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REVIEW

Targeting PANoptosis in Bacterial-Induced Inflammatory Diseases: Mechanisms and Therapeutic Interventions

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Abstract: PANoptosis is a novel form of cell death that integrates necroptosis, apoptosis, and pyroptosis, along with their crosstalk, mediated and regulated by the PANoptosome. This review focuses on bacterial PANoptosis, systematically summarizing through distinct pathways and virulence factors, and analyzing its role in inflammatory diseases. Furthermore, we discuss potential therapeutic interventions related to PANoptosis in bacterial inflammation, establishing a framework for novel anti-inflammatory drug development. Understanding the mechanisms of bacteria-induced PANoptosis may provide new strategies for targeted intervention in inflammatory responses to infection.

Keywords: PANoptosis, PANoptosome, gram-positive bacteria, gram-negative bacteria, potential therapeutic targets

Introduction of PANoptosis

PANoptosis

Programmed cell death is a genetically regulated process that maintains cellular homeostasis through distinct death pathways in response to environment-specific stimuli.[1] Beyond conventional death modalities, a novel programmed cell death pathway termed PANoptosis has been recognized. The PANoptosis paradigm first emerged in 2019. Researchers analyzing the functions of Z-DNA binding protein 1 (ZBP1) and transforming growth factor-β-activated kinase 1 (TAK1) molecules demonstrated that apoptosis, pyroptosis, and necroptosis could be integrated into a synergistic PANoptosis pathway, establishing that these three forms of cell death are interconnected rather than independent.[2] Accumulating data revealed extensive crosstalk between these processes,[3] leading to the conceptual maturation of PANoptosis. PANoptosis represents a unique programmed cell death modality that integrates characteristic elements of apoptosis, pyroptosis, and necroptosis while maintaining its own identity distinct from each constituent pathway.

PANoptosome

The PANoptosome serves as the core complex regulating PANoptosis,[4] incorporating key regulatory proteins from all three death pathways to initiate downstream necroptosis, apoptosis, and pyroptosis. Currently, four distinct types of PANoptosomes have been identified: ZBP1-, absent in melanoma 2 (AIM2)-, receptor-interacting serine/threonine-protein kinase 1 (RIPK1)-, and NLR family pyrin domain containing 12 (NLRP12)-PANoptosomes, each possessing unique components and activation mechanisms.[5] (1) The ZBP1-PANoptosome assembles upon ZBP1 activation through its Zα2 domain recognition of viral Z-RNA. This triggers receptor-interacting protein (RIP) homotypic interaction motif (RHIM) domain mediated homotypic interaction with RIPK3, forming the core complex.[6,7] Caspase-6 reinforces this assembly by directly binding RIPK3 and enhancing RHIM-dependent ZBP1-

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RIPK3 engagement.[8] This stabilized core complex subsequently recruits Caspase-8 and activates the NLRP3 inflammasome, thereby amplifying inflammatory signaling and triggering PANoptosis. (2) The AIM2-PANoptosome assembles when AIM2 binds pathogenic or host-derived double-stranded DNA. Through its pyrin domain, AIM2 recruits the apoptosis-associated speck-like protein containing a CARD (ASC) adaptor to form the inflammasome core and activate Caspase-1.[9,10] Under specific conditions, AIM2 cooperates with pyrin and ZBP1 to form the AIM2-PANoptosome complex.[11,12] This complex integrates ASC, Caspase-1, Caspase-8, RIPK3, RIPK1 and Fas-associated protein with death domain (FADD), collectively activating PANoptosis. (3) The RIPK1-PANoptosome is activated during *Yersinia* infection or TAK1 inhibition. Its assembly depends on the protein phosphatase 6 (PP6) phosphatase complex, with RIPK1 and RIPK3 serving as the central protein in PANoptosis regulation.[13,14] The N-terminal kinase domain of RIPK1 is critical for inducing cell death.[15] RIPK3 serves as an essential component of the necrosome, interacts with RIPK1 to trigger programmed necrosis, and plays a pivotal role in PANoptosis regulation.[16] (4) The NLRP12-PANoptosome responds to signals including heme, tumor necrosis factor (TNF), and pathogen-associated molecular patterns (PAMPs),[17] driving PANoptosis in hemolysis and inflammatory diseases through caspase-8 and RIPK3.[18,19]

Shared Mechanisms of PANoptosis in Gram-Positive and Gram-Negative Bacteria

Both Gram-positive and Gram-negative bacteria can trigger PANoptosis through distinct molecular mechanisms. Virulence factors from both bacterial types activate host cell death signaling pathways through different molecular mechanisms, ultimately converging on PANoptosome complex formation. This molecular scaffold integrates key components from the inflammasome (ASC, NLRP3, caspase-1), apoptosome (caspase-8), and necrosome (RIPK3), simultaneously activating caspase-3-mediated apoptosis, gasdermin D (GSDMD)-mediated pyroptosis, and mixed lineage kinase domain-like protein (MLKL)-mediated necroptosis (Figure 1).

Bacterial Secretion Systems

The delivery of effectors mediated by bacterial secretion systems constitutes a crucial mechanism for triggering host cell PANoptosis. Predominantly found in Gram-negative bacteria, these secretion systems function to precisely inject effectors into host cells, thereby modulating host signaling pathways to facilitate bacterial invasion, survival, and immune evasion. Gram-negative bacteria employ diverse secretion systems including Type II secretion system (T2SS), T3SS, and T6SS. Notably, *Pseudomonas aeruginosa* utilizes the T2SS protease LasB to disrupt intercellular junctions[20] while simultaneously injecting effectors via T3SS to damage mucosal barriers;[21] its T6SS effector VgrG2b targets microtubule structures, with these three systems acting synergistically to enhance bacterial infection.[22,23] Similarly, *Escherichia coli* employs T3SS to inject effectors into the host cytoplasm, inducing impairment of intestinal epithelial tight junctions.[24]

Toll-Like Receptors (TLRs)

TLRs, a family of pattern recognition receptors (PRRs) in the innate immune system, mediate early pathogen detection.[25] While playing pivotal roles in antibacterial immune responses, TLRs exhibit distinct recognition mechanisms and immunoregulatory functions toward Gram-negative versus Gram-positive bacteria. For Gram-negative bacteria, TLR4 serves as the primary receptor that initiates myeloid differentiation primary response 88 (MyD88)-dependent signaling upon lipopolysaccharide (LPS) binding, eliciting robust inflammatory responses, which may progress to cytokine storms when hyperactivated.[26] In contrast, Gram-positive bacteria are predominantly recognized by TLR2 through specific components such as lipoproteins and peptidoglycan. For instance, TLR2-mediated detection of *Staphylococcus aureus* enhances neutrophil phagocytic activity to combat infection,[27] whereas excessive TLR2 recognition of *Clostridioides difficile* toxins may exacerbate tissue damage.[28]

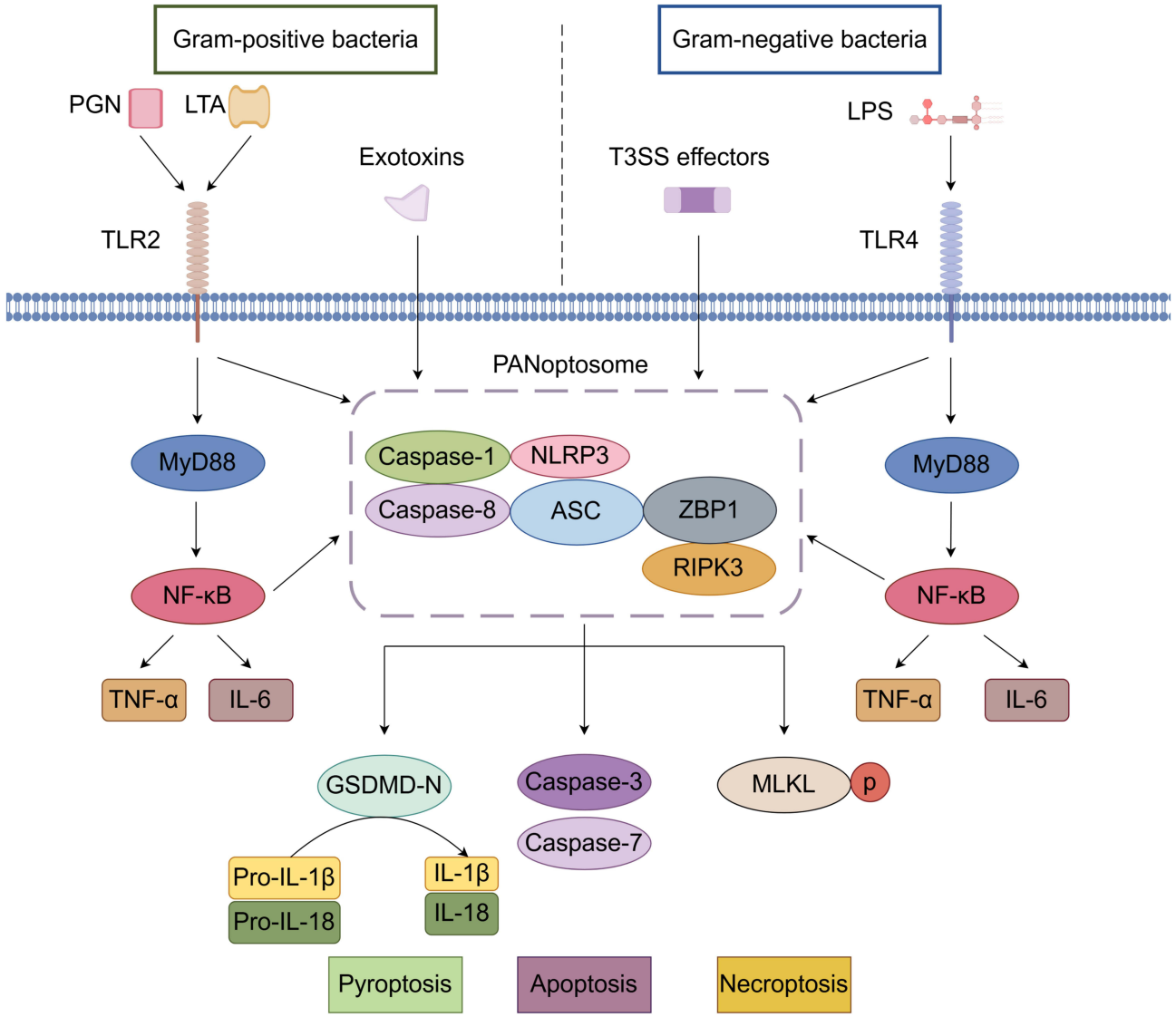

Figure 1 Mechanisms of PANoptosis Induction by Gram-negative and Gram-positive Bacteria.

PAMPs

PRRs detect PAMPs or damage-associated molecular patterns (DAMPs), triggering signaling cascades that initiate PANoptosis.[2,4] In Gram-positive bacteria, the predominant PAMPs are peptidoglycan (PGN) and lipoteichoic acid (LTA), which are exposed on the bacterial surface[29–31] and activate inflammatory pathways through TLR2 or nucleotide-binding oligomerization domain (NOD)-like receptors. The secreted exotoxins from these bacteria serve as major effector molecules that can activate inflammasomes and trigger PANoptosis. The primary PAMP of Gram-negative bacteria is LPS, which is expressed on the bacterial surface. LPS activates inflammasomes through TLR4,[29,30,32] inducing robust inflammatory responses that subsequently promote PANoptosis.

Exemplars of PANoptosis in Bacteria

Gram-Positive Cocci

Staphylococcus aureus (*S. aureus*)

S. aureus dynamically modulates host cell PANoptosis through multiple virulence factors. Regarding apoptosis, *S. aureus* secreted alpha-toxin (α-toxin) and staphylococcal enterotoxins (SEs) directly trigger apoptosis.[33] Its extracellular vesicles

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(EVs) invade cells via lipid raft-mediated endocytosis, inducing mitochondrial damage and activating mitogen-activated protein kinase (MAPK) and nuclear factor-κB (NF-κB) pathways to promote apoptosis.[34] Conversely, this pathogen can also suppress apoptosis by inhibiting caspase-8 to facilitate immune evasion,[35] or disrupt the crosstalk between neutrophil autophagy and apoptosis to sustain infection.[36] In pyroptotic regulation, the pore-forming toxin Panton-Valentine leukocidin (PVL) binds the LukS-PV subunit on monocytes and macrophages to activate the NLRP3 inflammasome, driving caspase-1-dependent interleukin-1 beta (IL-1β) and IL-18 release.[37] While LTA activates caspase-11 and caspase-1 via NLRP6 to regulate IL-18 secretion, demonstrating inflammasome synergy.[38] Regarding necroptosis, toxin-mediated activation of RIPK1/RIPK3/MLKL signaling is the key mechanism,[39] and AIM2 inflammasome-mediated macrophage necroptosis enhances bacterial pathogenicity.[40] This multi-pathway cell death modulation reveals *S. aureus* infection strategies: either promoting PANoptosis to facilitate toxin dissemination or suppressing PANoptosis to evade host clearance.

Streptococcus pneumoniae (*S. pneumoniae*)

S. pneumoniae modulates host cell PANoptosis through multiple pore-forming toxins. In apoptotic regulation, *S. pneumoniae* cholesterol-dependent cytolysins induce apoptosis in neurons and epithelial cells.[41] In chronic obstructive pulmonary disease (COPD) patients, *S. pneumoniae* triggers macrophage apoptosis and reactive oxygen species (ROS) release;[42] whereas alveolar macrophage caspase-dependent apoptosis associated with ROS and nitric oxide (NO) production is crucial for bacterial clearance.[43] This differential regulation demonstrates that *S. pneumoniae*-induced apoptosis disrupts tissue barriers, while macrophage apoptosis facilitates bacterial clearance and inflammation control. Pyroptosis is primarily activated by pneumolysin (PLY) through NIMA-related kinase 7 (NEK7)–NLRP3 inflammasome assembly, leading to caspase-dependent IL-1β maturation.[44] Different inflammasomes exhibit synergistic defense: NLRP6-deficient mice show reduced pyroptosis and higher survival rates than wild-type mice during *S. pneumoniae* infection,[45] while AIM2-deficiency impairs caspase-1 activation and IL-1β secretion, increasing infection susceptibility.[46] Regarding necroptosis, hemolysins and other pore-forming toxins activate both the typical RIPK1/RIPK3/MLKL pathway[47] and direct ion dysregulation.[48] RIPK3 forms complexes with RIPK1, MLKL, and mitochondrial calcium uniporter (MCU) to stimulate Ca^{2+} uptake into mitochondria and subsequent mitochondrial ROS (mROS) production in *S. pneumoniae* infection, promoting bacterial clearance.[49] However, aberrant necroptosis with low NF-κB activation exacerbates lung injury.[50] This dual role makes PANoptosis both a defensive weapon and potential contributor to infection pathology.

Gram-Positive Bacilli

Bacillus anthracis (*B. anthracis*)

B. anthracis exerts its pathogenic effects primarily through lethal toxin (LeTx)-mediated modulation of PANoptosis during infection. LeTx activates the NLRP3 inflammasome via TNF signaling, with caspase-8/RIPK3-deficient mice demonstrating enhanced resistance to infection, confirming this pathway's significance.[51] Simultaneously, LeTx specifically activates NLRP1b and NLR family CARD domain containing 4 (NLRC4) inflammasomes, exhibiting dual functionality: it recruits FADD through ASC to trigger caspase-8-dependent apoptosis[52] while also inducing caspase-1-dependent pyroptosis and IL-1β release through potassium efflux.[53,54] Regarding necroptosis, LeTx enhances TNF-α-induced intestinal epithelial cell death by suppressing p38α MAPK, concurrently activating both caspase-dependent apoptosis and RIPK3/MLKL-mediated necroptosis.[55] These findings reveal that *B. anthracis* orchestrates cell death through multifaceted regulation involving toxins and inflammasomes, simultaneously promoting pathogen dissemination and exacerbating tissue damage.

Listeria monocytogenes (*L. monocytogenes*)

L. monocytogenes primarily induces host cell death through its key virulence factor listeriolysin O (LLO). In lymphocytes, LLO directly triggers dose-dependent apoptosis and enhances host susceptibility.[56] In glial cells, *L. monocytogenes* induces apoptosis, while inhibition of bacterial ROS further promotes apoptotic cell death.[57] Regarding pyroptosis, in macrophages, *L. monocytogenes* promotes the interaction between Nek7 and NLRP3 through the c-Jun N-terminal kinase

(JNK) signaling pathway, driving caspase-1-dependent pyroptosis.[58] Bacterial DNA released during lysis triggers AIM2 inflammasome-dependent pyroptosis.[59] Depletion of Mint3 promotes pyroptosis in host macrophages and prevents *L. monocytogenes* infection spread, indicating that Mint3 deficiency enhances host defense.[60] Furthermore, in necroptosis regulation, the RIPK3-MLKL pathway exhibits dual modulation: it can clear infection through classical necroptosis while directly inhibiting intracellular bacterial replication in a cell death-independent manner.[61,62]

Other Gram-Positive Bacteria

Gram-positive bacteria with specialized morphologies play crucial roles in host–pathogen interactions by modulating programmed cell death. *Actinomyces* species activate the NLRP3 inflammasome through TLR2-dependent mechanisms, inducing macrophage pyroptosis characterized by GSDMD cleavage and IL-1β/IL-18 release.[63] *Nocardia* produces heme-binding protein (HBP) that targets mitochondria to trigger caspase-3-dependent apoptosis.[64] These bacteria display biphasic apoptotic control during macrophage infection: first activating extrinsic and intrinsic pathways with increased caspase-8/9 expression, then suppressing apoptosis.[65] *Streptomyces*-derived secondary metabolites can simultaneously induce tumor cell apoptosis and necroptosis.[66]

Gram-Negative Cocci

Neisseria

Neisseria gonorrhoeae exhibits cell type-specific regulation of apoptosis, delivering outer membrane protein PorB to mitochondria via outer membrane vesicles (OMVs) to induce THP-1 macrophage apoptosis[67] while suppressing apoptosis in U937 cells and primary human macrophages.[68] In polymorphonuclear leukocytes (PMNs), it inhibits caspase-3/7/9 to prolong PMN survival and promote bacterial dissemination.[69,70] For pyroptosis, this pathogen activates both canonical (caspase-1) and non-canonical (caspase-4) pathways through TLR2-NLRP3 signaling, triggering GSDMD-dependent pyroptosis with IL-1β/IL-18 release; NLRP3 deficiency enhances macrophage bactericidal activity, suggesting that pyroptosis may compromise host defense.[71,72] *Neisseria meningitidis* shows serotype-dependent apoptotic regulation: serogroup W induces stronger apoptosis in human epithelial cells and murine immune cells than serogroup Y, correlating with higher bacteremia levels.[73] PorB selectively inhibits intrinsic apoptosis to maintain intracellular survival.[74] Pyroptosis depends on the HrpA/HrpB two-partner secretion system (TPS) activating caspase-1/11 to cleave GSDMD, accelerating cerebral dissemination via IL-1β/IL-18 release.[75] HrpA interaction with neuronal dynein light-chain, Tctex-type 1 balances apoptosis and pyroptosis,[76] while lipooligosaccharide (LOS) coordinates inflammation through TLR4-mediated NF-κB activation and inflammasome assembly.[77]

Moraxella catarrhalis (*M. catarrhalis*)

M. catarrhalis activates caspase-4/11-GSDMD-dependent pyroptosis through its LOS and OMVs, a process requiring type I interferon (IFN-I) signaling and guanylate-binding proteins (GBPs) with involvement of NLRP3 inflammasome activation.[78] In lung epithelial cells, *M. catarrhalis* triggers the mitochondrial apoptotic pathway, characterized by caspase-3/6/9 activation, decreased B-cell lymphoma 2 (Bcl-2) expression, and Bcl-2-associated X protein (Bax) translocation.[79] Notably, while this bacterium activates B-cell proliferation and surface marker expression, it does not induce B-cell apoptosis.[80] Furthermore, in severe asthma patients, *M. catarrhalis* infection correlates with neutrophil extracellular trap pathway (NETosis) formation alongside activation of MAPK, NF-κB, and necroptosis signaling pathways.[81]

Gram-Negative Bacilli

Escherichia coli (*E. coli*)

E. coli regulates host cell PANoptosis through strain-specific mechanisms. Multidrug-resistant strains simultaneously activate apoptotic caspases-3/7/8, pyroptotic caspase-1/GSDMD, and necroptotic RIPK3/MLKL pathways, with amygdalin and chlorogenic acid mitigating this process by inhibiting PANoptosis core proteins.[82,83] In apoptosis, enteroaggregative *E. coli* induces intestinal epithelial cell apoptosis through both Bax/Bak upregulation and caspase-8 activation,[84] causing DNA fragmentation and cell cycle arrest.[85] Enterotoxigenic *E. coli* (ETEC) demonstrates selective

regulation in piglet models by suppressing caspase-9 while activating caspase-8.[86] For pyroptosis, ETEC K88 and mastitis-associated strains trigger canonical pyroptosis via NLRP3/caspase-1 axis,[87–89] exacerbating inflammation. Whereas, enteropathogenic *E. coli* (EPEC) activates non-canonical pyroptosis through T3SS-dependent caspase-4 activation.[90] GSDMB binding to caspase-4 promotes non-canonical pyroptosis, while caspase-7 creates negative feedback through GSDMB cleavage.[91] Regarding necroptosis, extraintestinal pathogenic *E. coli* enhances RIPK1/MLKL signaling via outer membrane protein TolC,[92] reversible by RIPK1 inhibitor necrostatin-1 (Nec-1).[93] Whereas EPEC degrades RIPK1, RIPK3, TIR-domain-containing adapter-inducing interferon-β, and ZBP1 through T3SS to actively suppress necroptosis for immune evasion.[94]

Salmonella spp.

Salmonella Typhimurium induces apoptosis, pyroptosis, and necroptosis in host cells. This pathogen triggers both apoptosis and necroptosis during Caco-2 cell invasion while promoting the release of proinflammatory cytokines IL-8 and TNF-α.[95] Additionally, *Salmonella* drives pyroptosis through inflammasome pathway activation, which worsens gut inflammation. A novel heteropolysaccharide (EPS 7–4) inhibits *Salmonella* Typhimurium-induced pyroptosis by blocking ASC oligomerization, helping to reduce intestinal damage.[96] These findings reveal how *Salmonella* differentially regulates cell death pathways to promote infection, offering new perspectives for targeted therapies.

Yersinia spp.

Yersinia modulates host cell death programs through multifaceted mechanisms. In PANoptosis regulation, these pathogens trigger RIPK1-dependent PANoptosome assembly, coordinately activating caspase-1, caspase-8, and MLKL pathways.[13] RIPK1 plays a central regulatory role, where its deficiency suppresses pyroptosis and apoptosis while enhancing necroptosis.[13] The *Yersinia* effector protein YopJ induces caspase-8-dependent GSDMD cleavage, driving non-canonical pyroptosis,[97] with RIPK1 autophosphorylation at T169 being critical for this process.[98] Metabolically, *Yersinia pseudotuberculosis* activates AMP-activated protein kinase (AMPK) through glucose depletion, promoting RIPK1 phosphorylation at S321 to inhibit pyroptosis.[99] Lysosomal supercomplexes precisely regulate pyroptosis intensity by recruiting RIPK1-caspase-8 assemblies.[100] This cell death regulation exhibits species specificity. *Yersinia*-infected murine macrophages undergo extrinsic apoptosis via the RIPK1-caspase-8 axis, while human macrophages trigger RIPK1-independent apoptosis through inhibitor of kappa B kinase (IKK) inhibition.[101]

Pseudomonas aeruginosa (*P. aeruginosa*)

In *P. aeruginosa*-induced PANoptosis, macrophage cell death can only be completely blocked when caspase-1, −11, −8 and RIPK3 are simultaneously absent.[102] The RIPK1/MLKL pathway shows compensatory enhancement when neuronal apoptosis inhibitory protein 5 and NLRC4 are deficient.[102] Regarding apoptosis, the T3SS effector ExoT activates JNK1/2 signaling through its GTPase-activating protein (GAP) domain, inducing caspase-9/caspase-3-mediated apoptosis,[103] while exotoxin A markedly increases caspase-3 activity to promote hemocyte apoptosis.[104] In pyroptosis regulation, flagellin activates the NLRC4 inflammasome, triggering caspase-1/GSDMD-dependent pyroptosis in macrophages and neutrophils.[105,106] In keratitis models, caspase-4/5/11-mediated non-canonical pyroptosis causes corneal cell death.[107] For necroptosis, *P. aeruginosa* employs quorum sensing-mediated precise control, where *rhl* subsystem deficiency enhances RIPK3/MLKL-dependent necroptosis.[108] During respiratory infection, CYP450 activation triggers club cell necroptosis which disrupts epithelial barriers, with Nec-1 showing reversal effects.[109] These mechanisms collectively represent *P. aeruginosa*'s multifaceted strategies to breach host defenses.

Other Gram-Negative Bacteria

Vibrio species, as a major group of Gram-negative bacteria, modulate host PANoptosis through diverse virulence mechanisms. *Vibrio alginolyticus* triggers caspase-8/-9/-3-dependent apoptosis and cytolysis in fish cells via T3SS.[110] *Vibrio proteolyticus* hemolysin VPRH activates caspase-1 by NLRP3 inflammasome, inducing IL-1β release and pyroptosis.[111] *Vibrio fluvialis* hemolysin activates the NLRP3-caspase-1-GSDMD axis via K^+ efflux and Ca^{2+} influx.[112] For necroptosis, *Vibrio vulnificus* cytolysin upregulates pMLKL to drive necroptosis, which resveratrol can ameliorate in sepsis models.[113]

PANoptosis in Bacterial Inflammatory Diseases

Sepsis

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[114] This condition represents a major global health challenge, with annual estimates of 31.5 million cases and 5 million deaths worldwide,[115] prompting the World Health Organization to designate sepsis as a global health priority.[116]

Analysis of PANoptosis-related genes (PRGs) and associated immune signatures in sepsis datasets reveals dysregulated PRG expression in patients, highlighting the complex interplay between sepsis and PANoptosis.[117] Our previous studies also revealed that severe apoptosis occurs in the liver, kidney, and other tissues during the progression of sepsis.[118] Proinflammatory cytokines play pivotal roles in sepsis-associated PANoptosis. Combined TNF-α and IFN-γ treatment induces PANoptosis, while neutralizing antibodies against these cytokines suppresses PANoptosis progression and improves survival in septic mice.[119]

Addressing sepsis-induced organ dysfunction remains a critical challenge, with distinct PANoptosis activation patterns across organs. In cardiac tissue, Xiao Chai Hu Tang exerts protective effects by suppressing ZBP1-mediated PANoptosis, whereas ZBP1 overexpression exacerbates cardiomyocyte death.[120] During renal injury, AIM2 expression is significantly upregulated and promotes PANoptosis in renal tubular epithelial cells through eukaryotic translation initiation factor 2-alpha kinase 2 (EIF2AK2) regulation.[121] In the lungs, which represent the most frequently affected organ in sepsis, the ZBP1 and RIPK1 play a key role in pulmonary epithelial PANoptosis.[122] Lactic acidosis aggravates ZBP1-dependent PANoptosis in pulmonary vascular endothelial cells during acute lung injury.[123] Collectively, these findings demonstrate marked organ-specificity in PANoptosis activation during sepsis: ZBP1 predominantly mediates cardiac and pulmonary injury, while AIM2 plays a more prominent role in renal damage. This organ-specific pattern provides a theoretical basis for developing targeted organ-protective strategies.

Lung Diseases

Community-acquired pneumonia (CAP) represents the most common infectious cause of adult hospitalizations and deaths in the United States. A substantial proportion of CAP cases progress to sepsis and acute respiratory distress syndrome (ARDS).[124] Pneumonia serves as the primary infectious trigger for ARDS.[125] As a frequent cause of respiratory failure in critically ill patients, ARDS meets diagnostic criteria in approximately 10% of global intensive care unit admissions, with mortality rates reaching 30–40%.[126]

Abnormal PANoptosis activation is closely associated with bacterial pneumonia progression, involving coordinated regulation of multiple signaling pathways. Transcriptomic analysis reveals significantly altered expression of PANoptosis signature genes including zinc finger protein 304 (ZNF304), AKT serine/threonine kinase 3 (AKT3), MAPK8, and Rho GTPase activating protein 10 (ARHGAP10) in CAP patients, indicating their biomarker and therapeutic potential.[127] During pathogen infection, IFN-γ is a key PANoptosis regulator. In *Pasteurella multocida* toxin (PMT)-induced pneumonia models, IFN-γ deficiency significantly reduces expression of executioner proteins including caspase-3, GSDMD and MLKL, while decreasing lung myeloperoxidase activity and IL-1β release, thereby alleviating lung injury.[128]

In pulmonary diseases, PANoptosis activation involves coordinated regulation through multiple pathways. The stimulator of interferon genes (STING) agonist activates NF-κB to promote IFN-I and pro-inflammatory cytokine production, inducing ZBP1-dependent PANoptosis.[129] Overactivation of the cyclic GMP-AMP synthase (cGAS)-STING pathway promotes PANoptosome assembly, whereas the kaempferol-3-*O*-α-L-(4″-*E*-p-coumaroyl)-rhamnoside (KAE) significantly attenuates lung injury by inhibiting this pathway.[130] MiR-29a-3p targets ZBP1 expression, substantially reducing levels of key PANoptosis execution proteins including Caspase-3, Caspase-8, GSDMD, and MLKL in alveolar epithelial cells.[131] Baicalin effectively suppresses PANoptosis in macrophages by blocking mitochondrial Z-DNA formation and ZBP1-PANoptosome assembly.[132] Collectively, these studies demonstrate that PANoptosis in lung tissue is regulated by multiple signaling nodes including STING, cGAS, and ZBP1, suggesting that targeting these key nodes may represent a promising therapeutic strategy for bacterial pneumonia.

Gastrointestinal Diseases

The global epidemiological evolution of inflammatory bowel disease (IBD) shows developing countries in the emerging stage, while newly industrialized nations are experiencing accelerating incidence.[133] Concurrently, Clostridium difficile infection (CDI), an important bacterial gastrointestinal disease, remains primarily hospital-associated but shows significantly increasing community-associated cases affecting younger, healthier populations.[134]

Bacterial infections contribute to gastrointestinal disease pathogenesis by modulating PANoptosis in intestinal epithelial cells (IECs). Studies reveal significant PANoptosis activation in ulcerative colitis (UC) patients' IECs, characterized by upregulated key genes including ZBP1, AIM2, caspase-1/8, and interferon regulatory factor 1 (IRF1), where IRF1 potentially acts as a transcription factor promoting PANoptosome complex formation and subsequent intestinal barrier disruption.[135] In IBD, PANoptosis signature genes strongly correlate with TNF, NF-κB signaling, and immune cell infiltration.[136] IBD-associated mitochondrial dysfunction and mtROS accumulation exacerbate this process, while selenium-modified exosomes can suppress PANoptosis by scavenging mtROS.[137] Mechanistically, the *Salmonella* effector protein SopF inhibits caspase-8 via phosphoinositide-dependent protein kinase-1 (PDK1)-p90 ribosomal S6 kinase signaling, blocking apoptosis and pyroptosis while promoting necroptosis to facilitate bacterial immune evasion.[138] Colitis mice exhibit elevated expression of PANoptosis-related genes including ZBP1 and caspase-1, which the natural compound diosmin can reverse while maintaining epithelial barrier function and modulating gut microbiota, demonstrating therapeutic potential for colitis.[139] These findings illustrate how bacteria activate PANoptosis either directly by hijacking cell death programs or indirectly through dysbiosis, ultimately compromising intestinal barrier integrity, with targeting PANoptosis key components representing a promising strategy against bacterial gastrointestinal infections.

Potential Therapeutic Targets and Drugs for PANoptosis in Bacterial Inflammatory Diseases

Bacterial infection-induced inflammatory diseases can activate PANoptosis through multiple mechanisms, with their molecular targets and intervention strategies emerging as research priorities. At the target level, PRR pathways, cell death regulatory nodes, and immune modulators constitute core components of PANoptosis regulation. Potential therapeutic agents can be categorized into three classes: chemical drugs, natural extracts, and traditional Chinese medicine formulations, which differentially modulate inflammatory factors and cell death execution proteins to provide novel therapeutic possibilities for conditions like sepsis and acute lung injury. The following tables systematically summarize the mechanisms of relevant targets and potential drugs (Tables 1 and 2).

Discussion

PANoptosis, as an inflammatory programmed cell death pathway that integrates pyroptosis, apoptosis, and necroptosis, forms a sophisticated PANoptosome complex. ZBP1-PANoptosome activates by binding RIPK3 through its Zα2 domain. AIM2-PANoptosome detects double-stranded DNA and integrates pyrin with ZBP1. RIPK1-PANoptosome activates during *Yersinia* infection or TAK1 inhibition. NLRP12-PANoptosome responds to heme and TNF signals. These complexes possess distinct characteristic components while sharing common elements including caspase-8, RIPK3, and ASC, creating molecular crosstalk that synchronizes multiple cell death programs. Bacterial pathogens engage this network through their characteristic signatures. Gram-positive bacteria primarily activate TLR2/NOD pathways, while Gram-negative bacteria activate LPS-TLR4 signaling. Despite their different starting points, all these pathways eventually lead to activation of the core PANoptosis process.

Currently, the primary challenge in PANoptosis-targeted therapy lies in the lack of specific inhibitors. Existing drugs mainly exhibit two limitations: (1) Uncontrollability of single-target agents. Certain inhibitors like necroptosis inhibitor Nec-1 only act on a single node of one cell death pathway. The crosstalk among cell death pathways enables mutual regulation through negative feedback mechanisms. Disruption of this dynamic balance may trigger abnormal activation or suppression of compensatory pathways, thereby increasing therapeutic unpredictability and

Table 1 Potential Therapeutic Targets for PANoptosis in Bacterial Inflammatory Diseases

Potential Therapeutic Targets	Target/Mechanism	Diseases	References
TLR9	Downregulation of TLR9 inhibits the p38 MAPK and extracellular signal-regulated kinase (ERK) signaling pathways, alleviating PANoptosis	Sepsis-associated encephalopathy (SAE)	[140]
Cellular Inhibitor of Apoptosis Protein 1/2 (cIAP1/2)	cIAP1/2 reduces RIPK1 phosphorylation and suppresses PANoptosis	Sepsis-induced acute lung injury (ALI)	[141]
TNF α-induced protein 8-like 2 (TIPE2)	Overexpression of TIPE2 inhibits ZBP1-dependent PANoptosis pathway	Sepsis-induced ALI	[142]
Piezo1	The Piezo1 inhibitor suppresses Piezo1 expression in cardiomyocytes via TLR4-NF-κB signaling, inhibiting PANoptosis	Sepsis-induced cardiomyopathy (SIC)	[143]
Phospholipase C γ (PLC-γ)	Inhibition of PLC-γ mitigates mitochondrial damage and attenuates PANoptosis	Sepsis-induced hemolysis	[144]
Ninjurin-1 (NINJ1)	Inhibition of NINJ1 reduces platelet activation and PANoptosis in sepsis-associated disseminated intravascular coagulation	Sepsis-induced disseminated intravascular coagulation (DIC)	[145]
STING	STING agonist diABZI activates IFN-I-dependent acute pulmonary inflammation, inducing PANoptosis	ALI	[129]
IFN-γ	IFN-γ deficiency attenuates PANoptosis pathway activation	Lethal pneumonia	[128]
MiR-29a-3p	Downregulation of miR-29a-3p reduces TNF-α, IL-1β, and IL-6 levels in the lung, suppressing ZBP1-dependent PANoptosis pathway	ALI	[131]

potential risks. (2) Nonspecificity of multi-target drugs. Some natural extracts or traditional Chinese medicine components exhibit broad-spectrum regulatory effects. For example, our previous studies demonstrated that human urinary kallidinogenase (HUK), a natural substance extracted from human urine, can inhibit PANoptosis-related apoptosis and necroptosis, thereby protecting damaged human umbilical vein endothelial cells (HUVECs). It also exerts protective effects by modulating cell migration and oxidative stress.[153] Their polypharmacology may cause systemic effects, making it difficult to precisely distinguish direct actions on PANoptosis, while failing to achieve personalized intervention for different bacterial infectious diseases. This highlights the urgent need to develop highly selective PANoptosis modulators through computational modeling and biological approaches to identify specific binding domains that balance efficacy and safety.

As an integral part of host defense mechanisms, complete inhibition of PANoptosis may impair immune clearance functions, potentially increasing risks of persistent bacterial infection or dissemination. Therefore, avoiding complete PANoptosis suppression while preventing infection risks remains a critical challenge. Future studies could explore targeted modulation strategies rather than complete blockade, such as locally selective PANoptosis inhibition at inflammatory foci to improve overall infection outcomes. Additionally, combined antibiotic therapy may achieve sequential bactericidal and anti-inflammatory effects. Antibiotics first eliminate pathogens to reduce infection burden, followed by precise PANoptosis modulator intervention on overactivated cell death pathways, thereby controlling inflammatory damage while preserving host defense functions.

By systematically elucidating the mechanisms through which Gram-negative and Gram-positive bacteria activate PANoptosis via distinct pathways, and summarizing PANoptosis occurrence in bacterial inflammatory diseases along with therapeutic drugs and targets, this review aims to create more possibilities for precision medicine targeting PANoptosis.

Table 2 Potential Therapeutic Drugs for PANoptosis in Bacterial Inflammatory Diseases

	Potential Drugs	Target/Mechanism	Diseases	References
Chemical Drugs	Dimethyl fumarate (DMF), 1-Methoxy PMS (MPMS)	DMF and MPMS block mtROS production and PANoptosome formation	Sepsis	[146]
	Bis (4-morpholinyl thiocarbonyl)-disulfide (JX06)	JX06 inhibits GSDMD-mediated PANoptosis	Sepsis	[147]
	Ursodeoxycholic acid	Ursodeoxycholic acid alleviates PANoptosis through STING pathway	Sepsis-induced ALI	[148]
	Diosmin	Diosmin Inhibits intestinal epithelial cell PANoptosis, preserves barrier function, and modulates gut microbiota and metabolite profiles	IBD	[139]
Natural Extracts	Sulforaphane	Sulforaphane attenuates PANoptosis via TLR4/NF-κB pathway	Sepsis-induced ALI	[149]
	Myricetin	Myricetin inhibits platelet PANoptosis in sepsis, delaying disseminated intravascular coagulation	DIC	[150]
	Baicalin	Baicalin blocks mitochondrial Z-DNA formation and ZBP1-PANoptosome assembly	ALI	[132]
	KAE	KAE downregulates key components of cGAS-STING pathway, reducing PANoptosome assembly and activation	ALI	[130]
	Echinacea polyphenols	Echinacea polyphenols suppresses PANoptosis by reducing NO production	ALI	[151]
Traditional Chinese Medicine Formulations	Xiao Chai Hu Tang	Downregulating PANoptosis-related genes (NLRP3, cleaved caspase-3, MLKL, ZBP1) and inhibits IL-6, IL-1β, and TNF-α expression	SIC	[120]
	Da Chai Hu Tang	Inhibiting PANoptosis by downregulating PI3K/AKT/NF-κB signaling pathway	Sepsis-induced ALI	[152]
	Dachengqi decoction granules	Suppressing expression of PANoptosis-related proteins including key upstream regulators ZBP1 and RIPK1	ALI	[122]

Abbreviations: ZBP1, Z-DNA binding protein 1; TAK1, transforming growth factor-β-activated kinase 1; AIM2, absent in melanoma 2; RIPK1, receptor-interacting serine/threonine-protein kinase 1; NLRP12, NLR family pyrin domain containing 12; RIP, receptor-interacting protein; RHIM, RIP homotypic interaction motif; ASC, apoptosis-associated speck-like protein containing a CARD; FADD, Fas-associated protein with death domain; PP6, protein phosphatase 6; TNF, tumor necrosis factor; PAMPs, pathogen-associated molecular patterns; GSDMD, gasdermin D; MLKL, mixed lineage kinase domain-like protein; T2SS, Type II secretion system; TLRs, Toll-like receptors; PRRs, pattern recognition receptors; MyD88, myeloid differentiation primary response 88; LPS, lipopolysaccharide; DAMPs, damage-associated molecular patterns; PGN, peptidoglycan; LTA, lipoteichoic acid; NOD, nucleotide-binding oligomerization domain; *S. aureus, Staphylococcus aureus*; α-toxin, alpha-toxin; SEs, staphylococcal enterotoxins; EVs, extracellular vesicles; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-κB; PVL, Panton-Valentine leucocidin; IL-1β, interleukin-1 beta; *S. pneumoniae, Streptococcus pneumoniae*; COPD, chronic obstructive pulmonary disease; ROS, reactive oxygen species; NO, nitric oxide; PLY, pneumolysin; NEK7, NIMA-related kinase 7; MCU, mitochondrial calcium uniporter; mROS, mitochondrial ROS; *B. anthracis, Bacillus anthracis*; LeTx, lethal toxin; NLRC4, NLR family CARD domain containing 4; *L. monocytogenes, Listeria monocytogenes*; LLO, listeriolysin O; JNK, c-Jun N-terminal kinase; HBP, heme-binding protein; OMVs, outer membrane vesicles; PMNs, polymorphonuclear leukocytes; TPS, two-partner secretion system; LOS, lipooligosaccharide; *M. catarrhalis, Moraxella catarrhalis*; IFN-I, type I interferon; GBPs, guanylate-binding proteins; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; NETosis, neutrophil extracellular trap pathway; *E. coli, Escherichia coli*; ETEC, enterotoxigenic *E. coli*; EPEC, enteropathogenic *E. coli*; Nec-1, necrostatin-1; AMPK, AMP-activated protein kinase; IKK, inhibitor of kappa B kinase; *P. aeruginosa, Pseudomonas aeruginosa*; GAP, GTPase-activating protein; PRGs, PANoptosis-related genes; EIF2AK2, eukaryotic translation initiation factor 2-alpha kinase 2; CAP, community-acquired pneumonia; ARDS, acute respiratory distress syndrome; ZNF304, zinc finger protein 304; AKT3, AKT serine/threonine kinase 3; ARHGAP10, Rho GTPase activating protein 10; PMT, *Pasteurella multocida* toxin; STING, stimulator of interferon genes; cGAS, cyclic GMP-AMP synthase; KAE, kaempferol-3-*O*-α-L-(4″-*E*-p-coumaroyl)-rhamnoside; IBD, inflammatory bowel disease; CDI, clostridium difficile infection; IECs, intestinal epithelial cells; UC, ulcerative colitis; IRF1, interferon regulatory factor 1; PDK1, phosphoinositide-dependent protein kinase-1; HUK, human urinary kallidinogenase; HUVECs, human umbilical vein endothelial cells; ERK, extracellular signal-regulated kinase; SAE, sepsis-associated encephalopathy; ALI, sepsis-induced acute lung injury; cIAP1/2, Cellular Inhibitor of Apoptosis Protein 1/2; TIPE2, TNF α-induced protein 8-like 2; SIC, sepsis-induced cardiomyopathy; PLC-γ, Phospholipase C γ; NINJ1, Ninjurin-1; DIC, disseminated intravascular coagulation; DMF, Dimethyl fumarate; MPMS, Methoxy PMS; JX06, Bis (4-morpholinyl thiocarbonyl)-disulfide.

Data Sharing Statement

No new data were generated for this review. All discussed information is based on previously published studies cited in the references.

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Figure 1 was created with Figdraw (www.figdraw.com).

Author Contributions

Wang T: Conceptualization, Writing – original draft, Writing – review & editing. Lu Y: Conceptualization, Formal analysis, Writing – review & editing. Zhang X and Yu F: Conceptualization, Supervision, Writing – review & editing. All authors took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published and agreed on the journal for submission, accepted full accountability for the content.

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Disclosure

The authors declare no known competing financial or personal interests that could influence this work.

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