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REVIEW

Salmonella-NLRP3 Inflammasome Crosstalk: Host Defense Activation Versus Bacterial Immune Evasion Strategies

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Abstract: The innate immune system plays a crucial role in defending against *Salmonella* infection. Inflammasomes are macromolecular complexes that assemble in response to the recognition of pathogen- or danger-associated molecular patterns. These complexes serve as signaling platforms for the activation of inflammatory Caspases, which subsequently triggers the maturation and secretion of the pro-inflammatory cytokines IL-1β and IL-18. This process also initiates pyroptosis, a highly inflammatory form of programmed cell death characterized by lytic cell lysis. *Salmonella* are intracellular pathogens that proliferate within epithelial cells and macrophages, posing a significant public health risk in both developed and developing countries. During *Salmonella* infection, the canonical NLRP3 and NLRC4 inflammasome, as well as non-canonical inflammasome, are activated. Unlike NLRC4 and non-canonical inflammasomes, which play crucial roles during intestinal infection phases, the role of NLRP3 inflammasome in resisting *Salmonella* infection demonstrates a higher degree of complexity and uncertainty. Nonetheless, the activation of NLRP3 inflammasome, along with the downstream innate and adaptive responses, form a robust host immune barrier against potential pathogens. Therefore, successful pathogens must evolve multiple mechanisms to circumvent or counteract these immune barriers. Here we review and discuss the mechanisms of NLRP3 inflammasome activation triggered by intracellular *Salmonella*, as well as the multiple strategies employed by *Salmonella* to avoid or delay NLRP3 inflammasome activation. A deeper understanding of how NLRP3 inflammasomes recognize *Salmonella* and how pathogens evade NLRP3 activation has the potential to facilitate the development of novel prevention and control measures for *Salmonella* infection.

Keywords: inflammasome, *Salmonella*, NLRP3, caspases, immune evasion

Introduction

The innate immune response constitutes the initial barrier of host defense against pathogenic bacterial infections. Pattern recognition receptors (PRRs) within host cells can recognize the pathogen-associated molecular patterns (PAMPs) of bacteria and swiftly initiate countermeasures, effectively eliminating intracellular pathogens via phagocytosis and inflammatory responses. The inflammasome activation is a pivotal innate immune defense mechanism in combating bacterial infections.[1] Inflammasomes are macromolecular multimeric protein complexes that function as an activation platform for cysteinyl aspartate specific proteinase (Caspase).[2] Inflammasomes are adept at recognizing various danger signals within host cells, including PAMPs, microbial-associated molecular patterns (MAMPs), and damage-associated

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molecular patterns (DAMPs). Upon activation, inflammasomes can trigger pro-inflammatory pathways and antimicrobial responses, leading to the secretion of various pro-inflammatory cytokines and chemokines, as well as the up-regulation of immunoreceptors and cell adhesion molecules.[3] According to different activation pathways, inflammasomes can be divided into two categories: canonical and non-canonical inflammasomes.

Canonical inflammasomes are formed by the sensor PRRs, the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD [caspase activation and recruitment domain]), and the effector pro-Caspase-1.[4] The activation of canonical inflammasome triggers the self-cleavage and activation of Caspase-1, which subsequently cleaves the pro-inflammatory cytokines pro-IL-1β and pro-IL-18 into their active, secreted forms.[5] Additionally, the pro-Gasdermin D (pro-GSDMD) is identified as a substrate for Caspase-1/4/5/11, the N-terminal product of GSDMD cleavage can form pores in the plasma membrane. This pore-forming activity leads to a form of pro-inflammatory programmed necrosis known as pyroptosis, which further contributes to the host immune defense by eliminating infected cells.[6] Among the canonical inflammasomes, Nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain-containing protein 1 (NLRP1), NLRP3, and NOD-like receptor family CARD domain containing protein 4 (NLRC4) inflammasomes play pivotal roles as surveillance machinery during bacterial infection.[7–9] They act as front-line sentinels, constantly monitoring for the presence of bacteria and initiating appropriate immune responses. Unlike the canonical inflammasomes, the activation of non-canonical inflammasomes does not rely on PRRs sensors. This divergence in activation mechanisms reflects the complexity and flexibility of the immune system to adapt to different types of threats. Instead, Caspase-4/5 (in humans) and Caspase-11 (in mice) take on the role of pathogen sensors. They recognize and directly bind cytosolic lipopolysaccharide (LPS) through their CARD domains.[10] This direct interaction with LPS bypasses the need for PRR-mediated sensing, allowing for a more rapid response to the presence of intracellular Gram-negative bacteria. Once Caspase-4/5/11 bind to LPS, they then initiate IL-1β proteolytic maturation and pyroptosis in a GSDMD-dependent manner. This process is crucial as it provides a crucial host defense against intracellular Gram-negative bacteria, complementing the functions of canonical inflammasomes in maintaining immune homeostasis.[11]

In addition to its critical role in bacterial defense, the NLRP3 inflammasome has emerged as a central mediator in multiple human pathologies, underscoring its potential as a therapeutic target. Recent studies highlight its involvement in vascular diseases, where excessive NLRP3 activation drives atherosclerotic lesion formation, vascular dysfunction, and aneurysm development through Caspase-1- dependent IL-1β/IL-18 secretion and pyroptosis.[12] Inflammatory bowel diseases such as Crohn's disease (CD) are also linked to NLRP3 inflammasome hyperactivation and distinct blood microbiome signatures, including enrichment of *Staphylococcus sciuri* and altered IL-1β profiles.[13] These findings highlight NLRP3 as a potential diagnostic biomarker and suggest that microbial-targeted interventions may modulate inflammatory responses in CD. Emerging evidence further implicates NLRP3 in neurodegenerative disorders, with studies demonstrating its contribution to amyloid-β aggregation and neuroinflammation in Alzheimer's disease.[14] Moreover, metabolic dysfunction-associated steatotic liver disease (MASLD) exhibits a bidirectional relationship with NLRP3, where gut microbiota-derived metabolites promote inflammasome activation in hepatocytes, exacerbating hepatic steatosis and fibrosis.[15] These findings collectively position the NLRP3 inflammasome as a key node in inflammation-driven pathologies, prompting ongoing development of targeted therapies including small molecule inhibitors and microbiome modulation strategies.

Salmonella enterica is a flagellated facultative anaerobic Gram-negative bacterium, more than 2600 serovars have been characterized based on the differences in flagellin (H) and lipopolysaccharide (O) antigens.[16] *Salmonella* is one of the most important and dangerous foodborne zoonotic pathogens globally, accountable for approximately 93.8 million foodborne disease cases and roughly 155,000 fatalities annually,[17] the contaminated poultry, eggs, vegetables, and dairy products are the most common sources of infection.[18] After invading the host through the gastrointestinal tract, *Salmonella* crosses the epithelial barrier by invading intestinal epithelial cells or microfold cells and subsequently disseminates to systemic sites by invading nearby phagocytes.[19] The ability of *Salmonella* to invade host cells is dependent on the *Salmonella* pathogenicity island-1 (SPI-1)-encoded type III secretion system-1 (T3SS-1).[20] Once internalized, *Salmonella* swiftly establishes a specialized *Salmonella*-containing vacuole (SCV) via SPI-2-encoded T3SS-2 for replication.[21,22] Over 60 effector proteins are secreted via T3SS, aiding in maintaining SCV homeostasis, modulating host cells progression, and evading host immune responses to achieve persistent infection.[23]

Previous studies have demonstrated that the canonical NLRP3 and NLRC4 inflammasome, as well as the non-canonical Caspase-4/5/11 inflammasome are mainly activated during *Salmonella* infection.[24] The activation of these inflammasomes plays a crucial role in limiting *Salmonella* infection. Mice lacking Caspase-1/11 succumb to *Salmonella* infection more rapidly than wild-type (WT) mice, exhibiting significantly elevated bacterial burdens in organs.[25,26] Given the antimicrobial properties of inflammasomes, *Salmonella* has also developed various mechanisms to avoid or delay the activation of inflammasome.

Currently, the canonical NLRC4 and non-canonical Caspase-11 inflammasome pathways have been established as playing a crucial role in resisting *Salmonella* infection of the gut through inflammasome-dependent sloughing of infected epithelial cells.[10,27–29] However, several unresolved questions persist regarding NLRP3 inflammasome activation during *Salmonella* infection. Foremost among these is the divergent role of NLRP3 in different infection models, with conflicting evidence regarding its necessity for host defense. In systemic *Salmonella* infection models, NLRC4 and NLRP3 have been shown to exhibit redundant functions in inducing Caspase-1 activation, with mice deficient in both NLRC4 and NLRP3 displayed significantly increased susceptibility to infection.[30] Conversely, another study suggests that NLRP3 is dispensable during *Salmonella* infection, as there are no significant differences in bacterial counts, cytokine levels, and histological inflammation between WT and *Nlrp3*$^{-/-}$ mice.[31] In contrast, numerous studies have emphasized the indispensable role of NLRP3 inflammasome activation in host defense against *Salmonella* infection.[32–34] Moreover, the molecular mechanisms underlying NLRP3 recognition of *Salmonella* remain incompletely characterized, particularly the specific ligands or upstream signaling events that trigger its activation. The interplay among canonical, non-canonical, and alternative NLRP3 pathways during infection also requires further clarification. Equally critical are the bacterial evasion strategies targeting NLRP3, with many effector proteins and metabolic adaptations yet to be fully understood. Addressing these gaps will advance our understanding of host-pathogen interactions and inform therapeutic development. In this review, we delve into recent findings concerning the role of NLRP3 inflammasome in resisting *Salmonella* infection and explore the complex interplay of detection and evasion between NLRP3 inflammasome and *Salmonella*.

Mechanisms of NLRP3 Inflammasome Activation

Canonical NLRP3 Inflammasome

NLRP3 is one of the most extensively studied NLR family proteins, which consists of an amino-terminal pyrin domain (PYD), a central nucleotide-binding and oligomerization domain (NACHT), and a C-terminal leucine-rich repeat (LRR) domain.[35] Previous studies suggest that the LRR domain mediates auto-inhibition of NLRP3 by folding back into the NACHT domain.[36] However, a recent study indicates that the LRR domain is dispensable for NLRP3 auto-inhibition.[37] Notably, NIMA-related kinase (NEK7), a serine/threonine kinase contributing to mitosis, has been found to play an essential role in NLRP3 inflammasome activation through direct binding to the LRR domain of NLRP3.[38] The activation of the canonical NLRP3 inflammasome requires a priming step and an activation step. First, upon recognition of PAMPs or DAMPs by PRRs, transcription factors such as NF-κB are activated, leading to the up-regulation of NLRP3 and pro-IL-1β expression.[39,40] Importantly, multiple post-translational modifications of NLRP3, including ubiquitination, phosphorylation, sumoylation, and S-nitrosylation, also prime NLRP3 for activation while maintaining its auto-inhibited state.[41,42] Second, the activation step involves the recognition of NLRP3 agonists, leading to the assembly and activation of NLRP3 inflammasome. Unlike PRRs, which typically recognize one or several structurally similar stimuli, NLRP3 can be activated by a diverse range of structurally and chemically dissimilar agonists, including PAMPs such as bacterial, fungal, and viral toxins, DAMPs such as extracellular ATP, particulates such as silica and uric acid crystals.[43,44] Upon stimulation, NLRP3 oligomerizes through homotypic interactions between NACHT domains. This oligomerized NLRP3 then recruits ASC through homotypic PYD-PYD interactions.[39] Following ASC oligomerization and speck formation, ASC recruits pro-Caspase-1 through CARD-CARD interactions, initiating pro-Caspase-1 self-cleavage and activation.[45] Active Caspase-1 subsequently cleaves and activates GSDMD, which triggers pyroptosis, and converts pro-IL-1β and pro-IL-18 into mature pro-inflammatory cytokines.[46]

It is noteworthy that the precise mechanism by which NLRP3 recognizes its various stimuli remains elusive, as no direct interaction between NLRP3 and these known stimuli has been observed. Despite the similarity in the terminal signaling events triggered by these stimuli, the initial mechanisms are likely to differ. It is suggested that NLRP3 senses common upstream cellular events induced by these stimuli, although the identity of these signal events remains controversial within the field. Proposed upstream cellular events include ionic flux,[47–49] lysosomal rupture,[50,51] reactive oxygen species (ROS) production,[52,53] and mitochondrial dysfunction.[54–56] Although NLRP3 stimuli can activate inflammasome signals via the aforementioned upstream signal events, none of these signal events is applicable to all NLRP3 stimuli. Therefore, the specific mechanisms by which NLRP3 senses these stimuli and how the NLRP3 inflammasome is assembled and activated remain areas requiring further characterization.

Non-Canonical NLRP3 Inflammasome

Cytoplasmic LPS triggers non-canonical Caspase-4/5/11 inflammasome activation, leading to the cleavage of GSDMD and pyroptosis. Notably, Caspase-11 does not participate in the cleavage and maturation of pro-inflammatory cytokines IL-1β and IL-18.[57] Human Caspase-4 resembles Caspase-1 in its ability to cleave GSDMD and pro-IL-18, but it does not cleave pro-IL-1β. The ability of Caspase-5 to cleave both pro-IL-18 and pro-IL-1β is extremely limited, closely resembling that of Caspase-11.[58] Activated Caspase-4/5/11 and cleaved GSDMD subsequently trigger the NLRP3-ASC-Caspase-1 signaling pathway, a process known as the non-canonical NLRP3 inflammasome activation, which is crucial for the subsequent maturation and secretion of IL-18 and IL-1β.[59] This non-canonical NLRP3 inflammasome activation does not necessitate a priming signal and relies on Caspase-11 for functionality. However, the exact mechanism of non-canonical NLRP3 inflammasome activation remains controversial and not fully characterized. Previous studies suggest that Caspase-11 forms a complex with NLRP3/ASC and pro-Caspase-1.[57,60] It is proposed that Caspase-11 and NLRP3 can mutually activate each other through direct interaction between the scaffold domain of Caspase-11 and the LRR/PYD domain of NLRP3, which requires concurrent detection of bacterial mRNA by NLRP3 and binding of LPS by Caspase-11.[59] This interaction is reported to occur upstream of inflammasome formation and pro-Caspase-11 cleavage. However, other studies have demonstrated that Caspase-11 activation and GSDMD cleavage are upstream signals of NLRP3 activation.[11,61–63] Thus, the exact sequence of events leading to non-canonical NLRP3 inflammasome activation remains an area of ongoing research.

After being cleaved by activated Caspase-4 and Caspase-11, the N terminus of GSDMD forms pores on the cell membrane, resulting in K^+ efflux, which is crucial for subsequent activation of the non-canonical NLRP3 inflammasome.[63,64] Additionally, Caspase-11 can activate pannexin-1 via catalytic cleavage, thereby promoting ATP efflux, which in turn stimulates NLRP3 inflammasome activation.[65] Recently, the nuclear orphan receptor Nur77 has been identified as a receptor for cytoplasmic LPS and mitochondrial dsDNA released through Caspase-11-dependent GSDMD pores. When Nur77 simultaneously binds to LPS and mitochondrial dsDNA, it becomes fully activated and directly binds to NLRP3, leading to enhanced NEK7 recruitment, ASC oligomerization, and non-canonical NLRP3 inflammasome activation.[62] Similar to the canonical NLRP3 inflammasome, there is no singular, unified pathway for the non-canonical NLRP3 inflammasome activation. While some upstream signal events observed in non-canonical NLRP3 inflammasome pathway are consistent with those in the canonical NLRP3 inflammasome pathway, such as K^+ efflux and ATP efflux.[63,65] The overlap of these upstream signal events between canonical and non-canonical NLRP3 inflammasome activation suggests that the activation of NLRP3 is not triggered by a specific stimulant, the initial signal is an undiscovered minimal common cellular event that is both necessary and sufficient to activate the NLRP3 inflammasome.

Recent studies have revealed that the non-canonical NLRP3 inflammasome can be activated by various lipids beyond LPS.[66] Specifically, the parasite membrane glycoconjugate lipophosphoglycan (LPG) has been identified as a key molecule in activating Caspase-11 and the non-canonical NLRP3 inflammasome. However, it is noteworthy that additional, yet unidentified molecules are required for this activation, as purified LPG alone fails to activate Caspase-11 or Caspase-4 in vitro.[67] In environments with limited phosphate availability, bacteria reduce LPS production and synthesize phosphorus-free alternatives, such as ornithine lipid, which has been shown to activate Toll-like receptor 4 (TLR4) and induce K^+ efflux-dependent non-canonical NLRP3 inflammasome activation.[68] Interestingly, in the presence of LPS, ornithine lipid can also function as a partial TLR4 antagonist, reducing LPS-induced non-canonical NLRP3

inflammasome activation and cytokine secretion. In dendritic cells (DCs), the oxidized phospholipid 1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphorylcholine (oxPAPC) has been found to promote IL-1β secretion through a mechanism dependent on Caspase-11, NLRP3, ASC, and Caspase-1, suggesting that oxPAPC serves as an agonist of the non-canonical NLRP3 inflammasome in DCs.[69] However, oxPAPC also inhibits LPS-induced pyroptosis and non-canonical NLRP3 inflammasome activation in macrophages by directly binding to Caspase-4 or Caspase-11, thereby competing with LPS binding.[70] These findings suggest that the activation or inhibition of the non-canonical NLRP3 inflammasome by these lipids is contingent on the cell type, location, and intracellular metabolic environment.

Alternative NLRP3 Inflammasome

Recently, LPS has been discovered to trigger an "alternative" inflammasome in human monocytes, which operates through the NLRP3-ASC-Caspase-1 signaling, distinct from both canonical and non-canonical pathways.[71] This alternative NLRP3 inflammasome activation has been observed in human and porcine monocytes but not in murine cells.[72] In comparison to the robust activation of canonical and non-canonical NLRP3 inflammasomes, the alternative pathway exhibits weaker activation and lacks classical inflammasome characteristics such as K^+ efflux dependency, ASC pyroptosome formation, and pyroptosis induction.[73] The alternative pathway is triggered by LPS and relies on TLR4, TIR-domain-containing adapter-inducing interferon-β (TRIF), receptor-interacting protein kinase 1 (RIPK1), FAS-associated death domain (FADD), and Caspase-8 upstream of NLRP3 activation.[5] Notably, the upstream TLR4–TRIF–RIPK1–FADD–Caspase-8 signaling has been shown to play no role in canonical and non-canonical NLRP3 inflammasome activation.[71] However, a recent study indicates that TLR4 and TRIF may not be indispensable upstream components of the alternative pathway, as ligands of TLR1/2, TLR2/6, TLR4 and TLR7 and/or TLR8 all have the potential to trigger the alternative NLRP3 pathway.[74] Furthermore, the alternative pathway can function independently of RIPK1 kinase activity, suggesting that the mechanism of alternative NLRP3 inflammasome activation requires further characterization.

In addition to LPS, apolipoprotein C3 (ApoC3) has been reported to induce alternative NLRP3 inflammasome activation via forming a heterotrimer with TLR2, TLR4, and SLP adaptor and CSK interacting membrane protein (SCIMP). This heterotrimer triggers Lyn/Syk-dependent calcium entry and ROS formation, leading to the activation of Caspase-8.[75] A previous study also indicated that ApoC3 activates the NLRP3 inflammasome by enhancing the binding of TXNIP to NLRP3 in the presence of ROS.[76] Furthermore, a study revealed that heat-killed *Salmonella* can serve as an alternative NLRP3 inflammasome stimulant in human monocytes. The short isoform of cellular FADD-like IL-1β converting enzyme inhibitory protein (cFLIPs), which is activated by NF-κB, negatively regulates Caspase-8 and halts the alternative NLRP3 inflammasome activation in response to heat-killed *Salmonella*.[77] This mechanism effectively prevents cell death caused by otherwise sustained NLRP3 inflammasome activation.

In comparison to the non-canonical and alternative pathways, the canonical pathway of NLRP3 inflammasome activation has been the most extensively researched. The non-canonical NLRP3 inflammasome primarily responds to cytosolic lipids, such as LPS, and is consistently associated with Caspase-4/5/11. Conversely, the alternative NLRP3 inflammasome remains the least studied, involving a multitude of stimuli and Caspases. Therefore, delving deeper into the molecular mechanisms underlying the activation of non-canonical and alternative NLRP3 inflammasomes holds significant promise for identifying the initiating ligands or signals that trigger NLRP3 activation.

NLRP3 Inflammasome Detecting Salmonella

Like other stimuli, the mechanism by which NLRP3 inflammasome recognizes *Salmonella* remains poorly characterized. It is hypothesized that NLRP3 activation occurs downstream of certain *Salmonella*-induced signaling events during infection. *Salmonella* T3SS-1 effector protein SipB has been previously discovered to directly bind and interact with Caspase-1, which is essential for Caspase-1 activation and IL-1β maturation.[78] A recent study suggests that NLRP3 activation induced by *Salmonella* is likely due to the activity of the SPI-1 T3SS, as the inflammasome activation level induced by Δ*sipB* was significantly lower than that of WT *Salmonella* in *Nlrc4*$^{-/-}$ human macrophages.[79] SipB has also been demonstrated to promote mitochondrial depolarization during *Salmonella* infection, which is essential for the release of fragmented mitochondrial DNA (mtDNA) and the production of ROS that converts mtDNA to an oxidized form (Ox-mtDNA) (Figure 1). Ox-mtDNA is currently the only identified intermediate product of upstream signal events

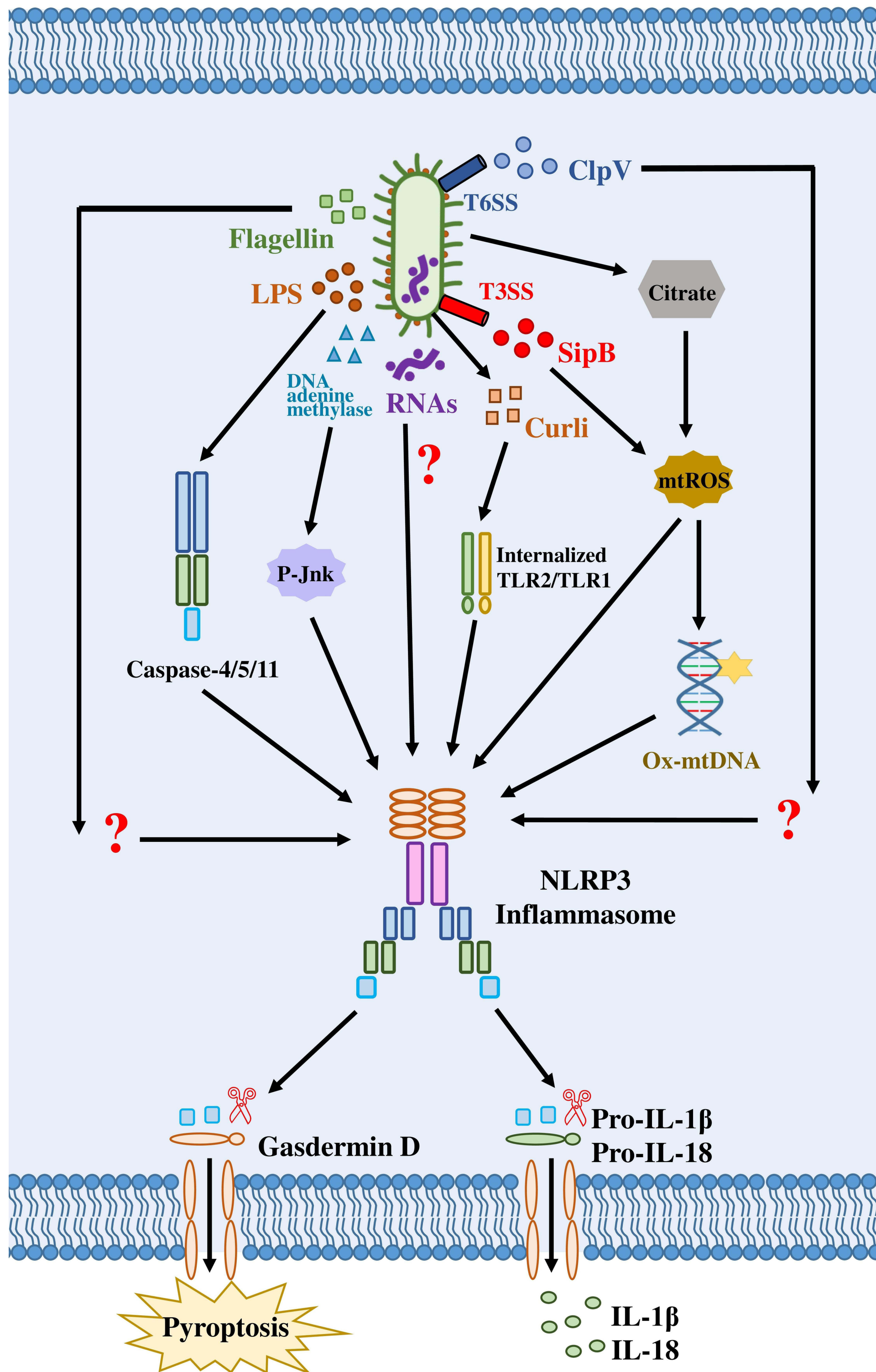

Figure 1 Detection of *Salmonella* by the NLRP3 inflammasome. *Salmonella* can be detected by intracellular NLRP3 inflammasome, resulting in pyroptosis and the release of IL-1β and IL-18. Lipopolysaccharide (LPS) stimulates non-canonical NLRP3 inflammasome activation by activating Caspase-4/5/11. The bacterial DNA adenine methylase (Dam) enhances NLRP3 inflammasome activation by promoting the phosphorylation of Jnk. The amyloid curli present in *Salmonella* biofilms stimulates the TLR2/TLR1 heterocomplex, which causes activation of NF-κB and expression of pro-IL-1β. The endocytosis of curli fibers via internalized TLR2/TLR1 then activates NLRP3 and Caspase-1. The type III secretion system-1 (T3SS-1) effector protein SipB facilitates the generation of mitochondrial reactive oxygen species (mtROS) and the conversion of mitochondrial DNA into its oxidized form (Ox-mtDNA), thereby initiating NLRP3 inflammasome activation. Excessive accumulation of bacterial citrate rapidly activates the NLRP3 inflammasome through an mtROS-dependent pathway. Furthermore, NLRP3 inflammasome recognizes flagellin, bacterial RNA components, and the T6SS-secreted protein ClpV of *Salmonella* via unknown mechanisms. Figure 1 was independently designed by the authors using Microsoft PowerPoint 2013, with all elements created using native software features.

that serves as the ultimate NLRP3 ligand, or at least a part of it.[55,80] However, another study has reported that mitochondrial damage and mtROS production, which can occur with NLRP3 activators, are not necessary for NLRP3 inflammasome activation.[47] These findings suggest that the pathway by which NLRP3 inflammasome recognizes *Salmonella* is not confined to a single specific signal event.

Indeed, in the context of *Salmonella* interactions with macrophages, the NLRP3 inflammasome can also respond to *Salmonella* through SPI-1 and SPI-2 T3SS-independent signals. A recent study has revealed that the *Salmonella* T6SS core-secreted protein ClpV promotes the expression of NLRP3 through an unknown mechanism (Figure 1). This mechanism is essential for intestinal barrier disruption, bacterial adhesion and colonization.[81] The NLRP3 inflammasome can recognize curli, a bacterial amyloid protein present in *Salmonella* biofilms, leading to caspase-1 activation and IL-1β production. This response relies on endocytosis of curli fibers via internalized TLR2/TLR1, which activate NF-κB, prime pro-IL-1β transcription and enable NLRP3 activation in macrophages.[82] The underlying mechanism involves the damage caused in the lysosomal compartment by intracellular amyloid fibers.[83] Notably, NLRP3 inflammasome activation in mouse macrophages infected with the curli mutant did not differ significantly from WT-infected macrophages. However, only under curli-inducing growth conditions, the curli mutant displayed significantly reduced IL-1β induction compared to WT *Salmonella*,[82] indicating that *Salmonella* employs mechanisms to limit curli expression during natural infection, thereby evading NLRP3 recognition. Furthermore, the NLRP3 inflammasome can sense *Salmonella* by recognizing bacterial nucleic acids. Prokaryotic mRNA, a viability-associated PAMP present only in viable bacteria, is responsible for subsequent NLRP3 inflammasome activation, even in the absence of virulence factors.[84] Further research has shown that the ability of mice and human NLRP3 inflammasome to sense bacterial RNA differs. Human NLRP3 inflammasome can detect all bacterial RNA components (Figure 1), including mRNA, tRNA, and rRNA, while only bacterial mRNA can be recognized by mice NLRP3 inflammasome.[85] How NLRP3 inflammasome senses *Salmonella* RNA components, the contribution of each RNA component to the host immune response during *Salmonella* infection are significant questions that require further investigation. Flagellin, a recognized activator of NLRC4 inflammasome that can directly bind to NAIP, has been shown to activate the NLRP3 inflammasome in human macrophages in a NAIP-independent manner through the canonical pathway (Figure 1).[86] Whether this effect exists in mouse cells remains to be verified, and the mechanism of how NLRP3 inflammasome recognizes *Salmonella* flagellin warrants further exploration.

Several studies have revealed that the NLRP3 activation events are tied to alterations in host cell most likely induced by intracellular *Salmonella* metabolism. Specifically, excessive accumulation of bacterial citrate, an oxidative metabolite produced by *Salmonella*, can rapidly activate the NLRP3 inflammasome through an mtROS-dependent pathway (Figure 1), which is abrogated upon deletion of *Salmonella* citrate synthase GltA.[32] Additionally, *Salmonella* disrupts glycolytic flux by consuming host-cell glucose, leading to the activation of NLRP3 inflammasome through sensing this metabolic shift. This activation is dependent on a reduction in NADH levels and the induction of mtROS production.[87] Our previous studies also support the notion that the NLRP3 inflammasome can sense intracellular *Salmonella* via metabolic pathways. We found that the bacterial DNA adenine methylase (Dam) is essential for the activation of the Jnk-dependent NLRP3 inflammasome during *Salmonella* infection (Figure 1).[88] Further research suggests that Dam is employed to repress the production and conversion of arachidonic acid to prostaglandin E2, mediated by cytosolic phospholipase A2 in macrophages.[89] These findings suggest that the innate immune responses mediated by the NLRP3 inflammasome can detect intracellular bacteria not only through sensing bacterial proteins and virulence activities but also by sensing bacterial metabolites.

In addition to the canonical NLRP3 inflammasome, the host innate immune system can recognize invading *Salmonella* through non-canonical and alternative NLRP3 pathways (Figure 1). Upon recognizing extracellular LPS of *Salmonella*, TLR4 induces the type I interferon response, along with the complement C3-C3aR axis, to promote Caspase-11 expression.[90] Type I interferons further induce the expression of guanylate-binding proteins (GBPs) and interferon-inducible protein IRGB10.[91] Once recruited to the intracellular *Salmonella* cell membrane via their conserved transmembrane domains and myristoylation motifs, GBPs and IRGB10 form oligomeric complexes that disrupt bacterial membrane integrity. This process involves IRGB10 inserting its amphipathic helices into the bacterial membrane, leading to structural destabilization and subsequent release of LPS into the cytosol. The liberated LPS then binds directly to Caspase-11, triggering non-canonical activation of the NLRP3 inflammasome and pyroptosis.[92] During the early stages

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of *Salmonella* infection, human monocytes can swiftly respond through the alternative NLRP3 inflammasome pathway, preceding the activation of the canonical, non-canonical NLRP3, or NLRC4 pathways.[93] The rapid activation of the alternative NLRP3 inflammasome may be dependent on TLR4 recognition of *Salmonella* LPS. Furthermore, early activation of alternative NLRP3 signaling may facilitate the subsequent triggering of canonical and non-canonical NLRP3 pathways, as the alternative pathway enhances the expression of NLRP3 and the release of IL-1β.

Strategies for Salmonella to Avoid NLRP3 Inflammasome Activation

The NLRP3 inflammasome swiftly responds to stimuli such as ATP, nigericin, or crystals within 1–2 hours,[94–96] resulting in rapid Caspase-1 activation and pro-inflammatory cytokines release. However, in bone marrow-derived macrophages (BMDMs) invaded by *Salmonella*, NLRP3 inflammasome activation is delayed, occurring only 12–16 hours post-infection.[30] The significance of this delayed activation of NLRP3 inflammasome during *Salmonella* infection remains controversial. The NLRP3 and NLRC4 inflammasome have been indicated to play redundant roles in resisting *Salmonella* infection.[30] Despite its role in cytokine maturation, NLRP3 and ASC have been reported to play a limited role during *Salmonella* infection.[31] NLRP3 is dispensable for *Salmonella* clearance in the cecum and mesenteric lymph nodes, even in the absence of NLRC4.[97] Consistent with these findings, our previous research showed no significant difference in bacterial colonization and inflammasome-dependent cytokine secretion between WT- and *Nlrp3*$^{-/-}$-mice infected with *Salmonella*.[33] Although flagellin and SPI-1 T3SS apparatus of *Salmonella* are readily recognized by NLRC4 inflammasome within 1 hour of invasion, these PAMPs, which are crucial for bacterial invasion of epithelial cells, remain highly expressed during the logarithmic growth phase. Undeniably, NLRC4 inflammasome is the main force in recognition and clearance of intestinal *Salmonella*. The high activity of NLRC4 inflammasome indeed masks the role of NLRP3 inflammasome in the early stages of *Salmonella* infection. Based on in-depth studies, the delayed activation of NLRP3 inflammasome and its limited role in resisting *Salmonella* infection could be attributed to multiple strategies employed by *Salmonella* to avoid or delay NLRP3 activation during infection.

Once inside the host cell, *Salmonella* engages in an intracellular battle for survival with host cell molecular defense pathways. *Salmonella* strains isolated from mice during the acute phase of infection display an enhanced potential to activate the NLRP3 inflammasome. Conversely, *Salmonella* strains isolated during the chronic phase of infection exhibit a significantly attenuated ability to activate NLRP3 signaling and induce the secretion of IL-1β.[98] The findings suggest that *Salmonella* possesses the capability to adjust its NLRP3 inflammasome-activating potential across various infection stages, enabling it to adapt to the host intracellular environment. During chronic infections, *Salmonella* further adapts by evading NLRP3 inflammasome recognition, which aids in bacterial survival and the establishment of persistent infections. Concealing within *Salmonella*-containing vacuoles (SCVs) devoid of inflammasome activity provides *Salmonella* with a protective shield from detection. While this evasion strategy appears effective, it is not flawless. Long-term residence within the SCV hinders disease progression, some *Salmonella* will spontaneously escape from nascent SCV and replicate within the host cell cytosol.[99] Additionally, the SCV is constantly under attack by host immune defenses, which strive to destabilize it and induce its fusion with lysosomes.[21,22] SifA, a critical *Salmonella* SPI-2 T3SS effector, plays a vital role in maintaining the stability of the SCV (Figure 2). *Salmonella* deficient in SifA are rapidly released into the cell cytosol within a few hours after invading.[100,101] Early studies suggested that the enhanced clearance of *sifA* deletion mutants is mediated by Caspase-11-driven pyroptosis, a process independent of NLRP3, NLRC4, and ASC.[26] However, it is worth noting that Caspase-11-mediated pyroptosis is also sufficient to induce the activation of non-canonical NLRP3 inflammasome. Our recent high-throughput screenings further reveal that SifA plays a role in inhibiting the NLRP3 inflammasome activation in the absence of flagellin.[33] While it remains undetermined whether SifA suppresses the canonical or non-canonical NLRP3 pathway, the SCV stabilization mediated by SifA contributes to bacterial evasion of NLRP3 inflammasome activation.

Once the SCV is breached, inflammasomes swiftly recognize *Salmonella* that have been released into the cytoplasm by detecting PAMPs such as LPS, flagellin, and SPI-1 T3SS. To counteract the recognition of these PAMPs, which are essential for bacterial invasiveness, *Salmonella* activates the PhoP-PhoQ regulatory system when surviving within macrophages.[102–104] This system potently represses the expression of flagellin and SPI-1 T3SS while concurrently enhancing the expression of SPI-2 T3SS.[105,106] By decreasing the expression of flagellin (Figure 2), *Salmonella* gains

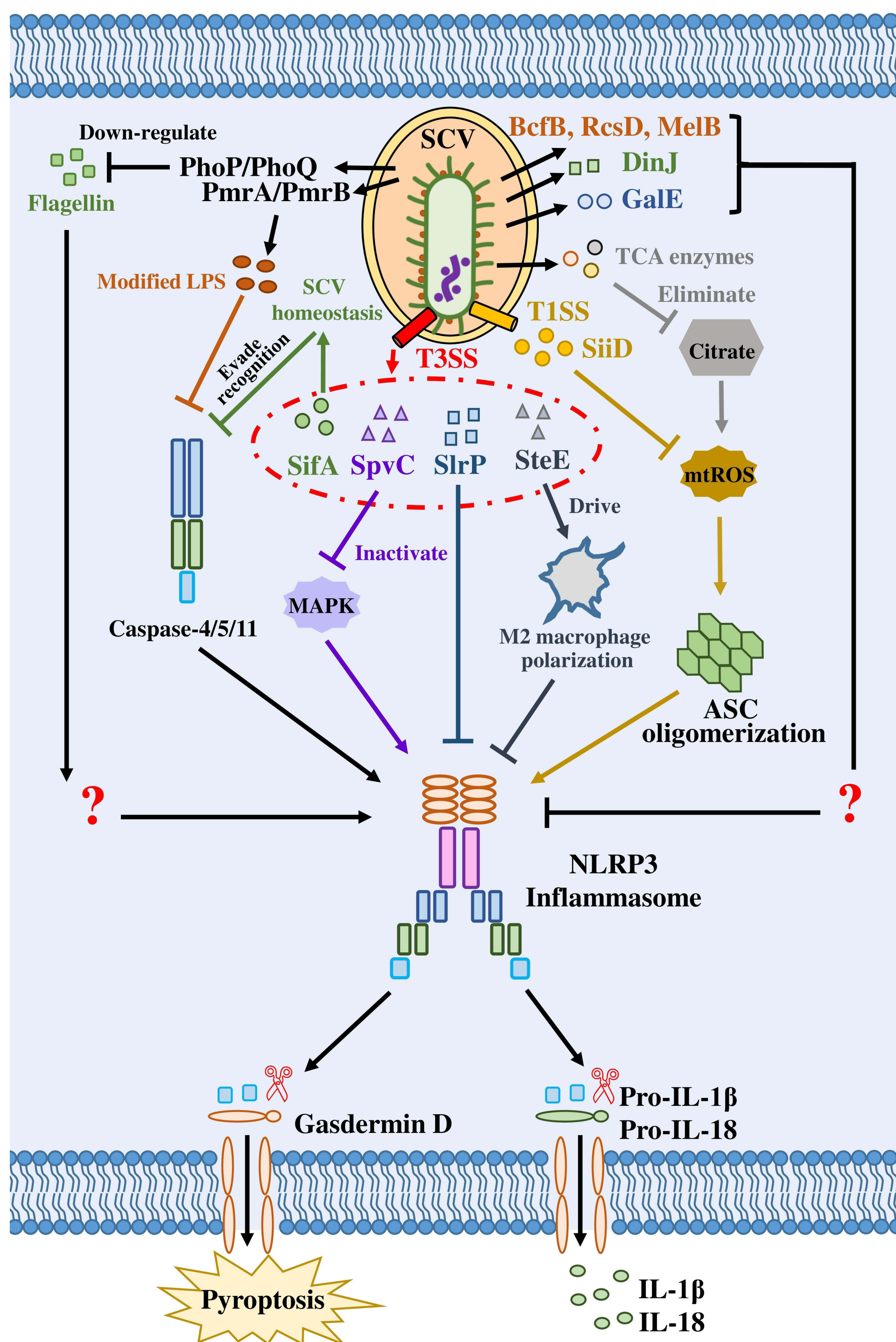

Figure 2 Multiple strategies utilized by *Salmonella* to suppress NLRP3 inflammasome activation. *Salmonella* employs the PhoP-PhoQ and PmrA-PmrB two-component regulatory systems to chemically modify Lipopolysaccharide (LPS), thereby evading recognition by the non-canonical inflammasome. Furthermore, PhoP-PhoQ significantly down-regulates the expression of flagellin and T3SS-1 when *Salmonella* resides within macrophages. The T3SS effector proteins are enclosed within the circle marked by the red dashed line. The type III secretion system-2 (T3SS-2) effector protein SifA plays a crucial role in maintaining the stability of the *Salmonella*-containing vacuole (SCV), which is essential for *Salmonella* to prevent non-canonical NLRP3 inflammasome activation triggered by Caspase-4/5/11. The T3SS-2 effector SpvC inhibits NLRP3 inflammasome activation by inactivating dual-phosphorylated MAPK. Another T3SS-2 effector, SlrP, suppresses the NLRP3 inflammasome in myeloid cells within the lamina propria, thereby preventing anorexia caused by IL-1β-mediated signaling to the hypothalamus via the vagus nerve. The T3SS effector SteE is utilized by *Salmonella* to induce M2 macrophage polarization, fostering an environment with low NLRP3 activity. The T1SS protein SiiD, as well as bacterial tricarboxylic acid cycle (TCA) enzymes is essential for *Salmonella* to repress the mtROS-ASC-mediated NLRP3 inflammasome activation. Furthermore, UDP-galactose-4-epimerase GalE, the toxin and antitoxin system antitoxin protein DinJ, the fimbrial chaperone BcfB, the two-component system phosphate transferase RcsD, and the symporter of melibiose and monovalent cations MelB all exhibit inhibitory effects on NLRP3 inflammasome activation through undefined mechanisms. Figure 2 was independently designed by the authors using Microsoft PowerPoint 2013, with all elements created using native software features.

an advantage in evading canonical NLRP3 inflammasome activation, as NLRP3 has been found to sense flagellin in a NAIP-independent manner.[86]

LPS is another target of the NLRP3 inflammasome induced by *Salmonella*. Intracellular LPS triggers non-canonical NLRP3 inflammasome activity via Caspase-4/5/11. In addition to down-regulation of PAMPs expression, *Salmonella* can also alter its detectable PAMPs by chemical modification. Specifically, *Salmonella* modifies its lipid A of LPS through the PhoP-PhoQ and PmrA-PmrB two-component regulatory systems (Figure 2).[107] Previous studies have shown that Caspase-11 exhibits reduced activity in response to tetra-acylated lipid IVa and penta-acylated LPS,[108,109] due to its inability to oligomerize once bound to these LPS forms. Notably, the LPS from intracellular WT *Salmonella* is hexa-acylated. The ability of *Salmonella* to stimulate IL-1β expression in human monocytes and infected mice is significantly reduced when LPS is modified into a penta-acylated form.[110] Moreover, two additional structural modifications of LPS, LPS with a hepta-acylated lipid A and LPS with phosphoethanolamine and aminoarabinose attached to the phosphate groups of its lipid A, have been reported to induce reduced IL-1β production in human monocytes and mouse macrophages.[111,112] Additionally, the LPS O-antigen length regulator FepE has been found to induce the production of very long O-antigen chains, which are crucial for *Salmonella* to evade recognition by Caspase-4 and subsequent non-canonical NLRP3 inflammasome activation.[113] The secretion of IL-1β promoted by activated Caspase-4/5/11 relies on the non-canonical NLRP3 signaling pathway, suggesting that diverse chemical modifications of LPS serve as an effective strategy for *Salmonella* to evade NLRP3 inflammasome activity and consequently promote its intracellular survival.

In addition to modulating PAMPs to avoid detection by the NLRP3 inflammasome, *Salmonella* employs multiple bacterial virulence factors to inhibit its activation by targeting the NLRP3 signaling pathway. Our recent study has identified a novel virulence factor in *Salmonella* that functions in anti-inflammatory responses during infection. Specifically, the T1SS protein SiiD, which is translocated into host cells in a T1SS-dependent manner and localized in the membrane fraction, is utilized by *Salmonella* to suppress the activation of the intracellular canonical NLRP3 inflammasome (Figure 2). Mechanistically, SiiD suppresses the generation of intracellular mtROS, which subsequently prevents ASC oligomerization from forming pyroptosomes, resulting in the inhibition of NLRP3-dependent Caspase-1 activation and the secretion of IL-1β and IL-18.[33] Importantly, SiiD is required for *Salmonella* virulence, enabling the bacterium to evade host immune clearance mediated by the NLRP3 inflammasome in vivo, which may be crucial for bacterial colonization and persistence during long-term infection. These findings reveal the essential role of bacterial T1SS in inhibiting NLRP3 inflammasome activation and enabling *Salmonella* to evade host innate immune defenses. Beyond T1SS, SPI-2 encoded T3SS-2 also plays a pivotal role in the intracellular replication and survival of *Salmonella*. The T3SS-2 effector SpvC is utilized by *Salmonella* to repress NLRP3 inflammasome activation,[114] potentially through the inactivation of dual-phosphorylated MAPK via beta elimination (Figure 2).[115] SpvC has also been verified to suppress pyroptosis and intestinal inflammation in the cecum via its phosphothreonine lyase activity, which is necessary for promoting bacterial dissemination.[114] Furthermore, a recent study has revealed that SPI-2 is employed by *Salmonella* to inhibit NLRP3 inflammasome activation in human macrophages, but not in mouse macrophages.[116,117] The mechanism by which SPI-2 inhibits the NLRP3 inflammasome activation in human cells, whether through the secretion of T3SS effector proteins or the regulation of other signaling pathways, remains to be elucidated by further research.

A prior study has demonstrated that three additional virulence factors of *Salmonella*, the fimbrial chaperone BcfB, the two-component system phosphate transferase RcsD, and the symporter of melibiose and monovalent cations MelB, all possess the capability to interfere with the activation of the NLRP3 inflammasome via unknown mechanisms (Figure 2).[32] Our recent high-throughput screening has further confirmed the role of the Rcs two-component system in regulating NLRP3 inflammasome activation.[33] Additionally, our previous research demonstrated that the bacterial toxin and antitoxin system antitoxin protein DinJ can be transported into host cells during *Salmonella* infection (Figure 2), which is crucial for *Salmonella* to specifically inhibit NLRP3 inflammasome activation and evade the immune clearance mechanisms mediated by NLRP3 in vivo.[118] However, it is worth noting that the inhibition of NLRP3 inflammasome activation mediated by *Salmonella* is not always beneficial to bacterial virulence. For instance, the *Salmonella* T3SS-2 effector protein SlrP inhibits the NLRP3 inflammasome in myeloid cells in the lamina propria, preventing anorexia caused by IL-1β-mediated signaling to the hypothalamus via the vagus nerve (Figure 2).[119] Mice orally infected with Δ*slrP* exhibited a more severe anorexic response, along with increased pathogen burdens and higher mortality, because of

a significant increase in the expression of appetite-suppressing genes in the hypothalamus.[34] SlrP-mediated inhibition of the NLRP3 inflammasome thus prevents anorexia induced by *Salmonella* infection, promoting the survival of both the pathogen and the host. This mechanism is essential for the bacterial transmission to new hosts, albeit at the expense of virulence. These findings indicate that *Salmonella* has evolved a sophisticated strategy to balance transmission and virulence by specifically targeting the NLRP3 inflammasome.

The ability of bacteria to sense metabolic alterations within host cells constitutes another crucial strategy for circumventing the detection of the NLRP3 inflammasome. Previous studies have demonstrated that *Salmonella* preferentially survives within macrophages that display an M2 phenotype, which primarily utilize oxidative metabolism rather than glycolysis.[120,121] *Salmonella* infection of M1 macrophages results in the consumption of glycolytic precursor molecules, which are critical energy sources for host cells. This disruption of glycolysis subsequently triggers robust activation of the intracellular NLRP3 inflammasome.[87] In contrast, *Salmonella*-infected M2 macrophages exhibit upregulated expression of the transcription factor PPARδ. This transcription factor plays a pivotal role in maintaining fatty acid β-oxidation metabolism. Mechanistically, PPARδ directly enhances glucose availability to intracellular *Salmonella*, thereby promoting bacterial replication.[120] Upon induction of the M1-to-M2 polarization shift via medication, a significant reduction in Caspase-1 activity, accompanied by decreased expression levels of NLRP3, IL-1β, and IL-18, was observed.[122] Another study reported an increase in the number of M2 macrophages in NLRP3-deficient mice.[123] A recent study reports that the SPI-2 T3SS effector SteE is employed by *Salmonella* to convert both the amino acid and substrate specificity of the host pleiotropic serine/threonine kinase GSK3, which enables GSK3 to phosphorylate a tyrosine residue on the non-canonical substrate STAT3, ultimately driving M2 macrophage polarization (Figure 2).[124] Compared to mouse BMDMs infected with WT *Salmonella* strain, cells infected with Δ*steE* mutant show diminished M2 polarization along with reduced phosphorylated-STAT3 level.[125] Another recent study reveals that *Salmonella* infection triggers macrophages to produce lactate, resulting in enhanced translocation of the SPI-2 effector SteE, which is essential for driving subsequent M2 macrophage polarization.[126] These findings suggest that *Salmonella* not only possesses the capability to target cellular niches exhibiting reduced NLRP3 inflammasome activity by sensing metabolic changes within host cells, but also promotes M2 macrophage polarization through the translocation of T3SS effectors to establish a favorable cellular niche for bacterial replication and persistence.

Salmonella tricarboxylic acid cycle (TCA) enzymes, including aconitase AcnB, isocitrate lyase AceA, and isocitrate dehydrogenase IcdA, are crucial for inhibiting the rapid NLRC4-independent NLRP3 inflammasome activation during the early stages of infection (Figure 2). Deletion of TCA cycle enzymes leads to excessive citrate production in *Salmonella*-infected cells, which in turn triggers rapid mtROS-dependent NLRP3 inflammasome activation. Furthermore, aconitase-deficient *Salmonella* demonstrated a notable impairment in acute systemic virulence after oral administration and exhibited a reduced capacity to persist in a chronic infection.[32] In addition, our recent study has shown that the *Salmonella* UDP-galactose-4-epimerase GalE, which catalyzes the interconversion between UDP-glucose and UDP-galactose, is involved in inhibiting the NLRP3 inflammasome activation and IL-1β expression within host macrophages (Figure 2).[127] This effect may depend on regulation of multiple inflammasome-related signaling pathways mediated by GalE and is crucial for bacterial virulence. These findings indicate that metabolic alterations serve as a pivotal target in the complex interplay of detection and evasion between *Salmonella* and the NLRP3 inflammasome.

Conclusion

With the relentless pursuit of research delving deeper into the intricate interplay between *Salmonella* and the NLRP3 inflammasome, the highly sophisticated molecular mechanisms driving NLRP3 inflammasome activation, as well as crucial mechanisms that enable the host to restrict the proliferation of this intracellular pathogen, have been progressively unveiled. The NLRP3 inflammasome signaling is dynamically modulated during the chronic infection of *Salmonella*. The delicate balance between pathogen proliferation and host immune defenses fosters a mutually beneficial coexistence for both organisms. Pathogens that exhibit high virulence will kill hosts, whereas those with reduced virulence may achieve persistent infection. The key strategy for chronic survival of the intracellular bacteria is to down-regulate their ability to trigger the NLRP3 inflammasome signaling. As the structural mechanisms underlying NLRP3 inflammasome assembly are progressively elucidated, future research endeavors will increasingly focus on elucidating the intricate structural

details of ligand-sensor interactions. Identifying more ultimate NLRP3 ligands or determining the minimal common cellular event that is both necessary and sufficient for activating the NLRP3 inflammasome during *Salmonella* infection will be a significant achievement. Furthermore, despite a growing body of research, our understanding of the molecular mechanisms by which *Salmonella* evades or inhibits the activation of NLRP3 inflammasome remains incomplete. Future research endeavors are necessary to identify the key *Salmonella* molecules that possess the ability to potently impede or facilitate NLRP3 inflammasome assembly or activation. Targeting these pivotal bacterial molecules for the design of therapeutic drugs may emerge as a promising strategy, contributing to the advancement of novel treatments and preventive measures for salmonellosis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest in this work.

References

1. Barnett KC, Li S, Liang K, Ting JP. A 360 degrees view of the inflammasome: mechanisms of activation, cell death, and diseases. *Cell*. 2023;186(11):2288–2312. doi:10.1016/j.cell.2023.04.025
2. Man SM, Kanneganti TD. Regulation of inflammasome activation. *Immunol Rev*. 2015;265(1):6–21. doi:10.1111/imr.12296
3. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. *Cell*. 2006;124(4):783–801. doi:10.1016/j.cell.2006.02.015
4. Broz P, Dixit VM. Inflammasomes: mechanism of assembly, regulation and signalling. *Nat Rev Immunol*. 2016;16(7):407–420. doi:10.1038/nri.2016.58
5. Kodi T, Sankhe R, Gopinathan A, Nandakumar K, Kishore A. New insights on NLRP3 inflammasome: mechanisms of activation, inhibition, and epigenetic regulation. *J Neuroimmune Pharmacol*. 2024;19(1):7. doi:10.1007/s11481-024-10101-5
6. Shi J, Gao W, Shao F. Pyroptosis: gasdermin-mediated programmed necrotic cell death. *Trends Biochem Sci*. 2017;42(4):245–254. doi:10.1016/j.tibs.2016.10.004
7. He Y, Hara H, Nunez G. Mechanism and regulation of NLRP3 inflammasome activation. *Trends Biochem Sci*. 2016;41(12):1012–1021. doi:10.1016/j.tibs.2016.09.002
8. Zhao Y, Yang J, Shi J, et al. The NLRC4 inflammasome receptors for bacterial flagellin and type III secretion apparatus. *Nature*. 2011;477(7366)):596–600. doi:10.1038/nature10510
9. Yang J, Zhao Y, Shi J, Shao F. Human NAIP and mouse NAIP1 recognize bacterial type III secretion needle protein for inflammasome activation. *Proc Natl Acad Sci U S A*. 2013;110(35):14408–14413. doi:10.1073/pnas.1306376110
10. Sellin ME, Muller AA, Felmy B, et al. Epithelium-intrinsic NAIP/NLRC4 inflammasome drives infected enterocyte expulsion to restrict Salmonella replication in the intestinal mucosa. *Cell Host Microbe*. 2014;16(2):237–248. doi:10.1016/j.chom.2014.07.001
11. Kayagaki N, Stowe IB, Lee BL, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. *Nature*. 2015;526(7575):666–671. doi:10.1038/nature15541
12. Takahashi M. NLRP3 inflammasome as a key driver of vascular disease. *Cardiovasc Res*. 2022;118(2):372–385. doi:10.1093/cvr/cvab010
13. Kirkik D, Kalkanli Tas S, Tanoglu A. Unraveling the blood microbiome: novel insights into inflammasome responses in crohn's disease. *Eur J Gastroenterol Hepatol*. 2024;36(8):975–984. doi:10.1097/MEG.0000000000002695
14. McManus RM, Latz E. NLRP3 inflammasome signalling in Alzheimer's disease. *Neuropharmacology*. 2024;252:109941. doi:10.1016/j.neuropharm.2024.109941
15. Yu T, Luo L, Xue J, Tang W, Wu X, Yang F. Gut microbiota-NLRP3 inflammasome crosstalk in metabolic dysfunction-associated steatotic liver disease. *Clin Res Hepatol Gastroenterol*. 2024;48(8):102458. doi:10.1016/j.clinre.2024.102458
16. Jajere SM. A review of Salmonella enterica with particular focus on the pathogenicity and virulence factors, host specificity and antimicrobial resistance including multidrug resistance. *Vet World*. 2019;12(4):504–521. doi:10.14202/vetworld.2019.504-521

17. Liu B, Zhang X, Ding X, Bin P, Zhu G. The vertical transmission of Salmonella enteritidis in a one-health context. *One Health*. 2023;16:100469. doi:10.1016/j.onehlt.2022.100469
18. Jung HR, Lee YJ. Prevalence and characterization of non-typhoidal Salmonella in egg from grading and packing plants in Korea. *Food Microbiol*. 2024;120:104464. doi:10.1016/j.fm.2024.104464
19. Crowley SM, Knodler LA, Vallance BA. Salmonella and the inflammasome: battle for intracellular dominance. *Curr Top Microbiol Immunol*. 2016;397:43–67. doi:10.1007/978-3-319-41171-2_3
20. Zhang K, Riba A, Nietschke M, et al. Minimal SPI1-T3SS effector requirement for Salmonella enterocyte invasion and intracellular proliferation in vivo. *PLoS Pathog*. 2018;14(3):e1006925. doi:10.1371/journal.ppat.1006925
21. LaRock DL, Chaudhary A, Miller SI. Salmonellae interactions with host processes. *Nat Rev Microbiol*. 2015;13(4):191–205. doi:10.1038/nrmicro3420
22. Keestra-Gounder AM, Tsolis RM, Baumler AJ. Now you see me, now you don't: the interaction of Salmonella with innate immune receptors. *Nat Rev Microbiol*. 2015;13(4):206–216. doi:10.1038/nrmicro3428
23. Shea JE, Hensel M, Gleeson C, Holden DW. Identification of a virulence locus encoding a second type III secretion system in Salmonella typhimurium. *Proc Natl Acad Sci U S A*. 1996;93(6):2593–2597. doi:10.1073/pnas.93.6.2593
24. Bierschenk D, Boucher D, Schroder K. Salmonella-induced inflammasome activation in humans. *Mol Immunol*. 2017;86:38–43. doi:10.1016/j.molimm.2016.11.009
25. Raupach B, Peuschel SK, Monack DM, Zychlinsky A. Caspase-1-mediated activation of interleukin-1beta (IL-1beta) and IL-18 contributes to innate immune defenses against Salmonella enterica serovar Typhimurium infection. *Infect Immun*. 2006;74(8):4922–4926. doi:10.1128/IAI.00417-06
26. Aachoui Y, Leaf IA, Hagar JA, et al. Caspase-11 protects against bacteria that escape the vacuole. *Science*. 2013;339(6122):6122):975–8. doi:10.1126/science.1230751
27. Knodler LA, Crowley SM, Sham HP, et al. Noncanonical inflammasome activation of caspase-4/caspase-11 mediates epithelial defenses against enteric bacterial pathogens. *Cell Host Microbe*. 2014;16(2):249–256. doi:10.1016/j.chom.2014.07.002
28. Han X, Allaire JM, Crowley SM, et al. Inflammasome activation links enteric Salmonella Typhimurium infection to a rapid, cytokine-dependent increase in intestinal mucin release. *Gut Microbes*. 2024;16(1):2413372. doi:10.1080/19490976.2024.2413372
29. Rauch I, Deets KA, Ji DX, et al. NAIP-NLRC4 inflammasomes coordinate intestinal epithelial cell expulsion with eicosanoid and IL-18 release via activation of caspase-1 and −8. *Immunity*. 2017;46(4):649–659. doi:10.1016/j.immuni.2017.03.016
30. Broz P, Newton K, Lamkanfi M, Mariathasan S, Dixit VM, Monack DM. Redundant roles for inflammasome receptors NLRP3 and NLRC4 in host defense against Salmonella. *J Exp Med*. 2010;207(8):1745–1755. doi:10.1084/jem.20100257
31. De Jong HK, Koh GC, van Lieshout MH, et al. Limited role for ASC and NLRP3 during in vivo Salmonella typhimurium infection. *BMC Immunol*. 2014;15:30. doi:10.1186/s12865-014-0030-7
32. Wynosky-Dolfi MA, Snyder AG, Philip NH, et al. Oxidative metabolism enables Salmonella evasion of the NLRP3 inflammasome. *J Exp Med*. 2014;211(4):653–668. doi:10.1084/jem.20130627
33. Guo Y, Gu D, Huang T, et al. Salmonella enteritidis T1SS protein SiiD inhibits NLRP3 inflammasome activation via repressing the mtROS-ASC dependent pathway. *PLoS Pathog*. 2023;19(5):e1011381. doi:10.1371/journal.ppat.1011381
34. Rao S, Schieber AMP, O'Connor CP, Leblanc M, Michel D, Ayres JS. Pathogen-mediated inhibition of anorexia promotes host survival and transmission. *Cell*. 2017;168(3):503–516e12. doi:10.1016/j.cell.2017.01.006
35. Hochheiser IV, Pilsl M, Hagelueken G, et al. Structure of the NLRP3 decamer bound to the cytokine release inhibitor CRID3. *Nature*. 2022;604(7904):184–189. doi:10.1038/s41586-022-04467-w
36. Dowds TA, Masumoto J, Zhu L, Inohara N, Nunez G. Cryopyrin-induced interleukin 1beta secretion in monocytic cells: enhanced activity of disease-associated mutants and requirement for ASC. *J Biol Chem*. 2004;279(21):21924–21928. doi:10.1074/jbc.M401178200
37. Hafner-Bratkovic I, Susjan P, Lainscek D, et al. NLRP3 lacking the leucine-rich repeat domain can be fully activated via the canonical inflammasome pathway. *Nat Commun*. 2018;9(1):5182. doi:10.1038/s41467-018-07573-4
38. He Y, Zeng MY, Yang D, Motro B, Nunez G. NEK7 is an essential mediator of NLRP3 activation downstream of potassium efflux. *Nature*. 2016;530(7590):354–357. doi:10.1038/nature16959
39. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nat Rev Immunol*. 2019;19(8):477–489. doi:10.1038/s41577-019-0165-0
40. Cao F, Deliz-Aguirre R, Gerpott FH, Ziska E, Taylor MJ. Myddosome clustering in IL-1 receptor signaling regulates the formation of an NF-kB activating signalosome. *EMBO Rep*. 2023;24(10):e57233. doi:10.15252/embr.202357233
41. Yang J, Liu Z, Xiao TS. Post-translational regulation of inflammasomes. *Cell mol Immunol*. 2017;14(1):65–79. doi:10.1038/cmi.2016.29
42. Gritsenko A, Green JP, Brough D, Lopez-Castejon G. Mechanisms of NLRP3 priming in inflammaging and age related diseases. *Cytokine Growth Factor Rev*. 2020;55:15–25. doi:10.1016/j.cytogfr.2020.08.003
43. Schroder K, Tschopp J. The inflammasomes. *Cell*. 2010;140(6):821–832. doi:10.1016/j.cell.2010.01.040
44. Fu J, Wu H. Structural mechanisms of NLRP3 inflammasome assembly and activation. *Annu Rev Immunol*. 2023;41:301–316. doi:10.1146/annurev-immunol-081022-021207
45. Lu A, Magupalli VG, Ruan J, et al. Unified polymerization mechanism for the assembly of ASC-dependent inflammasomes. *Cell*. 2014;156(6):1193–1206. doi:10.1016/j.cell.2014.02.008
46. Boucher D, Monteleone M, Coll RC, et al. Caspase-1 self-cleavage is an intrinsic mechanism to terminate inflammasome activity. *J Exp Med*. 2018;215(3):827–840. doi:10.1084/jem.20172222
47. Munoz-Planillo R, Kuffa P, Martinez-Colon G, Smith BL, Rajendiran TM, Nunez G. K(+) efflux is the common trigger of NLRP3 inflammasome activation by bacterial toxins and particulate matter. *Immunity*. 2013;38(6):1142–1153. doi:10.1016/j.immuni.2013.05.016
48. Triantafilou K, Hughes TR, Triantafilou M, Morgan BP. The complement membrane attack complex triggers intracellular Ca2+ fluxes leading to NLRP3 inflammasome activation. *J Cell Sci*. 2013;126(Pt 13):2903–2913. doi:10.1242/jcs.124388
49. Katsnelson MA, Rucker LG, Russo HM, Dubyak GR. K+ efflux agonists induce NLRP3 inflammasome activation independently of Ca2+ signaling. *J Immunol*. 2015;194(8):3937–3952. doi:10.4049/jimmunol.1402658

50. Hornung V, Bauernfeind F, Halle A, et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat Immunol*. 2008;9(8):847–856. doi:10.1038/ni.1631
51. Gupta R, Ghosh S, Monks B, et al. RNA and beta-hemolysin of group B Streptococcus induce interleukin-1beta (IL-1beta) by activating NLRP3 inflammasomes in mouse macrophages. *J Biol Chem*. 2014;289(20):13701–13705. doi:10.1074/jbc.C114.548982
52. Bauernfeind F, Bartok E, Rieger A, Franchi L, Nunez G, Hornung V. Cutting edge: reactive oxygen species inhibitors block priming, but not activation, of the NLRP3 inflammasome. *J Immunol*. 2011;187(2):613–617. doi:10.4049/jimmunol.1100613
53. Moon JS, Nakahira K, Chung KP, et al. NOX4-dependent fatty acid oxidation promotes NLRP3 inflammasome activation in macrophages. *Nat Med*. 2016;22(9):1002–1012. doi:10.1038/nm.4153
54. Zhou R, Yazdi AS, Menu P, Tschopp J. A role for mitochondria in NLRP3 inflammasome activation. *Nature*. 2011;469(7329):221–225. doi:10.1038/nature09663
55. Shimada K, Crother TR, Karlin J, et al. Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity*. 2012;36 (3):401–414. doi:10.1016/j.immuni.2012.01.009
56. Elliott EI, Miller AN, Banoth B, et al. Cutting edge: mitochondrial assembly of the NLRP3 inflammasome complex is initiated at priming. *J Immunol*. 2018;200(9):3047–3052. doi:10.4049/jimmunol.1701723
57. Kayagaki N, Warming S, Lamkanfi M, et al. Non-canonical inflammasome activation targets caspase-11. *Nature*. 2011;479(7371):117–121. doi:10.1038/nature10558
58. Bibo-Verdugo B, Snipas SJ, Kolt S, Poreba M, Salvesen GS. Extended subsite profiling of the pyroptosis effector protein gasdermin D reveals a region recognized by inflammatory caspase-11. *J Biol Chem*. 2020;295(32):11292–11302. doi:10.1074/jbc.RA120.014259
59. Moretti J, Jia B, Hutchins Z, et al. Caspase-11 interaction with NLRP3 potentiates the noncanonical activation of the NLRP3 inflammasome. *Nat Immunol*. 2022;23(5):705–717. doi:10.1038/s41590-022-01192-4
60. Rathinam VA, Vanaja SK, Waggoner L, et al. TRIF licenses caspase-11-dependent NLRP3 inflammasome activation by gram-negative bacteria. *Cell*. 2012;150(3):606–619. doi:10.1016/j.cell.2012.07.007
61. Broz P, Ruby T, Belhocine K, et al. Caspase-11 increases susceptibility to Salmonella infection in the absence of caspase-1. *Nature*. 2012;490 (7419):288–291. doi:10.1038/nature11419
62. Zhu F, Ma J, Li W, et al. The orphan receptor Nur77 binds cytoplasmic LPS to activate the non-canonical NLRP3 inflammasome. *Immunity*. 2023;56(4):753–767. doi:10.1016/j.immuni.2023.03.003
63. Ruhl S, Broz P. Caspase-11 activates a canonical NLRP3 inflammasome by promoting K(+) efflux. *Eur J Immunol*. 2015;45(10):2927–2936. doi:10.1002/eji.201545772
64. Schmid-Burgk JL, Gaidt MM, Schmidt T, Ebert TS, Bartok E, Hornung V. Caspase-4 mediates non-canonical activation of the NLRP3 inflammasome in human myeloid cells. *Eur J Immunol*. 2015;45(10):2911–2917. doi:10.1002/eji.201545523
65. Yin F, Zheng PQ, Zhao LQ, et al. Caspase-11 promotes NLRP3 inflammasome activation via the cleavage of pannexin1 in acute kidney disease. *Acta Pharmacol Sin*. 2022;43(1):86–95. doi:10.1038/s41401-021-00619-2
66. Pizzuto M, Pelegrin P, Ruysschaert JM. Lipid-protein interactions regulating the canonical and the non-canonical NLRP3 inflammasome. *Prog Lipid Res*. 2022;87:101182. doi:10.1016/j.plipres.2022.101182
67. de Carvalho RVH, Andrade WA, Lima-Junior DS, et al. Leishmania lipophosphoglycan triggers caspase-11 and the non-canonical activation of the NLRP3 inflammasome. *Cell Rep*. 2019;26(2):429–437e5. doi:10.1016/j.celrep.2018.12.047
68. Pizzuto M, Hurtado-Navarro L, Molina-Lopez C, et al. Ornithine lipid is a partial TLR4 agonist and NLRP3 activator. *Cell Rep*. 2024;43 (10):114788. doi:10.1016/j.celrep.2024.114788
69. Zanoni I, Tan Y, Di Gioia M, et al. An endogenous caspase-11 ligand elicits interleukin-1 release from living dendritic cells. *Science*. 2016;352 (6290):1232–1236. doi:10.1126/science.aaf3036
70. Chu LH, Indramohan M, Ratsimandresy RA, et al. The oxidized phospholipid oxPAPC protects from septic shock by targeting the non-canonical inflammasome in macrophages. *Nat Commun*. 2018;9(1):996. doi:10.1038/s41467-018-03409-3
71. Gaidt MM, Ebert TS, Chauhan D, et al. Human monocytes engage an alternative inflammasome pathway. *Immunity*. 2016;44(4):833–846. doi:10.1016/j.immuni.2016.01.012
72. Yang Y, Wang H, Kouadir M, Song H, Shi F. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. *Cell Death Dis*. 2019;10(2):128. doi:10.1038/s41419-019-1413-8
73. Starobova H, Nadar EI, Vetter I. The NLRP3 inflammasome: role and therapeutic potential in pain treatment. *Front Physiol*. 2020;11:1016. doi:10.3389/fphys.2020.01016
74. Unterberger S, Mullen L, Flint MS, Sacre S. Multiple TLRs elicit alternative NLRP3 inflammasome activation in primary human monocytes independent of RIPK1 kinase activity. *Front Immunol*. 2023;14:1092799. doi:10.3389/fimmu.2023.1092799
75. Zewinger S, Reiser J, Jankowski V, et al. Apolipoprotein C3 induces inflammation and organ damage by alternative inflammasome activation. *Nat Immunol*. 2020;21(1):30–41. doi:10.1038/s41590-019-0548-1
76. Zhou R, Tardivel A, Thorens B, Choi I, Tschopp J. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. *Nat Immunol*. 2010;11(2):136–140. doi:10.1038/ni.1831
77. Gao Y, Yu S, Chen M, et al. cFLIP(S) regulates alternative NLRP3 inflammasome activation in human monocytes. *Cell mol Immunol*. 2023;20 (10):1203–1215. doi:10.1038/s41423-023-01077-y
78. Hersh D, Monack DM, Smith MR, Ghori N, Falkow S, Zychlinsky A. The Salmonella invasin SipB induces macrophage apoptosis by binding to caspase-1. *Proc Natl Acad Sci U S A*. 1999;96(5):2396–2401. doi:10.1073/pnas.96.5.2396
79. Naseer N, Egan MS, Reyes Ruiz VM, et al. Human NAIP/NLRC4 and NLRP3 inflammasomes detect Salmonella type III secretion system activities to restrict intracellular bacterial replication. *PLoS Pathog*. 2022;18(1):e1009718. doi:10.1371/journal.ppat.1009718
80. Zhong Z, Liang S, Sanchez-Lopez E, et al. New mitochondrial DNA synthesis enables NLRP3 inflammasome activation. *Nature*. 2018;560 (7717):198–203. doi:10.1038/s41586-018-0372-z
81. Chen S, Du F, Shang K, et al. Colonization mediated by T6SS-ClpV disrupts host gut microbiota and enhances virulence of salmonella enterica serovar typhimurium. *J Agric Food Chem*. 2024;72(34):19155–19166. doi:10.1021/acs.jafc.4c03735
82. Rapsinski GJ, Wynosky-Dolfi MA, Oppong GO, et al. Toll-like receptor 2 and NLRP3 cooperate to recognize a functional bacterial amyloid, curli. *Infect Immun*. 2015;83(2):693–701. doi:10.1128/IAI.02370-14

83. Halle A, Hornung V, Petzold GC, et al. The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. *Nat Immunol*. 2008;9(8):857–865. doi:10.1038/ni.1636
84. Sander LE, Davis MJ, Boekschoten MV, et al. Detection of prokaryotic mRNA signifies microbial viability and promotes immunity. *Nature*. 2011;474(7351):385–389. doi:10.1038/nature10072
85. Sha W, Mitoma H, Hanabuchi S, et al. Human NLRP3 inflammasome senses multiple types of bacterial RNAs. *Proc Natl Acad Sci U S A*. 2014;111(45):16059–16064. doi:10.1073/pnas.1412487111
86. Gram AM, Wright JA, Pickering RJ, et al. Salmonella flagellin activates NAIP/NLRC4 and canonical NLRP3 inflammasomes in human macrophages. *J Immunol*. 2021;206(3):631–640. doi:10.4049/jimmunol.2000382
87. Sanman LE, Qian Y, Eisele NA, et al. Disruption of glycolytic flux is a signal for inflammasome signaling and pyroptotic cell death. *Elife*. 2016;5:e13663. doi:10.7554/eLife.13663
88. Guo Y, Gu D, Huang T, et al. Essential role of Salmonella Enteritidis DNA adenine methylase in modulating inflammasome activation. *BMC Microbiol*. 2020;20(1):226. doi:10.1186/s12866-020-01919-z
89. Wang M, Xiong D, Wang X, et al. The DNA adenine methylase of Salmonella Enteritidis promotes their intracellular replication by inhibiting arachidonic acid metabolism pathway in macrophages. *Front Microbiol*. 2023;14:1080851. doi:10.3389/fmicb.2023.1080851
90. Napier BA, Brubaker SW, Sweeney TE, et al. Complement pathway amplifies caspase-11-dependent cell death and endotoxin-induced sepsis severity. *J Exp Med*. 2016;213(11):2365–2382. doi:10.1084/jem.20160027
91. Meunier E, Dick MS, Dreier RF, et al. Caspase-11 activation requires lysis of pathogen-containing vacuoles by IFN-induced GTPases. *Nature*. 2014;509(7500):366–370. doi:10.1038/nature13157
92. Man SM, Karki R, Sasai M, et al. IRGB10 liberates bacterial ligands for sensing by the AIM2 and caspase-11-NLRP3 inflammasomes. *Cell*. 2016;167(2):382–396e17. doi:10.1016/j.cell.2016.09.012
93. Grinstein L, Endter K, Hedrich CM, et al. An optimized whole blood assay measuring expression and activity of NLRP3, NLRC4 and AIM2 inflammasomes. *Clin Immunol*. 2018;191:100–109. doi:10.1016/j.clim.2017.11.011
94. Mariathasan S, Weiss DS, Newton K, et al. Cryopyrin activates the inflammasome in response to toxins and ATP. *Nature*. 2006;440 (7081):228–232. doi:10.1038/nature04515
95. Martinon F, Petrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature*. 2006;440 (7081):237–241. doi:10.1038/nature04516
96. Miao EA, Rajan JV. Salmonella and caspase-1: a complex interplay of detection and evasion. *Front Microbiol*. 2011;2:85. doi:10.3389/ fmicb.2011.00085
97. Hausmann A, Bock D, Geiser P, et al. Intestinal epithelial NAIP/NLRC4 restricts systemic dissemination of the adapted pathogen Salmonella typhimurium due to site-specific bacterial PAMP expression. *Mucosal Immunol*. 2020;13(3):530–544. doi:10.1038/s41385-019-0247-0
98. Cai D, Brickey WJ, Ting JP, Sad S. Isolates of Salmonella typhimurium circumvent NLRP3 inflammasome recognition in macrophages during the chronic phase of infection. *J Biol Chem*. 2022;298(1):101461. doi:10.1016/j.jbc.2021.101461
99. Malik-Kale P, Winfree S, Steele-Mortimer O, Kwaik YA. The bimodal lifestyle of intracellular Salmonella in epithelial cells: replication in the cytosol obscures defects in vacuolar replication. *PLoS One*. 2012;7(6):e38732. doi:10.1371/journal.pone.0038732
100. Beuzon CR, Meresse S, Unsworth KE, et al. Salmonella maintains the integrity of its intracellular vacuole through the action of SifA. *EMBO J*. 2000;19(13):3235–3249. doi:10.1093/emboj/19.13.3235
101. Chandrasekhar H, Mohapatra G, Kajal K, et al. SifA SUMOylation governs Salmonella Typhimurium intracellular survival via modulation of lysosomal function. *PLoS Pathog*. 2023;19(9):e1011686. doi:10.1371/journal.ppat.1011686
102. Gao X, Han J, Zhu L, et al. The effect of the PhoP/PhoQ system on the regulation of multi-stress adaptation induced by acid stress in salmonella typhimurium. *Foods*. 2024;13(10):1533. doi:10.3390/foods13101533
103. Lobertti CA, Cabezudo I, Gizzi FO, et al. An allosteric inhibitor of the PhoQ histidine kinase with therapeutic potential against Salmonella infection. *J Antimicrob Chemother*. 2024;79(8):1820–1830. doi:10.1093/jac/dkae151
104. Miller SI, Kukral AM, Mekalanos JJ. A two-component regulatory system (phoP phoQ) controls Salmonella typhimurium virulence. *Proc Natl Acad Sci U S A*. 1989;86(13):5054–5058. doi:10.1073/pnas.86.13.5054
105. Miao EA, Alpuche-Aranda CM, Dors M, et al. Cytoplasmic flagellin activates caspase-1 and secretion of interleukin 1beta via Ipaf. *Nat Immunol*. 2006;7(6):569–575. doi:10.1038/ni1344
106. Bijlsma JJ, Groisman EA. The PhoP/PhoQ system controls the intramacrophage type three secretion system of Salmonella enterica. *Mol Microbiol*. 2005;57(1):85–96. doi:10.1111/j.1365-2958.2005.04668.x
107. Ernst RK, Guina T, Miller SI. Salmonella typhimurium outer membrane remodeling: role in resistance to host innate immunity. *Microbes Infect*. 2001;3(14–15):1327–1334. doi:10.1016/s1286-4579(01)01494-0
108. Kayagaki N, Wong MT, Stowe IB, et al. Noncanonical inflammasome activation by intracellular LPS independent of TLR4. *Science*. 2013;341 (6151):1246–1249. doi:10.1126/science.1240248
109. Hagar JA, Powell DA, Aachoui Y, Ernst RK, Miao EA. Cytoplasmic LPS activates caspase-11: implications in TLR4-independent endotoxic shock. *Science*. 2013;341(6151):1250–1253. doi:10.1126/science.1240988
110. Kong Q, Six DA, Liu Q, et al. Palmitoylation state impacts induction of innate and acquired immunity by the Salmonella enterica serovar typhimurium msbB mutant. *Infect Immun*. 2011;79(12):5027–5038. doi:10.1128/IAI.05524-11
111. Aldapa-Vega G, Moreno-Eutimio MA, Berlanga-Taylor AJ, et al. Structural variants of Salmonella Typhimurium lipopolysaccharide induce less dimerization of TLR4/MD-2 and reduced pro-inflammatory cytokine production in human monocytes. *Mol Immunol*. 2019;111:43–52. doi:10.1016/j.molimm.2019.03.003
112. Pastelin-Palacios R, Gil-Cruz C, Perez-Shibayama CI, et al. Subversion of innate and adaptive immune activation induced by structurally modified lipopolysaccharide from Salmonella typhimurium. *Immunology*. 2011;133(4):469–481. doi:10.1111/j.1365-2567.2011.03459.x
113. Mylona E, Sanchez-Garrido J, Hoang Thu TN, et al. Very long O-antigen chains of Salmonella Paratyphi A inhibit inflammasome activation and pyroptotic cell death. *Cell Microbiol*. 2021;23(5):e13306. doi:10.1111/cmi.13306
114. Zuo L, Zhou L, Wu C, et al. Salmonella spvC gene inhibits pyroptosis and intestinal inflammation to aggravate systemic infection in mice. *Front Microbiol*. 2020;11:562491. doi:10.3389/fmicb.2020.562491

115. Li H, Xu H, Zhou Y, et al. The phosphothreonine lyase activity of a bacterial type III effector family. *Science*. 2007;315(5814):1000–1003. doi:10.1126/science.1138960
116. Bierschenk D, Monteleone M, Moghaddas F, et al. The Salmonella pathogenicity island-2 subverts human NLRP3 and NLRC4 inflammasome responses. *J Leukoc Biol*. 2019;105(2):401–410. doi:10.1002/JLB.MA0318-112RR
117. Zhou L, Li Y, You J, et al. Salmonella spvC gene suppresses macrophage/neutrophil antibacterial defense mediated by gasdermin D. *Inflamm Res*. 2024;73(1):19–33. doi:10.1007/s00011-023-01818-9
118. Gu D, Li A, Zang X, et al. Salmonella Enteritidis antitoxin DinJ inhibits NLRP3-dependent canonical inflammasome activation in macrophages. *Infect Immun*. 2024;92(4):e0050523. doi:10.1128/iai.00505-23
119. O'Neill LAJ. The hunger games: Salmonella, anorexia, and NLRP3. *Cell Metab*. 2017;25(2):225–226. doi:10.1016/j.cmet.2017.01.015
120. Eisele NA, Ruby T, Jacobson A, et al. Salmonella require the fatty acid regulator PPARdelta for the establishment of a metabolic environment essential for long-term persistence. *Cell Host Microbe*. 2013;14(2):171–182. doi:10.1016/j.chom.2013.07.010
121. McCoy MW, Moreland SM, Detweiler CS, Bäumler AJ. Hemophagocytic macrophages in murine typhoid fever have an anti-inflammatory phenotype. *Infect Immun*. 2012;80(10):3642–3649. doi:10.1128/IAI.00656-12
122. Jourdan T, Godlewski G, Cinar R, et al. Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates beta cell loss in type 2 diabetes. *Nat Med*. 2013;19(9):1132–1140. doi:10.1038/nm.3265
123. Vandanmagsar B, Youm YH, Ravussin A, et al. The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance. *Nat Med*. 2011;17(2):179–188. doi:10.1038/nm.2279
124. Panagi I, Jennings E, Zeng J, et al. Salmonella effector SteE converts the mammalian serine/threonine kinase GSK3 into a tyrosine kinase to direct macrophage polarization. *Cell Host Microbe*. 2020;27(1):41–53e6. doi:10.1016/j.chom.2019.11.002
125. Pham THM, Brewer SM, Thurston T, et al. Salmonella-driven polarization of granuloma macrophages antagonizes TNF-mediated pathogen restriction during persistent infection. *Cell Host Microbe*. 2020;27(1):54–67e5. doi:10.1016/j.chom.2019.11.011
126. Wang X, Yang B, Ma S, et al. Lactate promotes Salmonella intracellular replication and systemic infection via driving macrophage M2 polarization. *Microbiol Spectr*. 2023;11(6):e0225323. doi:10.1128/spectrum.02253-23
127. Huang T, Gu D, Guo Y, et al. Salmonella Enteritidis GalE protein inhibits LPS-induced NLRP3 inflammasome activation. *Microorganisms*. 2022;10(5):911. doi:10.3390/microorganisms10050911

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