induced noncanonical inflammasome activation and pyroptosis (Jakka, Namani, Murugan, Rai, & Radhakrishnan, 2017). BtpB, a protein produced by *Brucella*, inhibits the expression of TLR2 and TLR4 and attenuates NLRP3 inflammasome activation in alveolar macrophages (Li et al., 2022). BtpB further suppresses the secretion of the proinflammatory cytokines, IL-1β, IL-6, and TNF-α, in alveolar macrophages, thereby reducing early host immune responses during *Brucella* infection (Li, Zhang, et al., 2022). The identification and characterization of *Brucella* effectors, aimed at modulating inflammasome activity and pyroptotic cell death, are important for the development of effective immunomodulatory strategies against *Brucella* infection.

5.2.5. Burkholderia

Burkholderia pseudomallei, the causative agent of melioidosis, thrives in tropical and subtropical environments (Meumann, Limmathurotsakul, Dunachie, Wiersinga, & Currie, 2024). Although *B. thailandensis* is typically nonpathogenic in mammals, it shares phenotypic characteristics with *B. pseudomallei* (Lowe, March, Bunnell, O'Neill, & Robison, 2014). Myeloid cell-specific caspase-11 is essential for the clearance of bacteria and host defense against *Burkholderia* infection (Kumari, Russo, Wright, Muthupalani, & Rathinam, 2021). Pyroptosis, apoptosis, and necroptosis (PANoptosis) play important roles in host defense against respiratory *B. thailandensis* infection (Place et al., 2021).

Mice deficient in extended synaptotagmin 1, which is an ER protein that regulates caspase-11, show increased susceptibility to

B. thailandensis. Caspase-11 and extended synaptotagmin 1 are important for defense against cytosol-invading bacteria, activating pyroptosis, and IL-1β secretion (Ma et al., 2023). In addition, IFN-γ-induced GBP1 activation plays an important role in the antimicrobial responses to *B. thailandensis* in macrophages, thus promoting noncanonical inflammasome activation. IFN-γ priming in human epithelial cells inhibits *B. thailandensis*-induced multinucleated giant cell formation in a GBP1-dependent manner (Dilucca, Ramos, Shkarina, Santos, & Broz, 2023). Moreover, caspase-1-induced pyroptosis facilitates the release of *B. thailandensis* and *L. pneumophila* from macrophages, which is cleared by ROS in neutrophils (Miao et al., 2010).

During *B. cenocepacia* infection, the T6SS effector TecA deactivates RhoA GTPase, which activates the pyrin inflammasome and induces proinflammatory IL-1β secretion to promote lung inflammation (Loeven et al., 2021). In human macrophages, the *B. pseudomallei* T3SS-3 needle protein BsaL triggers the canonical inflammasome and GSDMD-mediated cell death (Lichtenegger et al., 2020). In addition, the *B. pseudomallei* effector BsaK, along with other Gram-negative bacterial rod proteins, is recognized by NLRC4 and initiates innate immune activation (Miao, Mao, et al., 2010). Further studies are needed to identify the bacterial virulence factors that either evade or hyperactivate the host inflammasome machinery, which will lead to the development of therapeutic and preventive strategies against opportunistic infections.

5.2.6. Citrobacter rodentium

C. rodentium, an extracellular enteric pathogen specific to mice. It elicits intestinal inflammatory responses in murine hosts. It has been widely used as a model for studying infections involving human pathogenic *E. coli* and inflammatory bowel disease (Mullineaux-Sanders et al., 2019). Studies of *C. rodentium* infection models have revealed the important roles of NLRP3 and NLRC4 in protecting against intestinal pathogenic infections. NLRC4, which is particularly expressed in epithelial crypts, plays a protective role against *C. rodentium*-induced intestinal inflammation (Nordlander, Pott, & Maloy, 2014). The combined actions of caspase-8 and RIPK3 are important for protecting against intestinal pathogen loads. Systemic protection against *C. rodentium* relies on caspase-1, caspase-8, and RIPK3 (Eeckhout et al., 2023). The activation of NLRP3 in intestinal epithelial cells suppresses *C. rodentium* colonization and prevents subsequent pathology (Song-Zhao et al., 2014). However, tight regulation of inflammasome activation is essential to prevent exaggerated intestinal inflammatory responses. NLRP6 inflammasome activation, which is important for intestinal inflammation, is regulated by the deubiquitinase *Cyld* and prevents severe colonic inflammation and excessive IL-18 production (Mukherjee et al., 2020).

TRIF is required for NLRP3 inflammasome activation during enterohemorrhagic *E. coli* and *C. rodentium* infection. Moreover, TRIF-dependent activation of caspase-11, in synergy with NLRP3 inflammasome activation, results in caspase-1-independent cell death during Gram-negative bacterial infection (Rathinam et al., 2012). *C. rodentium* models will be valuable in future studies to unravel the intricate activation mechanisms and identify potential therapeutic candidates for regulating inflammasomes.

5.2.7. Clostridioides difficile

C. difficile (CD) is a significant nosocomial colitis pathogen that causes significant morbidity and mortality worldwide (Balsells et al., 2019). The CD toxins, TcdA and TcdB, breach the intestinal barrier to induce mucosal inflammation and damage. By activating an ASC-containing inflammasome, TcdA and TcdB induce IL-1β release, contributing to toxin-induced inflammation and damage *in vivo* (Ng et al., 2010). Endotoxin markedly increased the capacity of CD toxin B to enhance IL-1β production depending on the type of endotoxin and the combined activation of inflammasomes and TLR4 (Htwe et al., 2021). In addition, the pyrin inflammasome is activated in response to the Rho-glucosylation activity of cytotoxin TcdB, a significant virulence factor, and exhibits a protective role (Xu et al., 2014). Moreover, the

flagellin of CD activates the NLRC4 inflammasome, induces inflammatory cytokine production, and GSDMD activation after internalization into epithelial cells (Chebly et al., 2022). These findings suggest that distinct components of CD activate various inflammasome sensors, with the intensity of inflammasome activation being influenced by the endotoxin. Further studies are warranted to better understand the mechanisms by which CD triggers the inflammasome complex. Such insights are necessary for the development of novel therapeutics to treat severe CD colitis.

5.2.8. Escherichia coli

E. coli is a gut commensal involved in numerous intestinal and extraintestinal infections as an opportunistic pathogen. *E. coli* isolates are categorized into numerous strains with specific pathogenic characteristics (Denamur, Clermont, Bonacorsi, & Gordon, 2021). For example, enterotoxigenic *E. coli*, responsible for acute watery diarrhea, exhibits specific serotypes with plasmids encoding heat-stable/labile enterotoxins and fimbrial colonization factors. Nonmotile *Shigella*-like *E. coli* serogroups cause bacterial dysentery through tissue invasiveness. Traditional enteropathogenic *E. coli* lacks defined virulence factors but emphasizes intestinal colonization (Denamur et al., 2021).

E. coli cytotoxic necrotizing factor-1 triggers caspase-1-NLRP3 inflammasome activation by acting on the host Rho GTPase Rac2. The p21-activated kinases 1 and 2 (Pak1/2) and Pak1-mediated NLRP3 phosphorylation result in the NLRP3-Nek7 interaction and inflammasome activation, leading to the maturation of IL-1β. The Pak-NLRP3 axis is required for bacterial clearance of cytotoxic necrotizing factor-1-expressing UTI89 *E. coli* (Dufies et al., 2021). In addition, subtilase cytotoxin, an AB5 toxin produced by Shiga-toxigenic *E. coli* (STEC) strains, such as O113:H21, suppresses the noncanonical NLRP3 inflammasome and the maturation of IL-1β and IL-18 in murine macrophages. It also inhibits caspase-11 expression by downregulating IFN-β/STAT1 signaling (Tsutsuki et al., 2022). Furthermore, STEC stimulates neutrophils to produce IL-1β through the NLRP3 inflammasome and neutrophil serine proteases (NSPs). The inhibition of NSPs suppresses STEC-triggered IL-1β secretion without modulating the bactericidal effect of neutrophils. This suggests that NSPs are targets for limiting STEC-induced intestinal inflammation (Sabbione et al., 2023).

HlyF of pathogenic adherent-invasive *E. coli* is a cytoplasmic enzyme that results in the overproduction of OMVs to inhibit macroautophagic/autophagic flux, thereby preventing autophagosome clearance. Furthermore, HlyF-associated OMVs amplify the noncanonical inflammasome pathway, thus exacerbating pathogenesis (David et al., 2022).

Extraintestinal infection-associated *E. coli*, featuring distinct serogroups and serotypes, contain polysaccharide capsular antigens, hemolysin, and complex fimbrial colonization factors (Evans Jr. & Evans, 1983). Uropathogenic *E. coli*, which is the main causative agent of urinary tract infections, activates the NLRP3/caspase-1/GSDMD pyroptotic pathway, which is modulated by treatment with dendrobium officinale (Zhang et al., 2022). A recent study demonstrated that extracellular peroxiredoxin 1, which is increased by *E. coli* or *L. monocytogenes* infection, triggers the noncanonical TRIF-caspase-11-GSDMD pathways (Kang, Lee, Kim, Lee, & Yim, 2023). In addition, caspase-6 is required for the activation of caspase-11 and pyroptosis in macrophages after *E. coli* infection (Zheng et al., 2021). The regulatory mechanisms by which each *E. coli* subtype activates or inhibits inflammasome activation warrant further study. These data will lead to the development of specific therapeutic targets for *E. coli*-related intestinal and extraintestinal infections.

5.2.9. Francisella tularensis and F. novicida

F. novicida, a causative pathogen of murine tularemia, markedly induces AIM2 inflammasome activation, which is partly dependent on host-derived DNA from damaged mitochondria. *F. tularensis* DNA induced AIM2 oligomerization in macrophages and AIM2-deficient mice were more susceptible to infection compared with WT mice (Fernandes-Alnemri et al., 2010). A recent study also showed that

AIM2/Pyrin/ZBP1-induced PANoptosis (inflammatory cell death) resulted in host protection from *F. novicida* infection (Lee et al., 2021); however, macrophages infected with *F. tularensis* live vaccine strain exhibited less AIM2-dependent IL-1β secretion compared with those infected with *F. novicida*, presumably because of the induction of mitophagy. Mitophagy serves to eliminate leaked mtDNA, thereby mitigating inflammasome activation (Alqahtani et al., 2023).

GBP1 and GBP3 play important roles in inflammasome activation during infection with *F. novicida*. Mouse GBP1 and GBP3 can directly bind to and promote the killing of *F. novicida* and *N. meningitides*. This results in pathogen membrane rupture and the cytoplasmic release of intracellular contents like bacterial DNA, which is sensed by the inflammasome machinery (Feng, Enosi Tuipulotu, et al., 2022). These results strongly suggest that GBPs in cooperation with the inflammasome activation can recognize specific pathogens and exert antimicrobial activity during infections. Further mechanistic studies based on the functions of GBPs in relation to inflammasome activation may offer the exciting design and development of effective antimicrobial proteins for fighting infections.

5.2.10. Haemophilus influenzae and Moraxella catarrhalis

H. influenzae is a Gram-negative bacteria that causes a variety of infections, including bronchitis, meningitis, and septic arthritis (Moxon & Wilson, 1991). Nonencapsulated *H. influenzae*, a commensal of the airways, can activate the NLR inflammasome pathway to induce IL-1β, thereby triggering inflammatory responses in primary nasal epithelial cells (Brown et al., 2023). A whole genome sequencing study revealed that *H. influenzae* and *M. catarrhalis* are more abundant in severe neutrophilic asthma, with gene clusters associated with inflammasome and neutrophil activation (Versi et al., 2023). Additional studies are needed to elucidate the role of the inflammasome in determining *H. influenzae*-related pathologies in various disease settings.

M. catarrhalis, another Gram-negative bacterium, causes otitis media and chronic obstructive pulmonary disease. A recent study demonstrated that the OMVs or lipooligosaccharide of *M. catarrhalis* are responsible for inflammasome activation, which involves caspase-4/11, GSDMD-dependent pyroptosis, and the NLRP3 inflammasome in human and mouse macrophages. GBP2 and inflammasome activation are essential for resistance to *M. catarrhalis* infection in mice (Enosi Tuipulotu et al., 2023). Further studies are needed to clarify the functions of their effectors during inflammasome activation and to assess their impact on the clinical manifestations.

5.2.11. Helicobacter pylori

H. pylori, a major human pathogen with high global prevalence, can trigger various gastrointestinal diseases and gastric malignancies, posing a significant threat to human health due to increasing antibiotic resistance (Tshibangu-Kabamba & Yamaoka, 2021). A recent study demonstrated the essential role of NOD1 in IL-18 maturation in mouse epithelial cells responding to *H. pylori*. This process helps maintain epithelial homeostasis and protects pre-neoplastic transformation (Tran et al., 2023). Therefore, NOD1-mediated noncanonical inflammasome activation, which results in the production of IL-18, may serve a beneficial function against *H. pylori*-induced pathology (Tran et al., 2023).

The NLRP3 inflammasome is activated in gastric tissues of mice with chronic *H. pylori* infection both *in vivo* and *in vitro*. Tripartite motif 31 is a negative regulator of NLRP3 inflammasome activation, and its deficiency results in enhanced ROS production and impaired autophagy. This, in turn, promotes NLRP3 inflammasome activation, which contributes to gastritis pathologies (Yu et al., 2023). Furthermore, patients with peptic ulcer disease exhibit decreased levels of NLRC4, IL-18, and serum IL-1β, whereas AIM2 expression is increased (Davari, Shokri-Shirvani, Sepidarkish, & Nouri, 2023). In addition, AIM2 mRNA and protein expression levels are upregulated in *H. pylori*-positive human gastric biopsy samples compared with those under *H. pylori*-negative conditions. In a parallel observation, gastric inflammation and hyperplasia

were less severe in *H. felis*-infected AIM2-deficient mice compared with WT mice. These responses are associated with decreased inflammasome activity (caspase-1 cleavage and IL-1β maturation), suggesting a role of AIM2 in gastric pathogenesis (Dawson et al., 2023). Although these studies indicate pathological roles of NLRP3 and AIM2 inflammasome activation in *H. pylori*-induced gastric inflammation, further studies are needed to identify the precise functions of each inflammasome and their association with gastric pathologies.

The role of IL-1β in the development of *H. pylori*-associated gastric cancer is multifaceted, yet still controversial (Yuan, Zhang, Zhao, Chen, & Liu, 2023). Future studies should explore the role and mechanisms of inflammasome activation and *H. pylori*-induced carcinogenesis.

5.2.12. Klebsiella pneumoniae

K. pneumoniae (KP), a Gram-negative bacterium notorious for causing pneumonia and sepsis, remains a common pathogen that induces antimicrobial-resistant opportunistic infections (Wyres, Lam, & Holt, 2020). An early study indicated a role for caspase-11 in host protection against KP, not through cell death induction or lung pathology, but by activating blood coagulation in the lungs (Perlee et al., 2020). KP-induced ALI is associated with increased TLR4/NF-κB signaling and inflammasome activation in lung macrophages. Chrysophanol (chrysophanic acid), a natural anthraquinone extracted from *Rheum palmatum L.*, can reduce inflammatory responses mediated through the TLR4/NF-κB and JNK signaling pathway, which in turn suppresses the activation of the NLRP3 inflammasome (Jiang et al., 2023).

An early study demonstrated that a KP clinical strain inhibited inflammasome activation and pyroptosis through IL-10 induction and exhibited increased bacterial survival and dissemination. This suggests an immune escape mechanism employed by the clinical strain (Codo et al., 2018); however, recent studies contradict this. A hypervirulent KP strain activates the NLRP3 inflammasome and lysosomal cathepsin B activation to promote pyroptosis, thus impacting disease pathogenesis (Kim et al., 2023). Interestingly, miR-181-5p, generated by adipose-derived mesenchymal stem cells, targets and inhibits STAT3 expression in macrophages, and ameliorates inflammasome activation and the secretion of IL-1β and IL-18 *in vivo* (Hu et al., 2022).

Furthermore, *Nlrp6$^{-/-}$* mice exhibit a compromised host defense and disturbed neutrophil homeostasis during KP infection (Cai et al., 2021). Another study indicated that KP exploits the immune activation through sterile α and HEAT armadillo motif-containing protein, which promotes the anti-inflammatory cytokine IL-10 by fine-tuning the p38-IFN-I axis and negatively regulates the activation of the KP-induced AIM2 inflammasome. The results indicated increased virulence and intracellular survival of KP in sterile α and HEAT armadillo motif-containing protein KO mice (Feriotti et al., 2022). Thus, activation of various inflammasomes contributes to the host's responses to KP infection, and the outcomes depend on the specific strain and host cell characteristics. It is necessary to obtain a comprehensive understanding of bacterial escape and the mechanisms that trigger inflammasome activation along with their respective consequences. This is crucial for the development of alternative treatments aimed at MDR KP infections.

5.2.13. Legionella pneumophila

L. pneumophila (LP) is a Gram-negative, flagellated intracellular pathogen responsible for severe pneumonia, known as Legionnaires' disease. Protection from LP infection requires the NAIP/NLRC4 inflammasome and pyroptosis (Goncalves et al., 2019; Mascarenhas et al., 2017). Caspase-8 is required for GSDMD-independent pore formation and cell death under caspase-1/11-deficient conditions. It is recruited to the Naip5/NLRC4/ASC inflammasome during flagellin-positive bacterial infection (Mascarenhas et al., 2017). In addition, caspase-7 and GSDMD play essential roles in host protection downstream of NAIP5/NLRC4/CASP1/8 activation (Goncalves et al., 2019). Two coordinated innate immune pathways, orchestrated by C-C chemokine receptor type 2 contribute to the protection against inflammasome-related pulmonary

infection through NLRC4 inflammasome activation and monocyte-derived dendritic cell recruitment (Ataide, Manin, Oliveira, Guerra, & Zamboni, 2023).

LP induces inflammasome activation in human macrophages through GBP1. GBP1 colocalizes with *Legionella* and vacuoles containing LP through a T4SS-dependent mechanism, which facilitates damage to *Legionella*-containing vacuoles. The combined action of IFN and GBP1 increases bacterial exposure to the host cell cytosol (Bass et al., 2023). Moreover, caspase-1, −8, and −11 are required for optimal TNF-mediated restriction of bacterial replication in macrophages. Specifically, caspase-8-mediated pyroptosis controls pulmonary LP infection. Thus, TNF-dependent pyroptotic cell death, mediated through caspase-1, −8, and −11, is beneficial for restricting *Legionella* infection (Pollock, Vazquez Marrero, Brodsky, & Shin, 2023).

Because the data indicates that LP utilizes T4SS to inject over 300 bacterial proteins into host cells and modulate mitochondrial function (Garcia-Rodriguez, Buchrieser, & Escoll, 2023), a more comprehensive understanding is essential for the mechanistic modulation of bacterial effectors on host cell inflammasome activation and death. This will facilitate the development of strategies against Legionnaires' disease and other intracellular pathogenic infections.

5.2.14. Leptospira interrogans

L. interrogans, a causative pathogen of leptospirosis, triggers the activation of the NLRP3 inflammasome in human macrophages through a ROS- and cathepsin B-dependent mechanism (Li, Guo, et al., 2018). Doxycycline treatment significantly inhibits L. *interrogans*-induced NLRP3 inflammasome activation by suppressing the priming step involving the Na/K-ATPase pump (Lacroix-Lamande et al., 2012; Zhang et al., 2017); however, a recent study demonstrated that L. *interrogans* inhibits pyroptosis and apoptosis. *L. interrogans* and its atypical LPS prevents caspase-11 dimerization, GSDMD cleavage, and massive IL-1β release in murine, human, hamster, or bovine macrophages (Bonhomme et al., 2023). The evasion of L. *interrogans* from pyroptosis may contribute to dampening the excessive production of IL-1β, thereby contributing to pathogenesis (Bonhomme et al., 2023). Although the exact function of the NLRP3 inflammasome requires further investigation in the context of L. *interrogans*. These studies will provide insight into L. *interrogans* inhibition of pyroptosis and its benefit to pathogenesis.

5.2.15. Pasteurella multocida

P. multocida is a zoonotic pathogen responsible for respiratory and hepatic infections in various animal species, including cattle, sheep, pigs, chickens, and humans (Cai et al., 2023; Wilson & Ho, 2013). Bovine *P. multocida* type A (PmCQ2) can activate the NLRP3 inflammasome activation through mechanisms involving K⁺ efflux and Nek7 activation (Wang et al., 2022). In addition, the activation of the NLRP3 inflammasome and subsequent secretion of IL-1β by *P. multocida* is contingent upon virulence factors expressed by the bacterium (Fang et al., 2020). Furthermore, *P. multocida* activates the NLRP6 inflammasome, resulting in increased infiltration of inflammatory cells into the lungs of both WT and *Nlrp6*⁻/⁻ mice. NLRP6 plays an important role in regulating *P. multocida* infection and modulates the bacterium-induced secretion of inflammatory cytokines, such as IL-1β and IL-6 (Wu et al., 2022). Further studies are warranted to elucidate the distinct roles and contributions of various inflammasome activation pathways and pyroptosis in the context of disease pathogenesis associated with this emerging zoonotic infectious disease in humans and other animals.

5.2.16. Pseudomonas aeruginosa

P. aeruginosa (PA) is a Gram-negative opportunistic pathogen characterized by a MDR phenotype. It causes acute or chronic infections in immunodeficient individuals, such as those with cystic fibrosis, burn wounds, chronic obstructive pulmonary disorder, and cancer (Qin

et al., 2022). Previous studies have highlighted the involvement of virulence factors associated with the secretion system of PA in activating various inflammasomes within host cells. For example, PA strain PAO1, expresses the T3SS effectors ExoS and ExoT and induces IL-1β production in macrophages, which affects bacterial control and influences the severity of corneal disease. These effects, particularly in macrophages, are reliant on the NLRP3 inflammasome, whereas NLRC4 does not have a significant role. Conversely, IL-1β secretion in neutrophils infected with ΔexoST is dependent upon NLRC4, whereas responses to PAO1 infection are predominantly NLRP3-dependent, particularly because of the ADP-ribosyl transferase activity of ExoS. These results emphasize the pathogenic role of ExoS in directing inflammasome subtype activation, with distinctions observed between neutrophils and macrophages (Minns et al., 2023).

Furthermore, the enhancer-binding protein MifR, an important factor involved in α-ketoglutarate metabolism, contributes to NLRP3 inflammasome activation and the full virulence of PA PAO1-mediated pneumonia and sepsis (Xiong, Perna, Jacob, Lundgren, & Wang, 2022). However, NLRP3 inflammasome activation may play a role in host defense against PA isolated from patients with bronchiectasis harboring a truncated mutation in *mucA*. The PA mutant in *mucA* suppresses the expression of T3SS and the inflammasome ligand fliC, which provides escape mechanisms from host inflammasome defense, thereby supporting long-term colonization (Liu et al., 2022). Thus, the hyper- or hypo-activation of the NLRP3 inflammasome, regulated by different PA effectors, is intricately associated with the pathogenesis of PA infections.

Various PA effectors associated with the secretion system can trigger different types of inflammasomes within host cells. The PA T2SS activates the NLRP1 inflammasome. The release of exotoxin A, a ribotoxin via T2SS, induces alterations in eukaryotic elongation factor 2, which results in ribotoxic stress and subsequent NLRP1 inflammasome activation. Interestingly, this response was paradoxically heightened in patients with cystic fibrosis (Pinilla et al., 2023). In addition, T3SS recognition activates the NLRC4 inflammasome through a signaling pathway involving Abl/PKCδ/NLRC4 following PA infection. NLRC4 inflammasome activation and the ensuing inflammatory responses restrict PA infection of wounds. ExoT exerts an inhibitory function upon PA-induced inflammation by targeting CrkII (Mohamed et al., 2022). Moreover, the T3SS effector ExoU exhibits a noncytolytic function by associating with host mitochondria and NLRC4 to induce mitochondrial stress and damage (Hardy et al., 2022).

Several PA strains induce caspase-1-dependent pyroptosis in human and murine neutrophils, whereas the PA exotoxins, U or S, inhibit caspase-1-dependent pyroptosis. PA flagellin activates the NLRC4 inflammasome, IL-1β secretion, and GSDMD-dependent neutrophil pyroptosis, thereby increasing susceptibility to pyroptosis-inducing PA infection *in vivo* (Santoni et al., 2022). Noncanonical caspase-4 inflammasome activation has a beneficial role against PA lacking T3SS by inducing corneal epithelial cell death; however, T3SS effector ExoS contributes to survival and replication in the host epithelial cells, creating a replicative niche. Thus, the caspase-4 inflammasome functions as an epithelial defense system by enhancing host cell lysis (Kroken et al., 2023).

Previous studies emphasized the regulation of host factors in terms of inflammasome activation induced by PA infection. Activation of the cannabinoid-2 receptor suppresses PA-induced ALI by inhibiting the excessive activation of neutrophils and the NLRP3 inflammasome (Nagre et al., 2022). Furthermore, exposure to cigarette smoke enhances PA-induced mitochondrial damage and NLRP3 inflammasome activation in alveolar macrophages, thus exacerbating ALI *in vivo* (White et al., 2022). Further studies are needed to elucidate the roles of distinct types of inflammasome activation and pyroptosis in immunodeficiency models. This will lead to the development of inflammasome-modulating strategies against PA infections.

5.2.17. Salmonella enterica serovar Typhimurium

Diverse *Salmonella* strains in mice, whether in systemic or mucosal infections, involve NLRC4 recognition of *Salmonella* flagellin as the main defense mechanism. Needle proteins, along with flagellin and rod proteins from different bacteria, exhibit variable and cell type-dependent activity against NLRC4 inflammasome activation (Yang, Zhao, Shi, & Shao, 2013). *Salmonella* effectively evades NLRC4 inflammasome-mediated protective immunity during systemic infection by suppressing flagellin expression (Akhade et al., 2020). The NAIP/NLRC4 inflammasome, which is activated by flagellin and components of the virulence-associated T3SS apparatus in the cytosol of host cells through interaction with NAIPs, is an important element (Egan, Zhang, & Shin, 2023). NLRC4-mediated recognition of flagellin is the primary protective mechanism during mucosal infection. Deletion of *flgM* results in flagellin overproduction and significantly ameliorates systemic and mucosal *Salmonella* infections through the NLRC4 inflammasome. These findings highlight flagellin recognition as the primary innate defense against *Salmonella* during mucosal infection, whereas *flgM* evasion heightens virulence and tissue damage (Lopez-Yglesias et al., 2023).

In addition to *Salmonella* flagellin, the T3SS needle and inner rod activate the NAIP/NLRC4 inflammasome in murine intestinal epithelial cells, which restricts bacterial replication and prevents systemic infection (Naseer et al., 2022). These characteristics highlight differences in ligand specificity between humans and mice. For example, unlike murine intestinal epithelial cells (IECs), the NAIP/NLRC4 inflammasome is dispensable for *Salmonella* infection in human IECs (Naseer et al., 2022). NLRC4 generally plays a role in host defense during infection, although there are species- and cell type-specific differences with respect to various bacterial pathogens (Egan et al., 2023). In contrast, NLRP6 has deleterious effects on host control and iron homeostasis in the context of *S.* Typhimurium infections (Deng et al., 2022). Thus, the NLRP6 inflammasome has detrimental roles in various bacterial infections, including *S.* Typhimurium infections.

The fine-tuning of the GSDMD-mediated pyroptosis is important for host defense during systemic *Salmonella* infection. A recent report showed that the *S.* Typhimurium *spvC* gene suppresses pyroptosis in macrophages through the caspase-1/−11-dependent canonical and noncanonical pathways and ameliorates neutrophil infiltration during infection (Zhou et al., 2024). The function of *spvC* in the GSDMD-mediated inflammatory response counteracts the host defense (Zhou et al., 2024). In contrast, caspase-1 or GSDMD deficiency prolongs survival rates and inhibits coagulopathy, which contributes to pathogenesis. Notably, the NAIP/NLRC4 inflammasome and/or components of the SPI1 T3SS have important roles in *Salmonella*-induced coagulopathy; however, a *Salmonella* mutant strain devoid of flagellin and SPI1 still triggers coagulopathy through the caspase-11/NLRP3 pathway (Pandeya et al., 2023). Therefore, the host-*Salmonella* interaction plays distinct roles in the pyroptosis-associated regulation of protection and pathogenesis during *Salmonella* systemic infection depending on the context.

Galectin-4 is a member of the galectin family of glycan-binding proteins. It binds to the surface of cytosolic *Salmonella enterica* Serovar Worthington to restrict bacterial motility and activate caspase-1, leading to IL-18 production in intestinal epithelial cells (Li et al., 2023). In addition, *S. enteritidis* T1SS protein SiiD suppresses NLRP3 inflammasome activation during infection. SiiD significantly inhibits the production of mtROS, thereby repressing ASC oligomerization and NLRP3-dependent caspase-1 activation. Interestingly, SiiD-deficient *S. enteritidis* induces higher gut inflammation in mice to evade host immune responses (Guo et al., 2023). These data highlight the molecular interactions between bacteria and the host to achieve their goals during infection in the context of inflammation regulation.

LncRNA LNCGM1082, whose activity is modulated by TLR5, is required for the interaction of PKCδ with NLRC4 to activate the NLRC4 inflammasome, thus protecting against *S.* Typhimurium infection (Gao et al., 2023). Future studies are warranted to identify small RNAs that modulate inflammasome activation to alter host defense against *Salmonella* infection.

5.2.18. Shigella

Shigella spp. are Gram-negative bacteria consisting of four species: *S. flexneri*, *S. sonnei*, *S. dysenteriae*, and *S. boydii*. These bacteria are responsible for shigellosis, also known as bacillary dysentery, which is a diarrheal disease characterized by bacterial invasion and damage to gut epithelial cells (Matanza & Clements, 2023). To invade host cells, *Shigella* are colocalized and encapsulated by dynamin-like GBPs, such as GBP1, GBP2, GBP3, GBP4 as well as caspase-4 (Goers et al., 2023; Piro et al., 2017). *Shigella* effector IpaH9.8, in the absence of OspC3, inhibits caspase-4-mediated pyroptosis through the degradation of GBPs; however, GBP1 releases some LPS to promote caspase-4 activation and pyroptosis (Goers et al., 2023).

Interestingly, NAIP-NLRC4 inflammasome activation increases susceptibility to *S. flexneri* infection (Mitchell et al., 2020). Conversely, caspase-11 inflammasome activation, which recognize *Shigella* LPS, exhibits protective effects against *Shigella* in the absence of NAIP-NLRC4. *Shigella* OspC3 counteracts the protective activity mediated by caspase-11. Furthermore, TNF-α, through the activation of caspase-8-dependent apoptosis, confers protection against *Shigella* in mice lacking both NAIP-NLRC4 and caspase-11 (Roncaioli et al., 2023). Caspases-1, −11, and − 8 play protective roles against oral *Shigella* infection (Roncaioli et al., 2023). Thus, multiple cell death pathways may be involved in the protection against infection with an invasive gastrointestinal pathogen. Additional studies are needed to elucidate the functions of distinct types of inflammasome pathways in the context of various *Shigella* strains.

5.2.19. Vibrio cholerae

V. cholerae is the etiological agent of cholera, a gastrointestinal disease that causes significant mortality worldwide (Dominguez, Doan, & Rivera-Chavez, 2024). *V. cholerae* can activate both NLRP3-dependent and -independent inflammasome pathways, which is contingent upon the biotype and secreted toxins (Queen, Agarwal, Dolores, Stehlik, & Satchell, 2015). Previous studies demonstrated that the El Tor biotype of *V. cholerae* triggers NLRP3 and pyrin inflammasome activation in macrophages in a caspase-11- and cholera toxin-independent manner (Mamantopoulos et al., 2019). OmpU, a major porin of *V. cholerae*, induces NLRP3 inflammasome activation and IL-1β secretion in murine dendritic cells through TLR2 signaling as a priming signal, along with pathways involved in calcium signaling and mtROS production (Dhar, Gandhi, Sakharwade, Chawla, & Mukhopadhaya, 2023). In addition, two novel effectors from the *Vibrio* T6SS induce pyroptotic cell death by activating the NLRP3 inflammasome, thus contributing to pathogenesis and emergence of bacterial pathogens (Cohen et al., 2022). Taken together, these findings shed light on the role of inflammasomes and pyroptosis in modulating the host defense against *V. cholerae* infection and may lead to the identification of new effectors that influence susceptibility to cholera and other diarrheal diseases.

5.2.20. Yersinia

Yersinia, a Gram-negative zoonotic bacterium, exerts its virulence through a T3SS, effectively evading crucial components of the innate immune system, including inflammasomes. Several Yop effectors of *Yersinia* spp., such as YopE and YopT, can inactivate RhoA, leading to the activation of the pyrin inflammasome (Chung et al., 2016). In addition, YopM of *Y. pestis* and *Y. pseudotuberculosis* are involved in the inactivation of the pyrin inflammasome, thereby promoting bacterial virulence. YopM activates the host kinases, PRK1 and PRK2, to phosphorylate and inactivate pyrin activity (Chung et al., 2016). Interestingly, ancient FMF mutations harboring *pyrin* variants exhibit more resistant phenotypes against the YopM-mediated suppression of IL-1β, suggesting that FMF mutations confer increased resistance to

Y. pestis (Loeven et al., 2020; Park et al., 2020); however, more studies are needed to clarify the multiple molecular mechanisms through which the virulence factors of *Yersinia* spp. regulate innate immune responses and interact with host partners.

In the context of *Yersinia* infection, Fas-associated death domain, RIPK1, and caspase-8 are recruited to the lysosomal Rag-Ragulator, which results in pyroptosis activation via RIPK1 phosphorylation and caspase-8 activation. The induction of *Yersinia*-induced pyroptosis depends upon Rag GTPase activity and the lysosomal tethering of Rag-Ragulator. This emphasizes the important role of the lysosomal metabolic regulator Rag-Ragulator during the host response to *Yersinia* (Zheng et al., 2021). In both human IECs and macrophages, *Y. pseudotuberculosis* T3SS effectors, including YopE, YopH, and YopK, play an important role in evading the caspase-4 inflammasome. These findings highlight the species-specific differences in the regulation of the inflammasome response to specific bacterial pathogens (Zhang, Brodsky, & Shin, 2023). In addition, the regulation of pyroptosis through caspase-1 varies depending on the cell type. In neutrophils, caspase-1-induced GSDMD does not directly cause pyroptosis; instead, pyrin recognizes extracellular *Y. pseudotuberculosis* ΔyopM, inducing caspase-1-dependent GSDMD-mediated pyroptosis. Both caspase-1 and GSDMD are required for protection against *Y. pseudotuberculosis* ΔyopM strain (Oh et al., 2022). Furthermore, two E3 ligases of *Y. pestis*, YspE1 and YspE2, ubiquitinate GBPs for proteasomal degradation, thus enhancing the survival of *Y. pestis* in macrophages and suppressing inflammasome activation. In contrast, $Gbp^{chr3-/-,chr5-/-}$ macrophages exhibit reduced inflammasome activation, resulting in increased susceptibility to *Y. pestis*. Therefore, *Y. pestis* E3 ligases can subvert the GBP- and inflammasome-mediated host defense (Cao et al., 2022). Further studies are needed to elucidate the functions of individual effectors of *Yersinia* in terms of inflammasome activation to provide insight into intracellular growth and virulence.

5.3. Mycobacteria and others

5.3.1. Mycobacterium tuberculosis

Mtb is an obligate aerobe with a specialized cell wall structure that lacks phosphoric acid and LPS. It contributes to the development of tuberculosis, a severe infectious disease with high global mortality (Marimani, Ahmad, & Duse, 2018). Previous studies have identified a dual role for inflammasome activation in mycobacterial infection. Mice lacking both *Cybb*, a key subunit of phagocyte oxidase, and caspase-1/11 showed a significant decrease in IL-1β secretion, but rapidly progressed to severe tuberculosis with a high bacterial burden (Thomas & Olive, 2023). Conversely, the T7SS (ESX-1) of Mtb causes plasma membrane damage, NLRP3 inflammasome activation, and pyroptosis. Consequently, these results contribute to bacterial spread (Beckwith et al., 2020). Yang et al. identified a bacterial effector that activates the NLRP3 inflammasome. The PPE13 protein isolated from Mtb, *M. bovis*, and *M. marinum* activates the NLRP3 inflammasome through an NLRP3 interaction with the C-terminal repetitive MPTR domain of PPE13 (Yang et al., 2020). The removal of melanoma differentiation factor 5 (MDA5), a member of the retinoic acid-inducible gene-I–like receptor family, had a beneficial effect on the host, coinciding with decreased Mtb bacillary load. MDA5 contributes to IL-1β production and inflammasome activation during Mtb infection, whereas the absence of MDA5 results in a marked augmentation of autophagy (Bullen et al., 2023). For a gain-of-function mutation in the leucine-rich repeat kinase 2 ($LRRK2^{G2019S}$), inflammasome activation resulted in the generation of mtROS, guiding GSDMD to the mitochondrial membrane, where GSDMD induced pore formation followed by RIPK1/RIPK3/MLKL-dependent necroptosis. Mtb infection in $LRRK2^{G2019S}$ mice promoted hyper-inflammation and severe immunopathology, which was detrimental to host defense (Weindel et al., 2022). Although this study does not definitively clarify the role of inflammasome activation in Mtb infection, the data strongly suggest that hyperactivation of the inflammasome is associated with the pathogenesis of Mtb infection.

GSDMD-induced pyroptotic activation plays a dual role in host defense during Mtb infection. The Mtb protein phosphatase PtpB dephosphorylates host cell membrane phospholipid proteins, thus inhibiting the inflammasome and pyroptosis. Mtb PtpB, whose activity is regulated by ubiquitin and dephosphorylates phosphatidylinositol-4-monophosphate and phosphatidylinositol-(4,5)-bisphosphate in the host cell membrane to suppress the membrane localization of cleaved GSDMD. PtpB-induced evasion of the host GSDMD-dependent immune responses supports intracellular Mtb survival during chronic infection (Chai et al., 2022; Van Hauwermeiren & Lamkanfi, 2023). With respect to Mtb infection, the HDAC1 inhibitor 4-(dimethylamino)-N-[6-(hydroxyamino)-6-oxohexyl]-benzamide enhances NLRP3 inflammasome activation and IL-1β production by macrophages and dendritic cells. 4-(dimethylamino)-N-[6-(hydroxyamino)-6-oxohexyl]-benzamide upregulates defective IL-1β production by the early secretory antigenic target 6 kDa-deleted Mtb strain in dendritic cells (Moreira, Iakhiaev, Vankayalapati, Jung, & Samten, 2022); however, baicalein, derived from *Radix Scutellariae*, suppresses Mtb-induced pyroptosis by downregulating the assembly of AIM2 and NLRP3 inflammasomes and promoting autophagy (Ning, Shen, Liu, Zhang, & Jiang, 2023). These results suggest that Mtb-induced modulation of the inflammasome and pyroptosis results in different effects depending on the context. Elucidating the detailed regulatory network between the host inflammasome complex and Mtb effectors will lead to better methods to prevent and treat Mtb infection.

A recent study suggested that canonical and noncanonical inflammasome activation induced by *M. bovis* Bacillus Calmette-Guérin-trained macrophages results in higher inducible nitric oxide synthase expression and nitrite production, thus promoting the macrophage-killing capacity against intracellular *B. abortus* (de Araujo, de Queiroz, Marinho, & Oliveira, 2023). *M. bovis* Bacillus Calmette-Guérin-induced trained immunity in mice enhanced intracellular bacterial control via inflammasome activation. Further investigations are warranted to elucidate the mechanisms governing inflammasome regulation of trained immunity, thereby promoting host defense against diverse bacterial infections.

5.3.2. Mycoplasma pneumoniae

M. pneumoniae, a respiratory pathogen, is implicated in airway inflammation and lung infections. NLRP3 inflammasome activation plays a role in controlling the progression of mycoplasmal infections (Segovia et al., 2018). The Community-Acquired Respiratory Distress Syndrome (CARDS) toxin of *M. pneumoniae* induces the posttranslational modification of NLRP3 through ADP-ribosyltransferase activity, consequently enhancing inflammasome activity (Bose et al., 2014). Recombinant CARDS toxin induces NLRP3-mediated IL-1β secretion through a mechanism that requires the ADP-ribosyltransferase enzymatic activity of CARDS as well as the interaction between CARDS toxin and NLRP3 (Segovia et al., 2018). This suggests that ADP ribosylation results in increased NLRP3 activity. Hyperactivation of the NLRP3 inflammasome results in increased tissue damage during *M. pneumoniae* infection. Thus, targeting ADP-ribosylating NLRP3 may be a potential therapeutic strategy.

5.3.3. Rickettsia

Rickettsia spp. are obligate intracellular bacteria with life cycles that involve arthropod and vertebrate hosts (Sahni, Fang, Sahni, & Walker, 2019). These infections, transmitted by ticks, mites, fleas, or lice, typically target endothelial cells, monocytes, and macrophages (Sahni et al., 2019). Recent studies indicate that pathogenic *Rickettsia* species evade the host immune defense by modulating the IL-1-dependent pathway (Voss et al., 2021). Specifically, *R. typhi* and *R. rickettsii*, but not the nonpathogenic *R. montanensis*, decrease IL-1α secretion through

the caspase-11-GSDMD-dependent pathway, which is necessary for restricting intracytosolic replication. The caspase-11-GSDMD-IL-1α signaling axis in macrophages has emerged as an important mechanism for suppressing *Rickettsia* virulence (Voss et al., 2021). Because of the diversity of *Rickettsia* species and their various components at different stages of infection (Sahni et al., 2019), comprehensive studies are essential to elucidate the distinct effects of rickettsial ligands/effectors on inflammasome activation.

6. Therapeutics targeting inflammasomes in bacterial infections

Currently, studies are underway to identify modulators for different inflammasomes and their regulatory pathways which are associated with various disease pathologies, particularly inflammation. However, few molecules directly target inflammasome complexes and components. In addition, there are few reports on the effectiveness of inflammasome-targeted drugs in the context of infections. Several Food and Drug Administration-approved drugs may be used as interventions to target inflammasome-related pathways. In this review, we briefly summarize the modulators of inflammasome sensors and cytokines in the context of infections and inflammation. Additionally, we discuss the interventions for the individual pathogen infections throughout this review and they are also listed in Tables 4–7.

6.1. NLRP3 inhibitors

6.1.1. MCC950 and glyburide

There are currently no specific Food and Drug Administration-approved inhibitors for the NLRP3 inflammasome despite numerous efforts. In this section, we discuss NLRP3 inhibitors in terms of bacterial infections. An early study showed that the type 2 diabetes drug glyburide, a sulfonylurea-containing compound, is an NLRP3 inhibitor (Lamkanfi et al., 2009), however, it is now considered to have a nonspecific effect. Nevertheless, the glyburide backbone was used to develop specific NLRP3 inhibitors, such as MCC950, one of the best characterized NLRP3 inflammasome and pyroptotic inhibitors, with activities against canonical and noncanonical NLRP3 inflammasomes (Coll et al., 2015). MCC950 blocks the Walker B motif within the NACHT domain of NLRP3 (Coll et al., 2019). It has been used for the treatment of a variety of inflammatory and neurological diseases (Pandeya & Kanneganti, 2024; Yao et al., 2024). There have been several studies on the therapeutic activity of MCC950 against various viral infections. The beneficial activity of MCC950 against bacterial infectious diseases has been described in the prior sections involving PA (Minns et al., 2023), *C. perfringens* (Mathur et al., 2023), *S. pseudintermedius* (Guo et al., 2022), *P. gingivalis* (Gong et al., 2022), *C. septicum* (Jing et al., 2022), and *B. cereus* (Mathur et al., 2019). The effects of MCC950 through modulating NLRP3 inflammasome activation enhance host protection and reduce lethality triggered by inflammasome activation.

6.1.2. Inhibitors targeting NLRP3-NEK7 interaction

Several reagents target NLRP3-NEK7 interactions. For example, oridonin interacts with NLRP3 NACHT domain and inhibits NLRP3-NEK7 interactions, thus blocking NLRP3 inflammasome assembly (He et al., 2018). Because there are several reports that oridonin plays beneficial effects in viral and mycobacterial infections (Chen et al., 2023; Jiang, Feng, Qi, Ran, & Xie, 2022), future clinical trials are warranted to determine its usefulness against severe bacterial infections with inflammasome pathologies. Moreover, 4-hydroxynonenal (4-HNE), an endogenous lipid peroxidation product, suppresses the interaction between NLRP3 and NEK7, thereby inhibiting NLRP3 inflammasome activation and pyroptosis in mouse macrophages and human peripheral blood mononuclear cells (Hsu et al., 2022). 4-HNE is generated by the ROS-mediated oxidation of poly-unsaturated fatty acids in the host cell membrane during bacterial infection and exhibits antimicrobial activity against several bacteria including LM (Tabakh et al., 2021). Future

studies are needed to determine whether 4-HNE-induced antimicrobial activity is mediated through disrupting NLRP3 inflammasome complex.

Helenin, a compound isolated from *Inula helenium L.*, regulates the NLRP3 inflammasome and attenuates lethal sepsis and peritonitis by disrupting the binding of NEK7-NLRP3 (Fang et al., 2024). In addition, pristimerin, a quinonoid triterpene derived from traditional Chinese medical herbs, specifically suppresses NLRP3 inflammasome activation by disturbing the NEK7-NLRP3 interactions. The therapeutic effects of pristimerin was demonstrated in mouse models of LPS-induced systemic inflammation, peritonitis, and high fat diet-induced diabetes (Zhao et al., 2021). Another recent study showed that SB-222200 inhibits NLRP3 inflammasome assembly through the inhibition of the NEK7-NLRP3 interaction (Zhou et al., 2023), although its antimicrobial effects are unclear.

6.1.3. Inhibitors for NLRP3 inflammasome assembly

Numerous molecules have been identified that bind to specific domains of NLRP3. A recent study indicated that the small molecule octyl gallate elicits anti-inflammatory response by directly binding to the LRR domain of NLRP3 (Park et al., 2024). Tetrahydroquinoline, a synthetic compound, inhibits the NLRP3 inflammasome assembly and activation by binding to the NLRP3 NACHT domain and blocking ASC oligomerization (Dai et al., 2021). CY-09, which interacts with and inhibits NLRP3, has shown promise because of its strong therapeutic effects in mouse models of cryopyrin-associated autoinflammatory syndrome and type 2 diabetes (Jiang et al., 2017). In addition, the proteasome inhibitor NIC-0102 specifically disrupts the NLRP3-ASC interaction by inducing polyubiquitination of NLRP3 (Wu et al., 2022). Moreover, tanshinone I, a diterpenoid isolated from *Salvia miltiorrhiza* Bunge, specifically targets the NLRP3-ASC interaction, inhibits NLRP3 inflammasome activation in macrophages, and exhibits a protective effect in septic shock and non-alcoholic steatohepatitis (Zhao et al., 2023). D359–0396, a novel small molecule, exhibits anti-inflammatory and anti-pyroptotic effects through inhibition of the oligomerization of NLRP3, ASC, and GSDMD cleavage (Li et al., 2023). Furthermore, the traditional medicinal herb *S. miltiorrhiza* Bunge has a specific inhibitory effect on the NLRP3 inflammasome, but not on AIM2 or NLRC4 inflammasome activation in macrophages and *in vivo* (Liu et al., 2021). Another recent high-throughput screening study identified NP3–562, which interacts with the NLRP3 NACHT domain, as a novel NLRP3-binding scaffold (Velcicky et al., 2024). Because of the prominent roles of these molecules in NLRP3-associated inflammatory diseases and pathologies, future studies of these compounds are needed to clarify their roles in the host defense against various pathogenic infections.

6.1.4. Other mechanisms for suppressing NLRP3 inflammasome

Recently, NT-0796, a novel inhibitor containing a carboxylic acid moiety, was found to effectively convert carboxylate to an isopropyl ester, resulting in potent NLRP3 inhibition in human monocytes. This enhanced potency is important considering the ample expression of NLRP3 in human monocytes/macrophages that express carboxylesterase-1. NT-0796 shows promise for more effectively modulating human inflammasome activation (Smolak et al., 2024). In addition, INF39 was developed as a specific NLRP3 inhibitor with irreversible binding. It showed activity in intestinal inflammation (Pellegrini et al., 2018). The action of NLRP3 inhibitors INF39 and Maxing shigan decoction was reported in epithelial cells during *M. pneumoniae* infection (Liu et al., 2021); however, these reports did not clarify the function of the NLRP3 inhibitors in the context of *in vivo* infections. Moreover, OLT1177 (Dapansutrile) was reported as a specific inhibitor of the NLRP3 inflammasome and was shown to ameliorate the pathologies and severity of systemic inflammation and joint arthritis (Marchetti et al., 2018). Although the effects of OLT1177 have not been identified in the context of bacterial infections, it has shown promise. A Phase 2a single-center, safety and efficacy study of OLT1177 (EudraCT 2016–000943-14i) revealed a beneficial effect on

Table 4
Therapeutics targeting NLRP3 inflammasome.

Drug/Reagent	Pathogen/Inflammatory stimuli	Mechanism of action	Study model	Biological actions	Ref
MCC950, glyburide	LPS/ATP, Poly (dA:dT), MSU, *S.* Typhimurium, Pam₃CSK₄	Blockade of NLRP3	BMDMs, HMDMs, PBMCs, CAPS mice model, EAE mice model	Inhibition of IL-1β secretion, Blockade of NLRP3-induced ASC oligomerization, Attenuation of EAE severity and mouse model of CAPS	(Coll et al., 2015)
MCC950	*P. aeruginosa*	Blockade of NLRP3	*P. aeruginosa* corneal infection mice model, BMN, BMDMs	Increased bacterial survival, Decreased bioactive IL-1β level, Inhibition of GSDMD and IL-1β cleavage in PAO1-infected neutrophils	(Minns et al., 2023)
	C. perfringens virulence factors	Blockade of NLRP3	BMDMs, THP-1 cells, PBMCs, *In vivo*	Reduced the secretion of IL-18, Prolonged the survival of WT mice in response to lecithinase	(Mathur et al., 2023)
	S. pseudintermedius	Blockade of NLRP3	Canine corneal stromal cells	Downregulation of phosphorylation p65, IκBα, PI3K, and AKT, Decreased the expression of NLRP3, caspase-1 p20, cleaved IL-1β, ASC, and pro-inflammatory cytokines	(Guo et al., 2022)
	P. gingivalis OMVs	Blockade of NLRP3	BV2 microglia cells, Mouse neuroblastoma cell line N2a, Mouse behavioral test	Inhibition of NLRP3 inflammasome activation triggered by *P. gingivalis* OMVs and tau phosphorylation in neurons	(Gong et al., 2022)
	B. cereus	Blockade of NLRP3	BMDMs, *In vivo*	Prevention of *B. cereus*-induced lethality, Decreased secretion of IL-18 in the peritoneal cavity and circulation	(Mathur et al., 2019)
	C. septicum	Blockade of NLRP3	BMDMs, THP-1 cells, Different mice model	Prevention of *C. septicum*-induced lethality, Inhibition of α-toxin-induced inflammasome activation, Reduction of IL-18 secretion both in the peritoneal cavity and serum	(Jing et al., 2022)
Compound 6	LPS/ATP, Nigericin	Directly bound to the NACHT domain of NLRP3	DSS-induced colitis model, BMDMs, Human THP-1 cells	Inhibition of NLRP3 ATPase activity and ASC oligomerization, Anti-inflammatory activity in DSS-induced colitis mouse model	(Dai et al., 2021)
Oridonin	*M. marinum*		A549 cells, RAW264.7 cells, Zebrafish model	Suppression of inflammatory response and oxidative stress, Inhibition of proliferation of *M. marinum* in zebrafish, Increased the expression of NRF2/HO-1/NQO-1, Activation of AKT/AMPK-α1/GSK-3β signaling pathway	(Chen et al., 2023)
Oridonin	HSV-1	NLRP3 inflammasome-IL-1β pathway	HSK mice model, Vero cells	Inhibition of HSV-1 replication and progeny virus production both *in vitro* and *in vivo*, Reduced expression levels of NLRP3, IL-1β, and caspase-1	(Jiang et al., 2022)
4-HNE	LPS/Nigericin, ATP, Poly (dA:dT)	Directly binds to NLRP3 and disrupts the interaction with NEK7	THP-1 cells, BMDMs, Human PBMCs, PM, ALI and sepsis mice model	Inhibition of pyroptotic cell death, Inhibition of IL-1β and IL-18 secretion in mouse acute lung injury model and sepsis model	(Hsu et al., 2022)
4-HNE	*L. monocytogenes, B. subtilis*		BMDMs, J774A.1, TIB73 cells	Regulation of bacterial growth	(Tabakh et al., 2021)
Helenine	LPS/Pam₃CSK₄, Nigericin, ATP, Si02 or *Salmonella*, Poly(dA:dT)	Targeting the NEK7-NLRP3 interaction and inhibiting NLRP3 activation	BMDMs, THP-1 cells, MSU-induced peritonitis, LPS-induced lethal sepsis model	Inhibition of ASC oligomerization, Reduction of severity of MSU-induced peritonitis	(Fang et al., 2024)
Pristimerin	LPS, ATP, Nigericin, MSU, *S.* Typhimurium, Poly (dA: dT)	Inhibition of interaction between NEK7 and NLRP3	BMDMs, BMDCs, MSU-induced peritonitis and HFD-induced diabetic mouse model	Suppression of caspase-1 activation and IL-1β secretion, Inhibition of LPS-induced systemic inflammation, MSU-induced peritonitis, and HFD-induced metabolic disorders	(Zhao et al., 2021)
SB-222200	LPS/Nigericin or ATP, Imiquimod, MSU, Sio2, Pam₃CSK₄	Directly binds to the NLRP3 protein and inhibits NLRP3 inflammasome assembly	J774A.1 cells, BMDMs, MSU-induced peritonitis, DSS-induced colitis	Blockade of cleaved caspase-1 and IL-1β release, Inhibition of GSDMD activation and LDH release, Reduction of IL-1β and IL-6 production in peritoneal fluid, Alleviation of MSU-induced peritonitis and DSS-induced colitis	(Zhou et al., 2023)
Octyl gallate	LPS/Nigericin, ATP, MSU, Imiquimond	Targets the LRR domain of NLRP3	BMDMs, MSU-induced gout, CLP sepsis model for mice	Disruption of ASC oligomerization, Downregulation of Raf-MEK1/2-ERK1/2 axis, Amelioration of inflammation in foot gout and improved survival in sepsis mouse models	(Park et al., 2024)
CY-09	LPS or Pam₃CSK₄/MSU, ATP, Nigericin, *S.* Typhimurium	Binds to the ATP-binding motif of NLRP3 NACHT domain	THP-1 cells, BMDMs, Human PBMCs, Synovial fluid from gout patients, MWS mouse model, MSU-induced peritonitis model	Prevention of neonatal lethality in a mouse model of CAPS, Treatment of metabolic disorders in diabetic mice, Inhibition of NLRP3 inflammasome activation in SFCs from patients	(Jiang et al., 2017)
NIC-0102	LPS, Nigericin, FLA-ST Ultrapure, Poly (dA:dT)	Polyubiquitination of NLRP3 and prevention of NLRP3-ASC interaction	BMDMs, J774A.1 cells, DSS-induced colitis mice model	Inhibition of production of pro-IL-1β, Anti-inflammatory effects on DSS-induced ulcerative colitis model	(Wu et al., 2022)
Tanshinone I	LPS or Pam₃CSK₄/ATP, Nigericin, Sio2, *Salmonella*, Poly (dA:dT),	Disruption of NLRP3-ASC interaction	BMDMs, LPS-induced septic shock mice model, MCD-induced NASH mice model	Inhibition of nigericin-induced caspase-1 cleavage, IL-1β maturation, ASC oligomerization and LDH release, Amelioration of non-alcoholic steatohepatitis in mice	(Zhao et al., 2023)
Cryptotanshinone	Poly (I:C), Ultra-LPS			Inhibition of ASC oligomerization, Ca²⁺ signaling, and mtROS production, Protective effect in endotoxemia syndrome and MCD-diet-induced NASH	(Liu et al., 2021)

Table 4 (*continued*)

Drug/ Reagent	Pathogen/Inflammatory stimuli	Mechanism of action	Study model	Biological actions	Ref
D359–0396	LPS/ATP, Nigericin, MSU, Flagellin, Poly (dA:dT)	Suppresses the oligomerization of NLRP3, ASC, and the cleavage of GSDMD	iBMDMs, BMDMs, THP-1 cells, EAE mouse model, Septic-shock model	Inhibition of pyroptosis, IL-1β release, NLRP3-Caspase-1-GSDMD pathway, development of EAE in mice, Protection against LPS-induced sepsis model	(Li et al., 2023)
NP3–562	LPS, ATP	Bound to the NLRP3 NACHT domain	THP-1 cells, Human whole blood, Acute peritonitis mouse model	Inhibition of IL-1β release in a mouse acute peritonitis model	(Velcicky et al., 2024)
NT-0796	LPS, ATP	Inhibition of NLRP3 inflammasome	PMs from mice and human PBMCs, hCES-1 mice	Inhibition of IL-1β output from hCES-1 mouse blood	(Smolak et al., 2024)
INF39	DNBS	Direct inhibition of NLRP3 inflammasome	DNBS-colitis rat model	Reduction of systemic and bowel inflammatory alterations	(Pellegrini et al., 2018)
MXSG	*M. pneumoniae*	Inhibition of NLRP3 inflammasome	A549 cells, PBMCs	Inhibition of *M. pneumoniae*-induced pyroptosis, Reduction of expression of NLRP3, pro-IL-1β, Caspase-1, pro-Caspase-1, GSDMD-N, IL-1β and TNF-α levels	(Liu et al., 2021)
OLT1177	Zymosan/MSU	Inhibition of NLRP3 inflammasome	MSU crystal, Zymosan-induced arthritis mice model	Reduction of joint swelling, cell influx, and synovial levels of IL-1β, IL-6, CXCL1, and MSU-induced gouty arthritis	(Marchetti et al., 2018)
Dapansutrile	Phase-2 clinical trial (Adult patients with MSU-induced acute inflammation)	Inhibition of NLRP3 inflammasome	Phase 2a trial, adult patient's studies, PBMCs	Reduction of joint pain, joint inflammation, and levels of IL-1β and IL-6 in plasma	(Kluck et al., 2020)
DFV890	Phase 2 clinical trial (SARS-CoV-2 patients)	Oral NLRP3 inhibitor	Enrolled hospitalized patients (18–80 years) with CARDS	Acceleration of SARS-CoV-2 clearance, Improvement of clinical outcomes in hospitalized patients, Reduction of fatal incidents	(Madurka, et al., 2023)
Wogonin	Cerebral IR injury	Suppression of NLRP3 inflammasome	Male Sprague-Dawley rats, MCAO rat model, HT-22 cells	Activation of AMPK/SIRT1 pathway, Protection of cerebral IR injury	(Cheng et al., 2024)
Wogonin	HIV-1	Inhibition of NLRP3 inflammasome	J-Lat cells, J-mC cells PBMCs from healthy and HIV-1-infected patients	Inhibition of latent HIV-1 reactivation by reducing p300 expression and histone H3/H4 crotonylation within the HIV-1 promoter region, Inhibition of HIV-1 provirus expression in CD4$^+$ cells from patients	(Zhang et al., 2023)
Wogonin	*M. pneumoniae*	Inhibition of NLRP3 inflammasome	Female BALB/c mice	Downregulation of the expressions of TRPA1, SP, and CGRP in lung tissue of *M. pneumoniae* infection	(Liang et al., 2022)
Wogonin	*S. pneumoniae*	Targets both PLY and SrtA	Pneumonia mouse model	Inhibition of hemolytic activity of PLY and peptidase activity of SrtA, Inhibition of *S. pneumoniae* biofilm formation, adhesion, and colonization, Neutralization of PLY-mediated injury, Inhibition of PLY oligomer formation, Reduction of inflammatory response	(Gu et al., 2023)
NLRP12		Interaction with NLRP3	PBMCs from patients, HEK293T cells	NLRP12 blocks ASC inflammasome assembly triggered by both WT and gain-of-function mutant NLRP3, specifically in human NLRP3	(Coombs et al., 2024)
Colchicine	Randomized clinical trials in SARS-CoV-2	Blockade of NLRP3 inflammasome oligomerization	COVID-19 (out-patient/ hospitalized/ non-hospitalized) patients	Reduction of inflammatory burden and release of the main cytokines (IL-1β and IL-18)	(Bonaventura et al., 2022)
Colchicine	Pam$_3$CSK$_4$, Nigericin, ATP, Silica, MSU, Flagellin, Poly (dA:dT)	Binds to tubulin, interfering with microtubule polymerization	J774 Cells, BMMs, MSU crystals-induced acute gout mouse model	Inhibition of tubulin polymerization and mitochondria transport, Reduction of IL-1β production	(Misawa et al., 2013)
Berberine	High glucose exposure	Inhibition of NLRP3 inflammasome activation	H9C2 cells, C57BL/6 J db/db mice	Decreased expressions of p-mTOR, NLRP3, IL-1β, IL-18, caspase-1, and GSDMD, Inhibition of mtROS generation and pyroptosis	(Zhong et al., 2024)

ALI, acute lung injury; BMDCs, bone marrow dendritic cells; BMDMs, bone marrow-derived macrophages; BMN, bone marrow neutrophils; CAPS, cryopyrin-associated periodic syndromes; CARDS, coronavirus-associated acute respiratory distress syndrome; CES-1, carboxylesterase-1; CGRP, calcitonin gene-related peptide; CLP, cecal-ligation-and-puncture; COVID-19, coronavirus disease 2019; DNBS, dinitrobenzenesulfonic acid, DSS, dextran sulfate sodium; EAE, experimental autoimmune encephalomyelitis; HBL, haemolysin BL; HIV-1, human immunodeficiency virus type 1; HFD, high fat diet; hMDM, human monocyte-derived macrophages; HNE, 4-hydroxynonenal; HSK, herpes simplex keratitis; HSV-1, herpes simplex virus type 1; iBMDMs, immortalized bone marrow-derived macrophages; IR, ischemia-reperfusion; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MCAO, middle cerebral artery occlusion; MCD, methionine and choline deficient diet; MSU, monosodium urate crystal; mtROS, mitochondrial reactive oxygen species; MWS, Muckle-Wells syndrome; MXSG, maxing sighan decoction; NASH, nonalcoholic steatohepatitis; OMV, outer membrane vesicle; PBMCs, peripheral blood mononuclear cells; PLY, pneumolysin; PM, peritoneal macrophage; Poly dA:dT, poly(deoxyadenylic-thymidylic) acid sodium salt; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SFCs, synovial fluid cells; SP, substance P; SrtA, sortase A; TRPA1, transient receptor potential A1; WT, wild type.

joint pain in patients with acute gout flare (Kluck et al., 2020). A recent clinical trial showed the efficacy and safety of DFV890 for the treatment of COVID-19 pneumonia (NCT04382053ii) (Madurka, et al., 2023). Several other chemicals are now undergoing preclinical and clinical evaluation (Pandeya & Kanneganti, 2024), although their antimicrobial effects are unknown.

Several activators of the AMPK/SIRT1 signaling pathway have been identified that suppress NLRP3 inflammasome activation (Cheng et al., 2024). For example, wogonin is a natural flavonoid from *Scutellaria baicalensis* that stimulates the AMPK/SIRT1 pathway. Wogonin inhibits the upregulation of NLRP3 inflammasome-related molecules, providing relief from ischemia-reperfusion injury (Cheng et al., 2024). With

Table 5
Therapeutics targeting AIM2.

Drug/ Reagent	Pathogen/Inflammatory stimuli	Mechanism of action	Study model	Biological actions	Ref
RGFP966	LPS	A selective inhibitor of HDAC3	MCAO mice model, Primary microglia cells	Suppression of AIM2 via modulating the acetylation and phosphorylation of STAT1	(Zhang et al., 2020)
RGFP966	Mtb	HDAC3 inhibitor	PMA-differentiated U937 cells, Human alveolar macrophages, MDMs	Modulation of bacterial growth in macrophages and broth culture, proinflammatory cytokines	(Campo et al., 2021)
RGFP966, Panobinostat, Entinostat	*C. albicans, S. aureus*	HDAC3/ pan-HDAC inhibitor	PBMCs from healthy and STAT-1 GOF patients	Panobinostat inhibits innate and adaptive cytokines, Entinostat and RGFP966 increase the production of IL-22 and downregulate STAT-1 phosphorylation	(Rosler et al., 2018)
Demethylene-berberine	*P. aeruginosa*	Inhibition of AIM2 inflammasome	MH-S cells, BEAS-2B cells, Acute pneumonia mice model	Downregulation of acute pneumonia through anti-inflammatory and antioxidant effects	(Han, Ge, Ye, Li and Zhang, 2023)
Roxadustat (FG-4592)	Hypoxia-reoxygenation injury	Pan-PHD inhibitor	Human renal biopsy, IR-AKI mice, HK2 cell	Attenuation of IR-induced tubular damage and renal function, Enhanced the expression of HIF-1α/HIF-2α/VEGF, Improved the expression of CD73, Decreased inflammatory infiltration	(Yang et al., 2023)
Roxadustat	SARS-CoV-2	HIF prolyl hydroxylase inhibitor	Hypoxic mouse model, RKO, U2-OS, Caco-2, Vero E6 cell lines	Inhibition of the expression of SARS-CoV-2 entry factors and replication post-entry, Reduction of ACE2 and TMPRSS2 expression	(Wing et al., 2021)
EFLA 945	Poly(dA:dT), Nigericin, ATP	Attenuation of AIM2 inflammasome	THP-1 cells, IMQ-induced psoriasis	Reduction of psoriasis severity by attenuating caspase-1 activation, IL-1β maturation, and IL-17 production, Blockade of extracellular DNA entry into cells	(Chung et al., 2020)

ACE2, angiotensin-converting enzyme 2; GOF, gain-of-function; HIF-1α, hypoxia-inducible factor 1-alpha; IMQ, imiquimod; IR-AKI, ischemia-reperfusion model of acute kidney injury; MCAO, middle cerebral artery occlusion; MDA, malondialdehyde; Mtb, *Mycobacterium tuberculosis*; PBMCs, peripheral blood mononuclear cells; PMA, phorbol 12-myristate 13-acetate; PHD, prolyl hydroxylase; STAT-1, signal transducer and activator of transcription 1; TMPRSS2, transmembrane serine protease 2; VEGF, vascular endothelial growth factor.

numerous studies demonstrating the inhibitory effects of wogonin in human immunodeficiency virus-1 infection and bacterial pathologies (Gu et al., 2023; Liang et al., 2022; H. Zhang et al., 2023), further studies are needed to determine whether wogonin's antimicrobial actions are mediated through the regulation of the NLRP3 inflammasome. Furthermore, NLRP12 suppresses the assembly of the NLRP3 inflammasome, particularly in human cells (Coombs et al., 2024). Additional studies are needed to elucidate the interactions among NLRP subfamily members and their role in regulating inflammasome activation.

Colchicine is a widely used drug that inhibits NLRP3 and is used to treat gout, FMF, and COVID-19 clinical trials (Bonaventura et al., 2022; Pandeya & Kanneganti, 2024). Although colchicine has direct effects on mitosis through binding to tubulin to perturb the dynamics of microtubules (Bhattacharyya, Panda, Gupta, & Banerjee, 2008), it inhibits intracellular transport of ASC to NLRP3 on the ER, thereby blocking the co-assembly of NLRP3 inflammasome complexes (Misawa et al., 2013). Berberine inhibit the generation of mtROS as well as the activation of p- mammalian target of rapamycin complex 1, thereby suppressing pyroptosis triggered by NLRP3 inflammasome activation (Zhong et al., 2024). It is a commonly used plant extract that exhibits antidiabetic, anti-inflammatory, and antibacterial properties (Li et al., 2023). Further studies of its modulatory effects on the NLRP3 inflammasome are warranted for the development of antimicrobial agents that could be used for treating the co-morbidity of metabolic and infectious diseases in the future.

6.2. AIM2 inhibitors

Compared to NLRP3 inhibitors, there are few reports of AIM2 inflammasome inhibitors. A recent study showed that the HDAC3 inhibitor RGFP96 has an inhibitory effect on the AIM2 inflammasome (Zhang et al., 2020). It also has antimicrobial activity and regulates the macrophage proinflammatory cytokine generation in mycobacteria (Campo et al., 2021) and *Candida albicans* infections (Rosler et al., 2018). Although it is unclear whether its AIM2 inhibitory effects are related to an antimicrobial response, additional

studies are needed to determine the exact mechanisms by which RGFP96 and other HDAC inhibitors exhibit antibacterial activities. Demethyleneberberine, a novel derivative of berberine, alleviates the pulmonary inflammatory responses caused by PA. This effect may be related to the suppression of the AIM2 inflammasome, because it reduces the expression of AIM2 and ASC, and suppresses IL-1β secretion (Han, Ge, Ye, Li, & Zhang, 2023).

A recent study showed that roxadustat (FG-4592), a hypoxia-inducible factor prolyl hydroxylase inhibitor, attenuates acute kidney injury by suppressing the AIM2 inflammasome and IL-1β and IL-18 levels (Yang et al., 2023). Roxadustat has effects on SARS-CoV-2 RNA replication in lung epithelial cells (Wing et al., 2021) and was approved for chronic kidney diseases in various countries (Li et al., 2023). Its numerous adverse effects raise some concerns over the use of anti-infectives. In addition, EFLA 945, a product of red grape vine leaf extracts, restricts AIM2 inflammasome activity by attenuating imiquimod-induced pro-inflammatory responses and is useful for psoriasis treatment (Chung et al., 2020). Future studies are needed to clarify whether this natural product can be used to treat bacterial infections.

6.3. ASC inhibitors

Quercetin inhibits ASC speck formation and oligomerization, and it suppresses IL-1β production in Cryopyrin-Associated Periodic Syndromes macrophages (Domiciano et al., 2017). Caffeic acid phenethyl ester suppresses inflammasome activation through direct interaction with ASC, thereby blocking caspase-1 activation and IL-1β production (Lee et al., 2016). Lonidamine, a small-molecule inhibitor of glycolysis, directly binds to ASC and suppresses its oligomerization, thereby exerting anti-inflammatory activity (Chen et al., 2022). Moreover, 1,2,4-trimethoxybenzene, which was identified from active ingredients in essential oils, inhibits ASC oligomerization and the interaction between NLRP3 and ASC, thus ameliorating NLRP3-associated pathologies in a model with experimental autoimmune encephalomyelitis (Liao et al., 2022). Dehydrocostus lactone, isolated from the traditional

Table 6
Therapeutics targeting ASC.

Drug/ Reagent	Pathogen/Inflammatory stimuli	Mechanism of action	Study model	Biological actions	Ref
Quercetin	LPS, ATP, Nigericin, Alum, Poly(dA:dT)	Inhibition of ASC oligomerization	*In vivo* mouse model of LCWE-induced vasculitis, BMDMs	Inhibition of IL-1β secretion by disrupting signal-2, Reduction of ASC speck formation and oligomerization	(Domiciano et al., 2017)
CAPE	LPS, MSU, ATP	Blockade of NLRP3-ASC association	An air pouch inflammation model, A foot gout mice model, BMDMs	Prevention of MSU crystal-induced gout, Reduction of neutrophil infiltration and MPO activity	(Lee et al., 2016)
Lonidamine	LPS, ATP, MSU, Imiquimod, Nigericin, MDP	Inhibition of ASC oligomerization and cleavage of caspase-1	LPS-induced sepsis model MCAO mice model, BMDMs	Blockade of ASC specks formation, Inhibition of IL-1β secretion	(Chen et al., 2022)
1,2,4-Trimethoxyben-zene	LPS/Nigericin, ATP	Blockade of NLRP3 inflammasome assembly	iBMDMs, primary microglia cell, PMs, EAE animal model	Suppression of caspase-1 activation and IL-1β secretion, Attenuation of EAE severity	(Liao et al., 2022)
Dehydrocostus lactone	LPS, Nigericin, MSU, ATP, Poly (I:C), Pam₃CSK₄	Blockade of ASC oligomerization	LPS-induced inflammation in mice, THP-1 cells, hPBMCs, BMDMs	Reduction of IL-1β secretion and peritoneal neutrophils recruitment, Inhibition of caspase-1 activation and subsequent IL-1β production	(Chen et al., 2020)
Brevilin A	LPS, Pam₃CSK₄ Nigericin ATP, Sio2, Poly (I:C), Poly(dA:dT)	Inhibition upstream of ASC oligomerization	MSU-challenged peritonitis model, BMDMs, THP-1 cells	Inhibition of caspase-1 activation and IL-1β secretion, Inhibition of caspase-11-dependent caspase-1 activation and IL-1β release	(Qin et al., 2021)
Brevilin A	IAV	Inhibition upstream of ASC oligomerization	MDCK epithelial cells, IAV- infected mice	Inhibition of viral replication by targeting viral RNA synthesis, Inhibition of viral protein production from the M and NS segments and nuclear export of viral ribonucleoproteins	(Zhang et al., 2019)
J114	LPS, Nigericin, MSU, ATP, Poly(dA:dT)	Blockade of NLRP3/AIM2-ASC interaction	J774A.1 cells, THP-1 cells, BMDMs	Inhibition of caspase-1 and IL-1β release, reduction of ASC recruitment to NLRP3 or AIM2, Inhibition of ASC oligomerization	(Jiao et al., 2022)
Spirodalesol analog 8A	LPS, MSU	Blockade of ASC oligomerization	LPS-induced endotoxemia, gouty arthritis mice model, THP-1 cells, BMDMs	Reduction of IL-1β secretion and caspase-1 activation, Alleviation of MSU-induced peritonitis and arthritis, Reduction of ASC speck formation and inhibition the activation of caspase-1, Alleviation of LPS-induced endotoxemia and MSU-induced peritonitis and gouty arthritis in mice	(Liu et al., 2022)
Peptide corresponding to H2-H3 segment of ASC pyrin domain	LPS, Nigericin, ATP, Poly (dA:dT), Doxycycline	Inhibition of NLRP3 inflammasome by binding to NLRP3 pyrin domain	iBMDMs imicroglia, RAW Blue cells, Silica-induced peritonitis mouse model	Inhibition of cytokine release, caspase-1 activation, and ASC speck formation in response to diverse NLRP3 inflammasome activators, Reduction of neutrophil infiltration	(Susjan et al., 2020)

AKI, acute kidney injury; CAPE, caffeic acid phenethyl ester; CMC, chronic mucocutaneous candidiasis, EAE, experimental autoimmune encephalomyelitis; IAV, influenza-A virus; iBMDMs, immortalized murine bone marrow-derived macrophages; imicroglia, immortalized microglia; HIF-1a, hypoxia-inducible factor 1 alpha; LCWE, *Lacticaseibacillus casei* cell wall extract; LPS, lipopolysaccharide; MCAO, middle cerebral artery occlusion; MDA, malondialdehyde; MDCK, Madin–Darby canine kidney epithelial cells; MDP, muramyl dipeptide; MSU, mono-sodium urate crystals; MPO, myeloperoxidase; PBMCs, peripheral blood mononuclear cells; PMs, peritoneal macrophages.

Chinese medicine, inhibits the NLRP3 inflammasome and IL-1β production through the suppression of ASC oligomerization (Chen et al., 2020). Brevilin A reviling sesquiterpene lactone inhibits NLRP3 inflammasome by blocking the ASC oligomerization (Qin et al., 2021). Because the previous report shows an effect of brevilin A on the anti-influenza response (Zhang et al., 2019), subsequent studies are needed to determine the antimicrobial activities of these candidate drugs.

A recent phenotypic screening against NLRP3-dependent pyroptosis identified a hit compound that exhibited moderate anti-pyroptotic activity, through suppression of ASC interaction with NLRP3 or AIM2, and inhibition of ASC oligomerization (Jiao et al., 2022). An analog compound (8A), which was identified by screening analogs based on the structure of Spirodalesol, was identified as a potent inhibitor of NLRP3 inflammasome assembly by targeting ASC oligomerization (Liu et al., 2022).

Another study identified modulatory peptides corresponded to the H2-H3 segment of the ASC pyrin domain that selectively inhibits the NLRP3 inflammasome (Susjan et al., 2020). The peptide showed inhibitory effects upon neutrophil infiltration in silica-induced peritonitis and was transferred across the blood-brain barrier (Susjan et al., 2020). Future studies are needed to determine whether this peptide or other peptide drugs may be used to treat acute bacterial infections associated with massive neutrophil infiltration or meningitis.

6.4. Caspase inhibitors

An early study showed that pralnacasan, an inhibitor of caspase-1, ameliorates dextran sulfate sodium-induced murine colitis and the expression of intracolonic IL-18 and IFN-γ (Loher et al., 2004); however, there are few studies describing the effects of pralnacasan. A recent study showed that there is no therapeutic effect of pralnacasan in the suppression of mechanical ventilation-induced inflammation (Timmermans et al., 2013). A recent study of caspase-1 inhibitors indicated that VX-765 (belnacasan), a small molecule inhibitor of caspase-1, improves cognitive impairment, without any direct effect on microglial inflammation (Flores, Fillion, & LeBlanc, 2022). Sennoside A, an ingredient in weight-loss medicines and dietary supplements, suppresses caspase-1 and inflammasome activation in a P2X7-dependent manner (Wu et al., 2022). Additional studies are needed to determine whether caspase inhibitors have antibacterial effects by regulating excessive inflammasome activation.

6.5. GSDMD modulators

The inhibition of GSDMD by disulfiram, a drug for treating alcohol addiction, inhibits LPS-induced septic death in mice. Disulfiram modifies Cys191/Cys192 in GSDMD to inhibit pore formation, although disulfiram-mediated IL-1β and GSDMD processing are not affected

Table 7
Therapeutics targeting caspase, GSDMD, cytokine and combined modulators.

Drug/Reagent	Pathogen/Inflammatory stimuli	Mechanism of action	Study model	Biological actions	Ref
Pralnacasan	3.5% DSS	ICE inhibitor	Paraaortal lymphocytes, DSS-induced murine colitis	Reduction of DSS-induced murine colitis and T helper 1 T-cell activation, Suppression of the proinflammatory cytokines	(Loher et al., 2004)
Pralnacasan	Mechanical ventilation	A selective caspase-1 inhibitor	IL-1αβ KO mice, Caspase-1 KO mice	Caspase-1 appears not to be involved in ventilation-induced IL-1β and KC in lungs suggesting the involvement of neutrophils factors in IL-1β processing	(Timmermans et al., 2013)
VX-765		Inhibition of caspase-1	J20 mice	Enhanced cognitive function in aged mice without changing amyloid beta biochemically or inflammation markers, Normalization of dendritic spine density, synaptophysin levels, and decreased IL-10	(Flores et al., 2022)
Disulfiram	LPS	A potent inhibitor of GSDMD pore formation	THP-1 cells, $Casp11^{-/-}$ mice, $Casp1^{-/-}$ mice, $Gsdmd^{-/-}$ mice	Inhibition of pyroptosis, IL-1β secretion, and liposome leakage, Modification of Cys191/Cys192 in GSDMD, Protection from LPS-induced sepsis	(Hu et al., 2020)
NSA	β-amyloid (Aβ$_{1-42}$), LPS, Nigericin	Inhibition of p30-GSDMD oligomer formation	Motor cortex neurons, APP/PS1 transgenic mice model	Reduction of inflammatory factors release and Aβ$_{1-42}$-induced pyroptosis	(Han et al., 2020)
Anakinra	Placental *P. falciparum*	IL-1R antagonist	PM murine models, Trophoblast cells	Improvement of pregnancy outcomes by restoring fetal growth, Reduction of resorption rate, Protection of pregnant mice from placental malaria	(Reis et al., 2020)
YM-90709	LPS, Nigericin, ATP, MSU, Si02	IL-5 receptor antagonist	J774A.1 cells, BMDMs, THP-1 cells, DSS-induced colitis mice model	Reduction in the expressions of IL-1β and caspase-1 p20 in the colon and amelioration of colitis, Delayed body weight loss, colon ulceration, and acute inflammation in the DSS-induced colitis	(Ou et al., 2024)
Obovatol	LPS/Nigericin, MSU, ATP	Inhibition of ASC pyroptosome formation	BMDMs, THP-1 cells, Acute gout and MSU-mediated peritonitis mice model	Inhibition of pro-inflammatory cytokines production and mitochondrial ROS generation	(Kim et al., 2019)
Obovatol	*S.* Typhimurium	Inhibition of *Salmonella* T3SS	*In vitro* experiments using bacterial cultures	Inhibition of bacterial motility, effector protein expression, secretion, and bacterial growth	(Choi et al., 2017)
M84 protein	Cytomegalovirus	Interaction with the pyrin domain of AIM2 and ASC	iBMDMs, BMDMs expressing ASC mCherry, M2-10B4 cells, Phoenix-Ampho cells	Inhibition of ASC speck formation, Restriction of MCMV replication	(Deng et al., 2024)
Niclosamide	SARS-CoV-2	Inhibition of NLRP3, AIM2, and NAIP/NLRC4 inflammasomes	Human monocytes, PBMCs from patients with COVID-19, ATG5-transgenic mice	Disruption of pH-dependent membrane fusion required for virus entry, Induction of autophagy and autophagic machinery	(de Almeida et al., 2022)
HUWE1 and its inhibitor BI8622	*Salmonella*, *F. novicida*, *A. baumannii*	Interaction with AIM2, NLRP3 and NLRC4	BMDMs, HEK293T cells, HUWE1, AIM2 and NLRP3 KO mice	Regulation of host defense through mediation of the K27-linked polyubiquitination of AIM2, NLRP3, and NLRC4	(Guo et al., 2020)

ATG5, autophagy-related gene 5; DSS, dextran-sodium sulfate; ICE, interleukin-1β-converting enzyme; IL-1R, interleukin-1 receptor; KC, anti-keratinocyte-derived chemokine; KO, knockout; LPS, lipopolysaccharide; MSU, monosodium urate crystals; NSA, necrosulfonamide; MCMV, mouse cytomegalovirus; PM, placental malaria; ROS, reactive oxygen species.

(Hu et al., 2020). Although there are risks of disulfiram treatment in humans, it may be possible to repurpose disulfiram for the treatment of infections including *S. aureus*, *B. burgdorferi*, and viruses as well as other diseases (Lanz et al., 2023). In addition, necrosulfonamide inhibits GSDMD oligomerization, thus ameliorating Aβ1–42-induced pyroptosis of mice cortical neurons (Han et al., 2020). Future studies are warranted to identify the inflammasome- and pyroptotic modulatory mechanisms through which GSDMD-targeted drugs function in the amelioration of pathogenic infections. In addition, preclinical and well-controlled clinical trials are needed to establish their safety and efficacy for various human diseases.

6.6. Cytokine inhibitors

Numerous studies have identified therapies that target the inflammasome-mediated production of IL-1β in the context of infection. When the IL-1R pharmacological antagonist Anakinra was used to treat experimental malaria infection during pregnancy, it improved fetal growth (Reis et al., 2020). A recent study demonstrated that the IL-5 receptor antagonist YM-90709 inhibits the maturation of IL-1β and caspase-1 in the colon, thereby ameliorating experimental colitis (Ou et al., 2024). These results suggest that targeting IL-5/IL-5 receptor signaling is another approach to modulating NLRP3 inflammasome activation. Further studies of cytokine/cytokine receptor signaling networks may contribute to the

development of new strategies for attenuating NLRP3 inflammasome pathologies.

6.7. Combined modulators

Obovatol is a biphenolic chemical originating from *Magnolia obovata*. It functions by inhibiting several inflammasome components including NLRP3, AIM2, and non-canonical inflammasome activation (Kim et al., 2019). A previous study showed the inhibitory effect of obovatol on the *Salmonella* T3SS (Choi et al., 2017); however, future studies are needed to clarify the role of obovatol in a wide range of bacterial infections. Another recent report showed that the mouse cytomegalovirus M84 protein is an inhibitor of pyroptosis and inflammatory responses. Mechanistically, M84 binds to the PYD of AIM2 and ASC to inhibit inflammasome assembly and the activation of IL-1β, IL-18, and GSDMD (Deng, Ostermann, & Brune, 2024).

A high-throughput screening study revealed that niclosamide inhibits NLRP3 and AIM2 inflammasome activation through autophagy induction, whereas it inhibits NAIP/NLRC4 inflammasome in an autophagy-independent manner. Niclosamide treatment was effective in the suppression of SARS-CoV-2 replication (de Almeida et al., 2022). Moreover, HUWE1 is involved in the formation of inflammasome assembly through the K27-linked polyubiquitination of AIM2, NLRP3, and NLRC4 (Guo et al., 2020). *Huwe1* deficiency aggravated *Salmonella*, *Francisella*, or *A. baumannii* infection *in vivo* (Guo et al., 2020). Because

HUWE1 inhibitor BI8622 significantly inhibits multiple inflammasome activation (Guo et al., 2020), new targets for HUWE1 should be identified to improve the host defense against bacterial infections.

7. Conclusion

Innate immune defenses employ inflammasomes as central components to detect diverse microbial signals and initiate inflammatory responses, thus playing an important role in host defense. During bacterial infections, different effectors of bacteria can activate, suppress, and counteract various types of inflammasomes. Dysregulated inflammasome activation can lead to adverse outcomes, such as excessive inflammation or inappropriate cell death. Conversely, inadequate inflammasome activation and suppressed pyroptosis can result in compromised host defense against bacterial threats. Thus, in the real-world battle between bacteria and host inflammasomes, the inflammasome and pyroptosis have a dual role, influencing both host defense and pathological inflammation in distinct contexts during infections. Future research will likely focus on integrating multi-dimensional data to enable researchers to dissect the complex interplay between bacterial pathogens and the host immune system. This approach will provide a more comprehensive view of inflammasome activation through intricate mechanisms involving multiple signaling pathways.

While substantial progress has been made in understanding the diverse roles of inflammasomes and the molecular mechanisms that respond to microbial stimuli, numerous questions persist regarding the intricate interaction between bacterial effectors and individual inflammasome components. In particular, the current methods used to study inflammasome activation and bacterial evasion strategies have notable limitations. Although traditional *in vitro* approaches are valuable for elucidating molecular interactions, they often fail to capture the complexity of real-world conditions where multiple inflammasome components and diverse bacterial effectors interact dynamically with various host cell types. While *in vivo* models offer a more holistic and dynamic context for investigating infection-induced interactions between pathogens and the host immune system, they also have several limitations, including species-specific differences between animals and humans. Advanced techniques, such as omics studies, single-cell analysis, and organoid models, are beginning to provide deeper insights. Future efforts should focus on refining these methodologies to capture and integrate the full complexity of these interactions.

Understanding the complicated regulation of these interactions and how bacterial pathogens modulate and evade the host inflammasome machineries remains an active area of investigation. The burgeoning area of research is focused on the therapeutic potential of modulating inflammasome activity to combat bacterial infections. A more comprehensive understanding of the roles and mechanisms of inflammasomes during bacterial infections holds promise for developing therapeutic interventions in the ongoing battle against emerging, re-emerging bacterial pathogens, and drug-resistant bacteria. Thus, current research in progress is focused on uncovering the diverse strategies employed by bacterial pathogens to mitigate or subvert inflammasome activation. Therefore, although much remains to be learned, the future appears hopeful for determining the therapeutic potential of targeting inflammasomes to combat bacterial infections.

CRediT authorship contribution statement

Jin Kyung Kim: Writing – original draft, Visualization, Conceptualization. **Asmita Sapkota:** Writing – original draft, Data curation. **Taylor Roh:** Writing – original draft, Validation. **Eun-Kyeong Jo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The Authors report no conflicts of interest.

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Data availability

No data was used for the research described in the article.

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