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INFLAMMASOME ACTIVATION AND REGULATION BY PATHOGENIC BACTERIA: BALANCING HOST DEFENSE AND TISSUE DAMAGE

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Abstract

The inflammasome, a cytosolic multiprotein complex, is essential to the innate immune response by detecting danger-associated signals and pathogenic microorganisms. During bacterial infections, inflammasome activation contributes to pathogen clearance and the initiation of protective immune responses by promoting the maturation of the pro-inflammatory cytokines interleukin (IL)-1 and IL-18 and triggering pyroptotic cell death. However, dysregulated or excessive inflammasome activation may lead to tissue damage, chronic inflammation, and the development of severe inflammatory disorders. This review provides a summary of the current understanding of inflammasome biology, focusing on the molecular mechanisms that govern bacterial infection-related activation and regulation. The NLRP3, NLRC4, AIM2, NLRP1, and Pyrin roles in the inflammasome, as well as the canonical and non-canonical signaling pathways, are discussed. The review also discusses the various virulence mechanisms by which major pathogenic bacteria, such as *Salmonella enterica, Listeria monocytogenes, Helicobacter pylori, Mycobacterium tuberculosis, Pseudomonas aeruginosa, Shigella spp., Escherichia coli,* and *Staphylococcus aureus,* either activate or evade inflammasome signaling. The roles of mitochondrial dysfunction, reactive oxygen species, ion fluxes, autophagy, and post-translational modifications are also examined in light of recent advancements in the regulation of inflammasome activity. Last but not least, we look at promising new treatments that target inflammasome components and downstream inflammatory mediators as ways to control excessive inflammation while maintaining strong antibacterial immunity. A comprehensive understanding of inflammasome biology will support the development of novel host-directed therapies for bacterial infectious diseases.

Keywords: *Inflammasome, Pathogenic Bacteria, Infection, Immune response.*

1. INTRODUCTION

The innate immune system is necessary for maintaining tissue homeostasis and is the first line of defense against invading microorganisms [1]. In contrast to adaptive immunity, innate immunity responds quickly by means of pattern-recognition receptors (PRRs). These receptors identify conserved microbial structures that are referred to as pathogen-associated molecular patterns (PAMPs) and endogenous danger-associated molecular patterns (DAMPs) that are released from damaged tissues [2]. Recognition of these signals initiates inflammatory cascades that eliminate pathogens and activate adaptive immune responses. Among the most important innate immune signaling platforms are inflammasomes, intracellular multiprotein complexes that coordinate inflammatory responses against microbial infections [3]. Since their initial discovery in 2002, inflammasomes have become recognized as essential regulators of antimicrobial immunity, inflammatory diseases, metabolic disorders, autoimmune conditions, and cancer. The activation of caspase-1, which transforms the inactive precursors of IL-1 and IL-18 into biologically active cytokines, is followed by the recruitment of the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD). Gasdermin D is also cleaved by activated caspase-1, resulting in plasma membrane pore formation and pyroptotic cell death [4,5]. Pyroptosis is now recognized as an effective host defense mechanism because it rapidly eliminates intracellular niches exploited by bacterial pathogens while simultaneously releasing inflammatory mediators that recruit neutrophils, macrophages, and other immune cells [6]. However, cytokine storms, septic shock, acute respiratory distress syndrome, inflammatory bowel disease, and organ failure can all result from uncontrolled inflammasome activation [7]. There are numerous virulence factors in pathogenic bacteria that can activate the inflammasome. Through neuronal apoptosis inhibitory proteins (NAIPs), flagellin from motile bacteria activates the NLRC4 inflammasome, whereas

bacterial DNA released into the cytoplasm activates the AIM2 inflammasome [8]. NLRP3 inflammasome activation is facilitated by a number of bacterial toxins that cause potassium efflux, mitochondrial damage, and lysosomal rupture. In addition, caspase-4 and caspase-5 in humans and caspase-11 in mice are activated by intracellular lipopolysaccharide to initiate the non-canonical inflammasome pathway [9]. Strangely, pathogenic bacteria have developed sophisticated methods of evading inflammasome-mediated immunity through co-evolution with the immune system of the host. These include inhibition of inflammasome assembly, degradation of inflammasome components, interference with cytokine maturation, modulation of host cell metabolism, and suppression of pyroptosis. These immune evasion mechanisms aid in the persistence of bacteria and contribute to persistent or chronic infections [10].

Understanding the molecular mechanisms that control inflammasome activation has made significant progress over the past ten years [11]. The magnitude and duration of inflammasome responses are thought to be determined jointly by mitochondrial dysfunction, the production of reactive oxygen species, calcium signaling, ion fluxes, autophagy, ubiquitination, and post-translational modifications. As a result of these findings, extensive research has been conducted with the intention of developing selective inflammasome inhibitors that are capable of minimizing excessive inflammation while maintaining protective antimicrobial immunity [12]. A thorough comprehension of how inflammasomes are activated and controlled is necessary for the development of effective antibiotics against bacterial infections due to the inflammasomes' central role in balancing pathogen clearance and inflammatory tissue damage [13]. As a result, this review provides a synopsis of the most recent developments in the biology of the inflammasome, sheds light on the mechanisms by which bacteria are recognized by the immune system and evaded by it, explains the protective and pathological effects of activating the inflammasome, and looks into new therapeutic approaches that target inflammasome signaling pathways.

2. BIOLOGY OF INFLAMMASOMES

As essential parts of the innate immune system, inflammasomes are cytoplasmic multiprotein complexes that detect endogenous danger signals and microbial infections (figure 1). By activating inflammatory caspases, mainly caspase-1, they serve as molecular platforms that start inflammatory reactions [14]. The pro-inflammatory cytokines IL-1β and IL-18 mature as a result of inflammasome activation, which also triggers pyroptosis, a highly inflammatory kind of programmed cell death that aids in immune activation and pathogen clearance [15]. The adaptor protein apoptosis-associated speck-like protein with a caspase recruitment domain (ASC), the effector enzyme pro-caspase-1, and a sensor protein that recognizes microbial or danger signals make up the three main structural components of a typical inflammasome [16]. Sensor proteins change shape during activation, which facilitates oligomerization and ASC recruitment via pyrin domain (PYD) interactions. Pro-caspase-1 is then recruited by ASC through caspase recruitment domains (CARD), which causes pro-caspase-1 to be autocatalytically cleaved into its active form, Pro-IL-1β and pro-IL-18 are processed into mature cytokines by activated caspase-1, which also cleaves gasdermin D, whose N-terminal fragment creates membrane holes that facilitate pyroptosis[17]. The principal sensors, their ligands and their adaptor requirements are compared in Table 01.

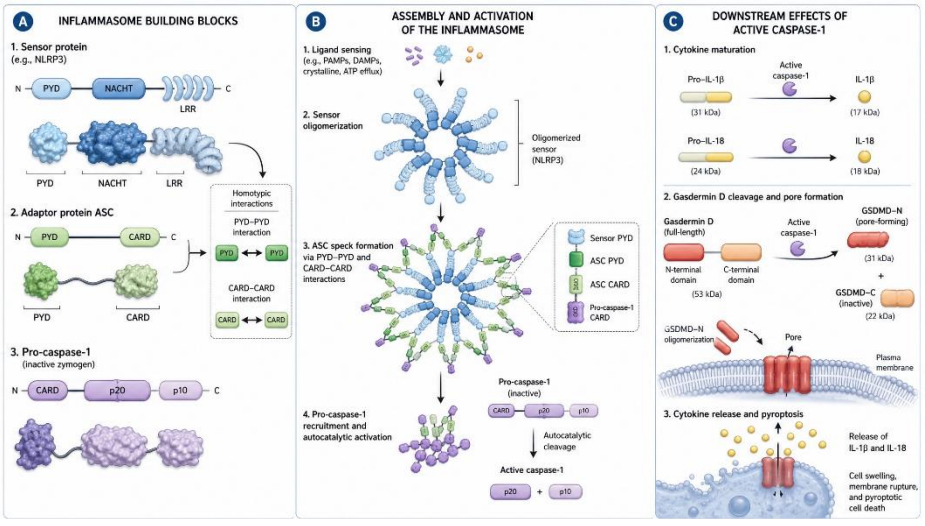

Figure 01: Architecture and activation of a canonical inflammasome. (A) The three building blocks: a sensor protein, the adaptor ASC and pro-caspase-1, linked through homotypic PYD–PYD and CARD–CARD interactions. (B) Ligand binding drives sensor oligomerisation and ASC speck formation, and pro-caspase-1 is autocatalytically cleaved into the active p20/p10 enzyme. (C) Active caspase-1 matures pro-IL-1β and pro-IL-18 and cleaves gasdermin D, whose N-terminal fragment forms membrane pores that release the cytokines and drive pyroptosis.

There are canonical and non-canonical pathways for inflammasomes. Sensor proteins like NLRP1, NLRP3, and AIM2 are involved in the canonical pathway's caspase-1 activation. In contrast, caspase-4 and caspase-5 in humans and caspase-11

in mice direct recognize Gram-negative bacteria's intracellular lipopolysaccharide (LPS) for the non-canonical pathway [9,18]. These caspases trigger gasdermin D cleavage and secondary potassium efflux activation of the NLRP3 inflammasome, thereby intensifying inflammatory responses. Due to its capacity to respond to an exceptionally wide range of stimuli, the NLRP3 inflammasome is the inflammasome that has received the most research attention out of all inflammasomes [20]. NLRP3, in contrast to other inflammasomes that recognize specific microbial ligands, is a general stress sensor for cells. NLRP3 is triggered by a variety of stimuli, including bacterial toxins, ATP release, crystalline particles, mitochondrial dysfunction, reactive oxygen species (ROS), potassium efflux, calcium influx, and lysosomal rupture. Dysregulated NLRP3 activation has been linked to a wide range of autoimmune and inflammatory conditions, making it a promising therapeutic target [21].

Intracellular bacterial flagellin and components of bacterial type III and type IV secretion systems are the primary targets of the NLRC4 inflammasome's response. Members of the neuronal apoptosis inhibitory protein (NAIP) family bind bacterial ligands, activating NLRC4, allowing for indirect recognition [22]. Pseudomonas aeruginosa, Legionella pneumophila, and Salmonella enterica are just a few of the intracellular pathogens that this inflammasome protects against. By increasing neutrophil recruitment and inducing pyroptosis, activation of NLRC4 speeds up the clearance of bacteria [23]. A cytosolic DNA sensor, the AIM2 inflammasome is a member of the absent in melanoma (AIM2)-like receptor family. Through its hematopoietic interferon-inducible nuclear protein with a 200-amino acid repeat (HIN) domain, it binds double-stranded DNA released from bacteria within the cell or damaged host cells. Caspase-1 is activated when DNA binding causes AIM2 oligomerization and the recruitment of ASC [24]. Host defense against intracellular bacterial pathogens like Listeria monocytogenes, Francisella tularensis, and Mycobacterium tuberculosis relies heavily on AIM2 [20-24].

Instead of directly detecting bacterial molecules, the Pyrin inflammasome recognizes bacterial toxins that disable Rho family GTPases. Pyrin activation is unintentionally triggered as a result of several pathogenic bacteria manipulating host cytoskeletal dynamics through toxin-mediated modification of Rho GTPases [25]. This mechanism enables host cells to detect pathogen-induced alterations rather than individual microbial components, representing an elegant example of immune surveillance. On the other hand, NLRP1, which was the first inflammasome to be identified, is still poorly understood in comparison to NLRP3 [26]. In contrast to other inflammasomes, NLRP1 has a pyrin and a caspase recruitment domain, making it possible to interact directly with pro-caspase-1 in certain circumstances. NLRP1 responds to bacterial toxins and proteolytic activities, although its role during bacterial infections continues to be actively investigated [27].

Different inflammasome pathways appear to have extensive crosstalk, according to recent research. During a bacterial infection, the simultaneous activation of multiple inflammasomes may boost antimicrobial immunity while also increasing the likelihood of excessive inflammation and tissue damage [28]. In addition, maintaining immune homeostasis requires fine-tuning inflammasome activity through a number of intracellular signaling pathways, including autophagy, ubiquitination, phosphorylation, SUMOylation, and microRNA-mediated regulation [29]. The coordinated activation of inflammasomes is therefore essential for maintaining an appropriate balance between effective pathogen clearance and prevention of immunopathology. These pathways may be dysregulated, resulting in either inadequate bacterial elimination or excessive inflammatory responses that cause severe tissue damage and organ dysfunction [30].

Table 01: Principal inflammasome sensors involved in the recognition of bacterial pathogens.

Sensor	Domain organisation	Principal trigger during bacterial infection	ASC requirement	Representative bacteria	Ref.
NLRP3	PYD–NACHT–LRR	K^+ efflux, mitochondrial ROS and oxidised mtDNA, lysosomal rupture, pore-forming toxins, extracellular ATP	Obligatory	*Staphylococcus aureus, Helicobacter pylori, Pseudomonas aeruginosa*, pathogenic *Escherichia coli*	20,21,35,39
NLRC4 (with NAIPs)	CARD–NACHT–LRR	Cytosolic flagellin and type III secretion system rod and needle proteins, sensed through NAIP proteins	Enhancing; caspase-1 can also be recruited directly through CARD–CARD contacts	*Salmonella enterica, Pseudomonas aeruginosa, Shigella flexneri, Legionella pneumophila*	22,28,29,86
AIM2	PYD–HIN-200	Double-stranded DNA released into the cytosol from bacteria or damaged host cells	Obligatory	*Listeria monocytogenes, Francisella tularensis, Mycobacterium tuberculosis*	24,26,27,49

NLRP1	PYD–NACHT–LRR–FIIND–CARD	Bacterial toxins and proteolytic activity directed at the sensor itself	Not obligatory (direct CARD–CARD interaction possible)	Role during bacterial infection still under active investigation	26,27
Pyrin	PYD–B-box–coiled-coil–B30.2	Indirect sensing of toxin-mediated inactivation of Rho family GTPases rather than a microbial molecule	Obligatory	Toxin-producing bacteria that modify Rho GTPases	25

3. EVALUATION MOLECULAR ACTIVATION MECHANISMS OF INFLAMMASOME

Inflammasome activation is a tightly controlled process that keeps the body's antimicrobial defenses working and keeps inflammation to a minimum. Priming (Signal 1) and activation (Signal 2) are typically the two sequential signals needed for activation. In physiological conditions, this two-step mechanism prevents inappropriate inflammasome assembly and enables swift responses to microbial invasion [31,32]. The two-signal model and its canonical and non-canonical branches are illustrated in Figure 02.

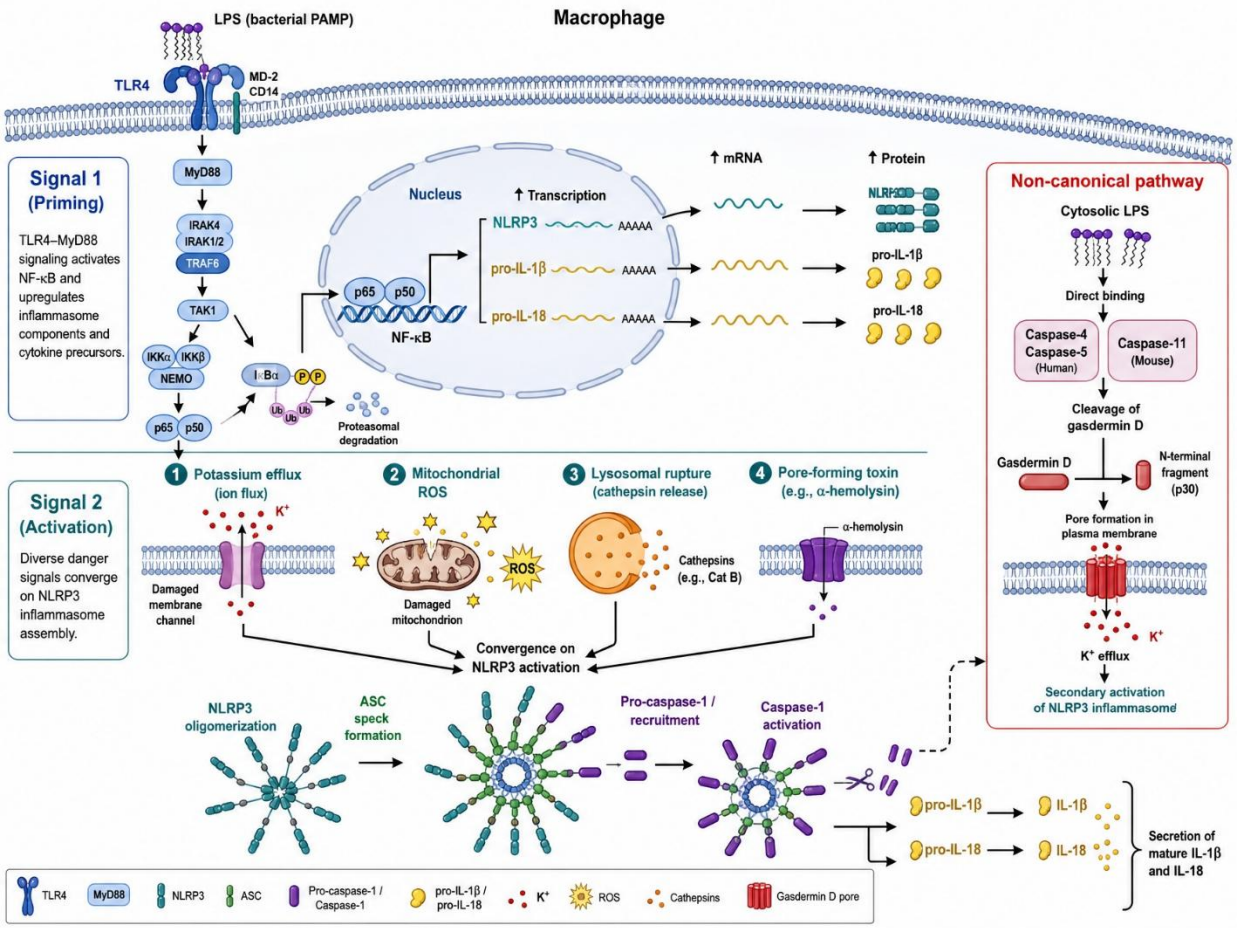

Figure 02: The two-signal model of inflammasome activation in a macrophage. Signal 1 (priming) is delivered by pattern-recognition receptors such as TLR4 and acts through NF-κB to raise the transcription of NLRP3, pro-IL-1β and pro-IL-18. Signal 2 (activation) is supplied by potassium efflux, mitochondrial reactive oxygen species, lysosomal rupture and pore-forming toxins, and assembles the complex. In the non-canonical pathway, cytosolic lipopolysaccharide is bound directly by caspase-4 and caspase-5 in humans, or caspase-11 in mice, which cleave gasdermin D and thereby activate NLRP3 secondarily.

3.1. Priming Signal

When pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) are recognized by pattern-recognition receptors (PRRs), which include Toll-like receptors (TLRs) and NOD-like receptors (NLRs), the priming step is initiated [33]. The NF-B signaling pathway is stimulated when these receptors are activated, which results in an increase in the transcription of NLRP3, pro-IL-1, and pro-IL-18. Phosphorylation and deubiquitination, two post-translational modifications that prime NLRP3 for activation, are also elicited [34].

3.2. Activation Signal

Cellular stress brought on by infection sets off the second signal. Instead of directly binding a single bacterial molecule, NLRP3 reacts to a variety of intracellular disruptions, in contrast to other inflammasomes that identify certain microbial ligands. [35]. Potassium efflux, calcium influx, mitochondrial malfunction, lysosomal rupture, ATP release, bacterial toxins that generate pores, and reactive oxygen species (ROS) are common activation events. These signals stimulate caspase-1 activation, ASC recruitment, and NLRP3 oligomerization [28-35]. Among the most crucial indications are:

3.3. Potassium Efflux

One of the most common causes of NLRP3 activation is thought to be a decrease in intracellular potassium content. Many bacterial pore-forming toxins, such as listeriolysin O and α-hemolysin, cause membrane integrity to be compromised, allowing potassium ions to exit the cell [36]. Inflammasome activation is significantly suppressed by experimental reduction of potassium efflux, highlighting its crucial involvement in inflammasome assembly [37].

3.4. Reactive Oxygen Species

Reactive oxygen species produced by mitochondria are crucial secondary messengers during bacterial infection. Overproduction of ROS oxidizes mitochondrial DNA, degrades mitochondrial membranes, and increases the activation of inflammasomes. ROS, however, are increasingly seen as contributors rather than the exclusive trigger, working in tandem with metabolic changes and ion fluxes [38].

3.5. Dysfunction of the Mitochondria

Oxidized mitochondrial DNA, cardiolipin, and other danger-associated molecules are released into the cytoplasm when intracellular infections and bacterial toxins damage the integrity of the mitochondria. During infection, these mitochondrial signals promote NLRP3 activation and maintain inflammatory reactions [39].

3.6. Damage to Lysosomes

Cathepsins can be released into the cytosol when lysosomal membranes are disrupted by phagocytosed bacteria or bacterial products. Inflammasome activation is facilitated by cathepsin release, especially in infections involving intracellular bacteria or particulate microbial components [40]

3.7. Pyroptosis and Caspase-1 Activation

Pro-caspase-1 is autocatalytically cleaved to produce active caspase-1 during inflammasome assembly [41]. Activated caspase-1 cleaves gasdermin D (GSDMD) and transforms pro-IL-1β and pro-IL-18 into their mature bioactive forms. Gasdermin D's N-terminal fragment penetrates the plasma membrane, creating holes that trigger pyroptosis, an inflammatory kind of programmed cell death. In addition to eliminating intracellular bacterial replication niches, pyroptosis releases danger signals and cytokines that attract neutrophils, macrophages, and other immune cells to the infection site [42]. The upstream events that make up Signal 2 are collected in Table 2.

Table 02: Upstream events that provide the activation signal, with their bacterial sources and their contribution to complex assembly.

Activation signal	Representative bacterial source	Molecular consequence	Contribution to assembly	Ref.
Potassium efflux	Listeriolysin O (*L. monocytogenes*), α-haemolysin (*S. aureus*), ATP acting on P2X7	Fall in intracellular K^+ concentration	Common and dominant trigger; experimental blockade strongly suppresses activation	35,36,37,75
Mitochondrial reactive oxygen species	Most intracellular bacterial infections	Oxidation of mitochondrial DNA and loss of membrane integrity	Amplifies activation together with ion fluxes rather than acting as the sole trigger	38,39
Mitochondrial dysfunction	Bacterial toxins and intracellular replication	Release of oxidised mtDNA and cardiolipin into the cytosol	Sustains NLRP3 activation during infection	39
Lysosomal destabilisation	Phagocytosed bacteria and particulate bacterial products	Release of cathepsins, particularly cathepsin B, into the cytosol	Facilitates assembly, especially for intracellular and particulate stimuli	40

Calcium influx	Membrane damage caused by pore-forming toxins	Rise in cytosolic Ca^{2+} and additional mitochondrial stress	Contributory signal acting with K^+ efflux	15,32
Cytosolic lipopolysaccharide	Gram-negative bacteria that reach the cytosol	Direct binding to caspase-4, caspase-5 or caspase-11	Initiates the non-canonical pathway and secondary NLRP3 activation	43,44,74,82

4. INFLAMMASOME PATHWAYS AND REVIEW TO IMPORTANT BACTERIAL INFECTIONS

Following the activation of inflammasome sensors such as NLRP3, NLRC4, AIM2, NLRP1, and Pyrin, caspase-1 acts as the mediator in the canonical pathway. In contrast, caspase-4 and caspase-5 (or caspase-11 in mice) directly sense cytosolic lipopolysaccharide (LPS) in the non-canonical pathway [43]. Gasdermin D is cleaved and potassium is released by activated inflammatory caspases, which in turn activate the NLRP3 inflammasome and increase cytokine production. If not tightly regulated, this coordinated interaction between canonical and non-canonical pathways increases the risk of excessive inflammation and provides a robust defense against bacterial infections [44]. The two pathways are compared feature by feature in Table 03.

Table 03: Comparison of the canonical and non-canonical inflammasome pathways.

Feature	Canonical pathway	Non-canonical pathway
Initiating caspase	Caspase-1	Caspase-4 and caspase-5 (human); caspase-11 (mouse)
Upstream sensor	NLRP3, NLRC4/NAIP, AIM2, NLRP1 or Pyrin	The caspase binds its ligand directly; no separate sensor protein is required
Principal ligand	PAMPs, DAMPs and indicators of cellular stress	Lipopolysaccharide that has reached the cytosol
Adaptor requirement	ASC, for sensors that carry a pyrin domain	Not required
Direct substrates	Pro-IL-1β, pro-IL-18 and gasdermin D	Gasdermin D
Route to mature IL-1β and IL-18	Direct cleavage by active caspase-1	Indirect: gasdermin D pores cause K^+ efflux, which activates NLRP3 and caspase-1
Cell death	Pyroptosis	Pyroptosis
Representative bacteria	*Salmonella enterica, Listeria monocytogenes, Staphylococcus aureus*	Pathogenic *Escherichia coli, Shigella flexneri*, cytosolic *Salmonella enterica*
Ref.	4,14,20,43	9,11,12,43,44,74

4.1. *Salmonella enteric*

In terms of inflammasome biology, Salmonella enterica is one of the bacterial pathogens with the best characteristics. The NAIP/NLRC4 inflammasome recognizes bacterial flagellin and components of the Type III Secretion System (T3SS) during infection [45]. This prompts the activation of caspase-1, release of IL-1 and IL-18, and pyroptotic death of infected macrophages. The NLRP3 inflammasome is activated by cellular stress signals, such as potassium efflux, mitochondrial reactive oxygen species (mtROS), and lysosomal damage, as the infection progresses, thereby intensifying inflammation. The non-canonical inflammasome can also be activated by cytosolic LPS via caspase-4/5 (human) or caspase-11 (mouse) [46]. Despite this potent immune response, Salmonella employs multiple immune-evasion strategies. By interfering with inflammasome activation, delaying pyroptosis, and modulating cytokine production through its secretion systems, effector proteins enable intracellular replication before host defenses are fully activated. Disease severity is largely determined by this fluid equilibrium between bacterial immune evasion and inflammasome activation [46,47].

4.2. *Listeria Monocytogenes*

Listeria monocytogenes is a facultative intracellular Gram-positive bacterium that uses the pore-forming toxin listeriolysin O (LLO) to escape from phagosomes and into the cytoplasm of its host [48]. Cytosolic bacterial DNA activates the AIM2 inflammasome, whereas membrane damage induced by LLO promotes potassium efflux and NLRP3 activation. As a result, by stimulating IL-1 production and pyroptosis, both AIM2 and NLRP3 contribute to host protection. Inflammasome signaling is crucial for controlling intracellular bacterial infections, as evidenced by the fact that mice lacking AIM2 or caspase-1 have decreased bacterial clearance and increased susceptibility to systemic listeriosis [49].

4.3. *Salmonella enterica*

The extracellular Gram-positive pathogen Staphylococcus aureus causes skin infections, pneumonia, osteomyelitis, and sepsis. The bacterium produces a number of toxins that form pores, particularly -hemolysin, which cause host-cell membrane disruption and potassium efflux, activating the NLRP3 inflammasome vigorously [50]. However, excessive NLRP3 activation during severe S. aureus infections may exacerbate tissue destruction and contribute to septic pathology, highlighting the dual role of inflammasome signaling in antimicrobial defense and inflammatory injury. Caspase-1 activation also increases neutrophil recruitment and bacterial clearance [56].

4.4. *Pseudomonasaeruginous*

Opportunistic Gram-negative pathogen Pseudomonas aeruginosa frequently causes severe infections in immunocompromised individuals, cystic fibrosis patients, burn victims, and mechanically ventilated patients [57]. The bacterium possesses numerous virulence factors, including flagellin, lipopolysaccharide (LPS), exotoxins, elastases, and a highly efficient Type III Secretion System (T3SS), all of which contribute to inflammasome activation and immune modulation [57]. NAIP proteins recognize flagellin that is delivered into the cytosol of the host and activate the NLRC4 inflammasome as a result. Infected macrophages are pyroptomized and caspase-1 is quickly activated, IL-1 and IL-18 are secreted, and NLRC4 is activated [58]. The recruitment of neutrophils to infected tissues and the restriction of intracellular bacterial survival are both facilitated by this mechanism [58]. Through mitochondrial dysfunction, potassium efflux, ROS, and pore-forming toxins like ExoU and ExoS, P. aeruginosa strongly activates the NLRP3 inflammasome in addition to NLRC4. Together, these signals increase the production of inflammatory cytokines and improve bacterial clearance [59]. However, during bacterial pneumonia, excessive inflammasome activation contributes to severe pulmonary inflammation. The destruction of alveolar tissue and impairment in respiratory function are the results of sustained production of IL-1, which increases vascular permeability, edema formation, and neutrophil infiltration [59]. In P. aeruginosa infections, inflammasome activation is therefore a double-edged sword. Recent studies also indicate that P. aeruginosa manipulates inflammasome signaling through T3SS effector proteins, which interfere with host immune pathways to prolong bacterial persistence while limiting excessive pyroptosis during early infection [60].

4.5 *Tuberculosis Mycobacterium*

Macrophages become infected with Mycobacterium tuberculosis (Mtb), the tuberculosis agent that causes the disease. Unlike many extracellular bacteria, Mtb induces a highly regulated inflammatory response that determines disease progression [61]. Mycobacterial lipoproteins and cell wall components promote NLRP3 activation through mitochondrial ROS generation, potassium efflux, and lysosomal destabilization following phagocytosis, whereas recognition of mycobacterial DNA in the cytoplasm activates the AIM2 inflammasome. Because it boosts macrophage antimicrobial activity and encourages the formation of granulomas, IL-1 that is produced following inflammasome activation is essential for tuberculosis host resistance [62]. A lack of IL-1 signaling has been shown to significantly increase bacterial burden and mortality in experimental models. Nevertheless, chronic activation of inflammasomes contributes to excessive pulmonary inflammation, tissue necrosis, and granuloma breakdown during advanced tuberculosis [63]. As a result, maintaining effective bacterial control and preventing irreversible lung damage necessitate balanced inflammasome activation. Interestingly, Mtb has evolved several mechanisms to suppress inflammasome activation. The ESX-1 secretion system, secreted phosphatases, and lipid mediators interfere with inflammasome assembly, thereby facilitating long-term intracellular survival [64].

4.6. *Shigella flexneri*

Bacillary dysentery is caused by Shigella flexneri, a Gram-negative intracellular bacterium. Bacterial T3SS components quickly activate the NLRC4 and NLRP3 inflammasomes following invasion of intestinal macrophages and epithelial cells [65]. Caspase-1 activation induces pyroptotic death of infected macrophages, releasing intracellular bacteria into surrounding tissues where they invade epithelial cells. [66]. Although excessive inflammatory responses contribute to the destruction of epithelium, the formation of ulcers, and severe intestinal inflammation, pyroptosis initially restricts bacterial replication. Several Shigella effector proteins demonstrate the ongoing evolutionary competition between bacterial virulence factors and host innate immunity by inhibiting inflammasome assembly, suppressing cytokine secretion, and modulating host ubiquitination pathways [67].

4.7. *Helicobacter pylori*

Helicobacter pylori are a Gram-negative, spiral-shaped bacterium that colonizes the gastric mucosa and infects approximately half of world population. Chronic infection with *H. pylori* is strongly associated with chronic gastritis, peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue (MALT) lymphoma [68]. This pathogen's remarkable capacity to evade host immune responses while maintaining chronic inflammation is the cause of its persistence. An important part of the host defense against *H. pylori* is inflammasome activation [69]. Several bacterial virulence factors, particularly CagA, VacA, lipopolysaccharide (LPS), and urease, stimulate activation of the NLRP3 inflammasome in gastric epithelial cells, macrophages, and dendritic cells. This activation promotes caspase-1 cleavage, resulting in the maturation and secretion of IL-1β and IL-18 [70]. IL-1β is considered one of the most important cytokines during H. pylori infection because it enhances neutrophil recruitment, amplifies inflammatory responses, and suppresses gastric acid secretion, thereby creating a favorable environment for persistent bacterial colonization [70]. However, prolonged production of IL-1 also contributes to gastric carcinogenesis, intestinal metaplasia, epithelial injury, and gastric atrophy. Interestingly, H. pylori have developed mechanisms that prevent the inflammasome from being

activated too much. VacA toxin suppresses T-cell activation, while several bacterial proteins interfere with NF-κB signaling and cytokine production, allowing long-term bacterial persistence despite continuous immune stimulation [80].

4.8. *Escherichia coli*

While many *Escherichia coli* strains are harmless members of the intestinal microbiota, pathogenic strains, such as enteropathogenic (EPEC), enterohemorrhagic (EHEC), enteroinvasive (EIEC), and uropathogenic (UPEC) *E. coli,* are major contributors to infections of the gastrointestinal and urinary tract all over the world [81]. During an *E. coli* infection, the bacterial strain and its virulence factors influence the activation of the inflammatory proteasome. In humans, intracellular LPS activates the non-canonical inflammasome pathway through caspase-4 and caspase-5, whereas bacterial toxins cause secondary activation of the NLRP3 inflammasome by causing potassium efflux and mitochondrial dysfunction [82]. The production of IL-1 increases neutrophil recruitment and bacterial clearance in urinary tract infections. However, chronic infections and renal inflammation may be exacerbated by excessive cytokine production, which may damage epithelial barriers. Inflammasome signaling is inhibited by host cytoskeletal proteins and inflammatory signaling pathways by several pathogenic *E. coli* strains that express secretion-system effectors. During the initial stages of infection, bacterial survival is made easier by this immune modulation [83].

3.9. *Staphylococcus aureus*

The extracellular Gram-positive pathogen Staphylococcus aureus causes skin infections, pneumonia, osteomyelitis, and sepsis [84]. The bacterium produces a number of toxins that form pores, particularly -hemolysin, which cause host-cell membrane disruption and potassium efflux, activating the NLRP3 inflammasome vigorously. The secretion of IL-1 and IL-18 by activating caspase-1 increases neutrophil recruitment and bacterial clearance. However, the dual function of inflammasome signaling in antimicrobial defense and inflammatory injury is highlighted by the fact that excessive NLRP3 activation during severe *S. aureus* infections may exacerbate tissue destruction and contribute to septic pathology [84,85].

4. COMPARATIVE OVERVIEW OF INFLAMMASOME ACTIVATION BY MAJOR BACTERIAL PATHOGENS

Despite the fact that distinct bacterial pathogens trigger distinct inflammasome sensors, a number of shared mechanisms have been identified. Intracellular bacteria frequently activate AIM2 following cytosolic DNA release, whereas Gram-negative bacteria primarily stimulate NLRC4 through the flagellin and type III secretion systems [86]. In contrast, pore-forming toxins produced by both Gram-positive and Gram-negative bacteria commonly activate NLRP3 through potassium efflux and mitochondrial damage. The balance between pathogen elimination and inflammatory tissue injury is what determines the outcome of inflammasome activation. Moderate inflammasome activation promotes bacterial clearance through cytokine production, pyroptosis, and recruitment of innate immune cells [87]. On the other hand, chronic inflammatory conditions, tissue necrosis, cytokine storm, and septic shock are all brought on by prolonged or excessive activation. Multiple inflammasome pathways may be activated simultaneously during bacterial infection, according to recent evidence. Crosstalk like this helps the host defend itself, but it also makes it more likely that immunopathology will happen if regulatory mechanisms fail [88]. Table 4 summarises the pathways engaged by each pathogen discussed above, and Figure 3 maps the sensors that each organism engages.

Table 04: Inflammasome activation, protective outcome, immunopathology and reported evasion for the major bacterial pathogens covered in this review.

Pathogen	Sensor(s)	Virulence factors	Protective outcome	Pathology	Evasion	Ref.
S. enterica	NAIP/NLRC4, NLRP3, non-canonical	Flagellin, T3SS, LPS	Caspase-1 activation, IL-1β and IL-18 release, pyroptosis of infected macrophages	Intestinal inflammation when activation is sustained	Effectors delay pyroptosis and modulate cytokine output, allowing intracellular replication	45,46, 73
L. monocytogenes	AIM2, NLRP3	Listeriolysin O, cytosolic bacterial DNA	AIM2- and caspase-1-dependent control of bacterial burden	Inflammatory tissue damage in systemic infection	Not defined in the sources reviewed	48,49
S. aureus	NLRP3	α-Haemolysin	Caspase-1 activation, neutrophil	Tissue destruction and septic	Not defined in the sources	50,84,85

		and other pore-forming toxins	recruitment and bacterial clearance	pathology in severe infection	reviewed	
P. aeruginosa	NLRC4, NLRP3	Flagellin, T3SS effectors (ExoU, ExoS), LPS, elastases	Rapid caspase-1 activation, pyroptosis and neutrophil recruitment	Severe pulmonary inflammation, oedema and alveolar injury	T3SS effectors limit excessive pyroptosis early in infection and prolong persistence	52,58,60
M. tuberculosis	NLRP3, AIM2	Cell-wall lipids and lipoproteins, mycobacterial DNA, mtROS	IL-1β-dependent macrophage antimycobacterial activity and granuloma formation	Necrosis and granuloma breakdown in advanced disease	ESX-1 secretion system, secreted phosphatases and lipid mediators interfere with assembly	54,62,64
S. flexneri	NLRC4, NLRP3, non-canonical	T3SS effectors, cytosolic LPS	Pyroptosis of infected macrophages restricts early replication	Epithelial destruction, ulceration and severe intestinal inflammation	Effectors inhibit assembly, suppress cytokine secretion and modulate host ubiquitination	57,66,67
H. pylori	NLRP3	CagA, VacA, urease, LPS	IL-1β and IL-18 maturation in gastric epithelium, macrophages and dendritic cells	Gastric atrophy, intestinal metaplasia and gastric carcinogenesis	VacA suppresses T-cell activation; bacterial proteins interfere with NF-κB signalling	69,70,80
Pathogenic *E. coli*	Non-canonical caspase-4/5, NLRP3	Cytosolic LPS, pore-forming toxins	IL-1β-driven neutrophil recruitment and clearance in urinary tract infection	Epithelial barrier damage and renal inflammation in chronic infection	Secretion-system effectors inhibit host cytoskeletal and inflammatory signalling	81,82,83

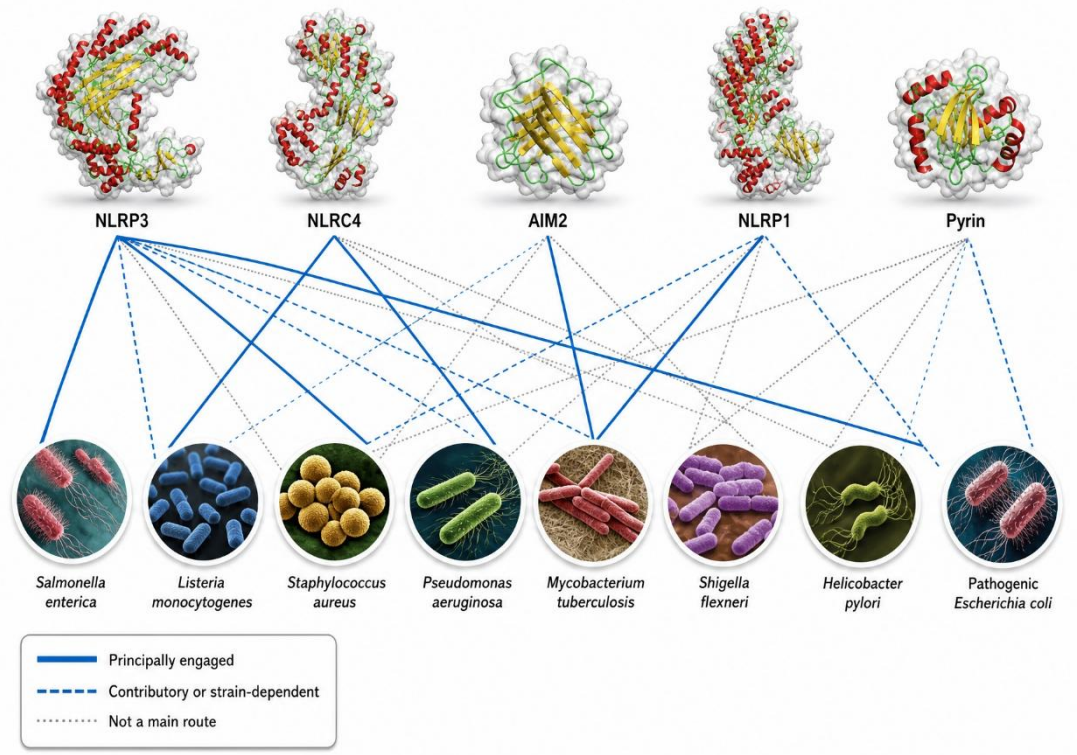

Figure 03: Inflammasome sensors engaged by the major bacterial pathogens discussed in this review. Filled circles indicate the sensor that is principally engaged, half-filled circles a contributory or strain-dependent route, and open circles a route that is not a main one for that organism.

5. BACTERIAL IMMUNE EVASION OF INFLAMMASOME SIGNALING

In order to circumvent immune response mediated by inflammasomes, successful bacterial pathogens have developed sophisticated strategies. Many bacteria fine-tune inflammasome activation rather than completely suppressing inflammation to support their survival and prevent rapid elimination by host immune cells. Inhibition of inflammasome assembly is a common tactic [89]. Caspase-1 activation and IL-1 maturation are hindered by a number of bacterial effector proteins interfering with the interaction between sensor proteins and the adaptor molecule ASC. Other pathogens effectively suppress pyroptotic cell death by directly inhibiting caspase activity or blocking gasdermin D cleavage [90]. In addition, intracellular bacteria reduce inflammasome activation by manipulating host cell metabolism. Alterations in mitochondrial function, ROS production, autophagy, and ion transport limit the intracellular danger signals required for NLRP3 activation. In addition, bacterial enzymes may alter ubiquitination pathways or degrade host signaling molecules to destabilize inflammasome complexes [91]. Some pathogens exploit host anti-inflammatory pathways by inducing IL-10 production or suppressing NF-κB signaling, thereby reducing the priming phase required for inflammasome activation. Others modify their surface structures, such as LPS or flagellin, to avoid recognition by innate immune receptors [92]. Highly complex regulatory mechanisms that determine the outcome of infection have emerged as a result of the ongoing evolutionary competition between bacterial pathogens and the immune system of the host. The development of novel therapeutics that aim to restore protective inflammasome responses without causing excessive inflammation may be facilitated by our comprehension of these bacterial immune-evasion strategies [90,93]. Figure 4 shows where bacterial effectors interrupt the host pathway, and Table 5 groups the main evasion strategies.

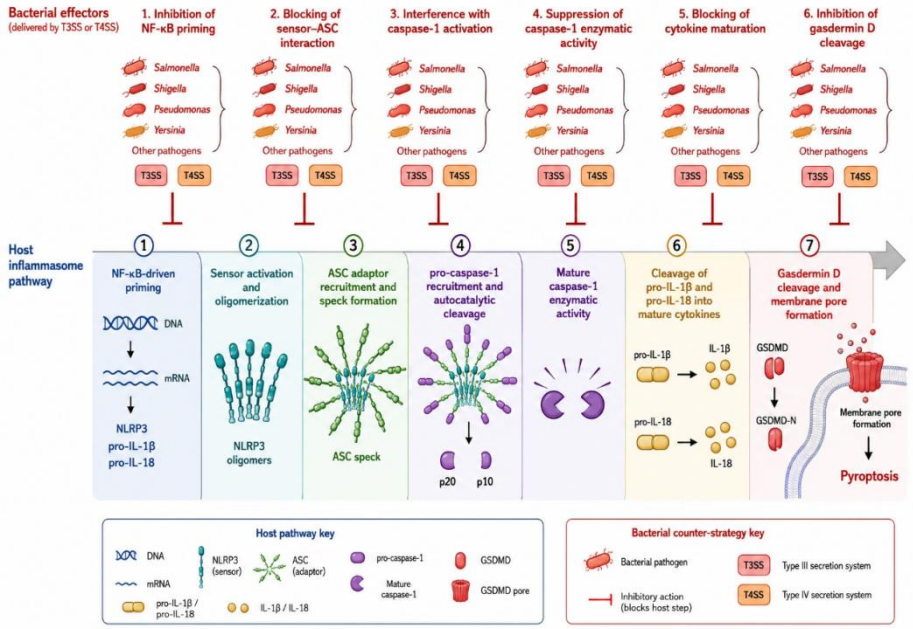

Figure 04: Points at which bacterial effector proteins interrupt inflammasome signalling. Each step of the host pathway, from NF-κB-driven priming to gasdermin D cleavage, is opposed by a bacterial counter-strategy delivered mainly through type III and type IV secretion systems.

Table 05: Bacterial strategies for evading inflammasome-mediated immunity.

Evasion strategy	Molecular target	Consequence for the host response	Ref.
Inhibition of complex assembly	Sensor–ASC interaction	Reduced caspase-1 activation and IL-1β maturation	89,90
Suppression of the effector step	Caspase activity and gasdermin D cleavage	Pyroptosis is blocked or delayed, preserving the intracellular niche	62,90
Degradation and modification of components	Ubiquitination pathways and host signalling proteins	Destabilisation of the inflammasome complex	91
Manipulation of host cell metabolism	Mitochondrial function, ROS, autophagy and ion transport	Fewer intracellular danger signals reach NLRP3	91,92
Exploitation of anti-inflammatory pathways	IL-10 induction and NF-κB suppression	Weaker priming, so less sensor and cytokine precursor is available	92
Remodelling of surface structures	Lipopolysaccharide and flagellin	Escape from recognition by innate immune receptors	92,93

5.1. Therapeutic Modulation of Inflammasome Signaling

Because the same pathway that clears bacteria also drives tissue injury, therapeutic interest has moved towards agents that reduce excessive signalling without abolishing protective immunity. Three levels can be targeted: the sensor itself, the effector caspase and gasdermin D, and the cytokines released downstream. Selective NLRP3 inhibitors act at the first level, caspase-1 and gasdermin D inhibitors at the second, and IL-1 and IL-18 blockade at the third; the agents in each class differ widely in how far they have been developed (Table 6). Because inflammasome activity is also required for bacterial control, the timing and the degree of inhibition matter as much as the choice of target during active infection [16,22,93].

Table 06: Approaches to the pharmacological modulation of inflammasome signalling and downstream inflammatory mediators.

Agent or approach	Molecular target	Mechanism	Stage of development	Ref.
MCC950 (CRID3)	NLRP3	Blocks the NACHT-domain conformational change required	Preclinical and early clinical evaluation	16,93

		for oligomerisation		
OLT1177 (dapansutrile)	NLRP3	Orally active selective inhibitor of NLRP3	Clinical trials	93
CY-09	NLRP3	Binds the ATP-binding site of the NACHT domain	Preclinical	93
Oridonin	NLRP3	Covalent modification of a cysteine residue in the NACHT domain	Preclinical	93
VX-765 (belnacasan)	Caspase-1	Prodrug inhibitor of caspase-1 catalytic activity	Clinical trials	16,93
Disulfiram, necrosulfonamide	Gasdermin D	Prevent pore formation and therefore pyroptosis	Preclinical	13,93
Anakinra	IL-1 receptor	Recombinant IL-1 receptor antagonist	Approved for inflammatory indications	16,22
Canakinumab	IL-1β	Neutralising monoclonal antibody	Approved for inflammatory indications	16,22
Rilonacept	IL-1α and IL-1β	Soluble decoy receptor that traps circulating IL-1	Approved for inflammatory indications	16,22
IL-18 binding protein	IL-18	Sequesters free IL-18 and limits its downstream signalling	Clinical trials	16

6. CONCLUSION

During bacterial infections, inflammasomes are key mediators that coordinate pathogen recognition, inflammatory cytokine production, and pyroptotic cell death. As a result, they are central regulators of innate immune responses. Through the recruitment of immune cells to infected tissues and the production of IL-1 and IL-18, their activation significantly limits the replication of bacteria and promotes efficient immune defense. Because excessive or persistent activation can cause tissue damage, organ dysfunction, chronic inflammation, and poor clinical outcomes, the protective effects of inflammasomes require strict regulation. Different pathogenic bacteria activate distinct inflammasome pathways through diverse virulence factors, while many have evolved sophisticated mechanisms to suppress or manipulate inflammasome signaling in order to enhance intracellular survival and evade host immunity. These complex host–pathogen interactions highlight the dual nature of inflammasome responses, where efficient antimicrobial activity must be balanced against the risk of immunopathology. Ion fluxes, mitochondrial dysfunction, reactive oxygen species, autophagy, and post-translational modifications all play important roles in the molecular mechanisms that control inflammasome activation, which have all received significant attention in recent years thanks to new discoveries. Several potential therapeutic targets for controlling excessive inflammation without compromising antimicrobial defense have been identified by these discoveries. Future studies should focus on clarifying the interactions among different inflammasome pathways, identifying reliable biomarkers of inflammasome activity, and developing selective immunomodulatory therapies tailored to specific bacterial infections. The development of more efficient therapeutic approaches that increase bacterial clearance while minimizing inflammatory tissue damage will be made easier with a deeper comprehension of inflammasome biology.

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9. INFORM CONSENT AND ETHICAL STATEMENT

Not Applicable

10. ACKNOWLEDGEMENT

Not Declared

11. CONFLICT OF INTEREST

Not Applicable

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