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REVIEW

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Unravelling the role of PANoptosis in diseases: from emerging molecular mechanisms-to-therapeutic implications

Yi Zhu[1,2]*, Shengming Ou[1,2]*, Xuer Ye[1,2]*, Juncheng Li[3], Xiaoya Nie[1,2], Hongwei Shao[1,2], Rongxin Zhang[1,2], Jinrong Zhu[1,2]

[1]Department of Oncology, First School of Clinical Medicine, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou 510000, China; [2]School of Life Sciences and Biopharmaceutics, Guangdong Pharmaceutical University, Guangzhou 510000, China; [3]School of Medicine, Jiaying University, Meizhou 514000, China

ABSTRACT PANoptosis represents a distinct form of programmed cell death (PCD) that is characterized by the integration of key features from apoptosis, pyroptosis, and necroptosis but cannot be fully explained by any single cell death pathway. A key trigger of PANoptosis is the assembly and activation of the PANoptosome. To date, four types of PANoptosomes have been identified, including PANoptosomes nucleated by Z-DNA binding protein 1 (ZBP1), absent in melanoma 2 (AIM2), receptor-interacting protein kinase 1 (RIPK1), and NOD-like receptor protein 12 (NLRP12). This review summarizes current advances in the molecular regulatory mechanisms underlying PANoptosis and delineates the assembly and activation processes of several PANoptosome complexes. Furthermore, the role of PANoptosis in various pathologic conditions, such as infectious diseases, autoimmune disorders, neurodegenerative diseases, and cancer, are discussed. Recent preclinical and clinical advances in targeting the PANoptosis pathway through small molecule inhibitors, nanomedicines, and combination therapies for the treatment of infectious diseases, inflammatory conditions, and malignancies are also highlighted. However, current research involving the mechanisms underlying PANoptosis are preliminary and the clinical translation faces significant challenges, necessitating further in-depth exploration. This review demonstrates that targeting molecular components and signaling pathways of PANoptosis represents a highly promising therapeutic strategy, aiming to provide a theoretical foundation for the development of novel clinical treatments for related diseases.

KEYWORDS PANoptosis; PANoptosome; immune; targeted therapy; clinical translation

Introduction

Programmed cell death (PCD) has a critical regulatory role in the maintenance of internal environment homeostasis, elimination of abnormal cells, host defense against diverse pathogens, and stress responses[1-4]. Previous studies have identified multiple forms of PCD, among which pyroptosis, apoptosis, and necroptosis are the best characterized with respect to the underlying mechanisms[5]. Earlier perspectives held that these PCD pathways operated independently without mutual interference. However, recent evidence reveals extensive and significant crosstalk among the three PCD modalities[1]. PANoptosis, a novel form of PCD that was first proposed by Malireddi et al.[6] in 2019, incorporates characteristic features of pyroptosis, apoptosis, and necroptosis. Nevertheless, the biological effects of PANoptosis cannot be attributed solely to any single type of PCD and blocking only one PCD pathway is insufficient to halt the progression of PANoptosis[7]. The occurrence of PANoptosis depends on the assembly and activation of the PANoptosome[8]. To date, the following 5 types of PANoptosomes have been identified: Z-DNA binding protein 1 (ZBP1); absent in melanoma 2 (AIM2); receptor-interacting serine/threonine-protein kinase 1 (RIPK1); NOD-like receptor family pyrin domain containing 12 (NLRP12); and Nod-like receptor C5 (NLRC5)[9,10]. These PANoptosomes provide a molecular scaffold for the execution of PANoptosis[11].

PANoptosis is a key component of innate immune responses, the dysregulation of which is closely linked to the pathogenesis and progression of infectious, inflammatory, autoimmune, neurodegenerative, and neoplastic diseases[9,12]. An in-depth investigation of the molecular mechanisms underlying PANoptosis

*These authors contributed equally to this work.
Correspondence to: Hongwei Shao, Rongxin Zhang and Jinrong Zhu
E-mail: shaohongwei@gdpu.edu.cn, rxzhang@gdpu.edu.cn and zhujinrong@gdpu.edu.cn
ORCID ID: https://orcid.org/0000-0001-5998-652X, https://orcid.org/0000-0002-4083-374X and https://orcid.org/0000-0001-6088-5646
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is essential for understanding the progression of numerous diseases[13]. For example, PANoptosis participates in host defense against bacterial and fungal infections[14]. PANoptosis also has a positive role in modulating the tumor microenvironment, reversing tumor drug resistance, and improving cancer immunotherapy[15,16]. However, PANoptosis has a dual effect. It has been shown that PANoptosis can adversely affect the treatment and prognosis of conditions, such as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS)[13,17]. In recent years targeted therapeutic strategies against PANoptosis have become a research hotspot, encompassing small molecule inhibitors, nanomedicine, and combination therapies[18,19]. To date several related drugs have entered clinical trials, although most inhibitors remain in the preclinical research phase[20]. Further exploration of its mechanisms and translational applications is needed to promote the clinical advancement of relevant targeted therapeutic strategies.

This review discusses the role of PANoptosis in the pathogenesis and progression of various diseases with a focus on the potential as a therapeutic target. The review outlines the molecular mechanisms underlying PANoptosis, as well as the assembly and activation of PANoptosomes, and further elaborates on the role of PANoptosis in the progression of multiple diseases. Emphasis is placed on the application prospects of targeting PANoptosis regulation and related small molecule compounds in disease prevention and treatment. A deep understanding of the molecular mechanisms underlying PANoptosis will facilitate the identification of new therapeutic targets and provide a critical basis for optimizing existing treatment strategies, thereby laying a theoretical foundation for developing novel clinical interventions.

Pyroptosis, apoptosis, and necroptosis

Among the various forms of PCD, apoptosis, pyroptosis, and necroptosis represent the most thoroughly characterized forms with respect to molecular mechanisms.

Pyroptosis is a form of programmed inflammatory cell death that is mediated by the pore-forming protein, gasdermin D (GSDMD). GSDMD activation has been considered strictly caspase-dependent. Intra- or extra-cellular pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) trigger inflammasome assembly and caspase-1 activation in the canonical pathway, which cleaves pro-IL-1β and pro-IL-18 into mature forms, while simultaneously processing GSDMD to release the N-terminal pore-forming fragment. These fragments oligomerize within the plasma membrane, leading to membrane rupture and cytokine release. Caspase-4/5/11 directly sense cytosolic lipopolysaccharide (LPS) in the non-canonical pathway, inducing membrane perturbation that secondarily activates the NLRP3 inflammasome and amplifies inflammatory signaling.

Recent work by Du et al.[21] refines this framework by demonstrating that proteolytic cleavage alone is insufficient for functional pore formation. Instead, mitochondrial reactive oxygen species (ROS)-dependent S-palmitoylation at Cys191 (human) or Cys192 (mouse) acts as a decisive regulatory checkpoint. Mitochondrial ROS upregulates the palmitoyltransferases, ZDHHC5 and ZDHHC9, promoting GSDMD palmitoylation, which is required for efficient membrane translocation and oligomerization of cleaved GSDMD. Under conditions of robust oxidative stress, extensive palmitoylation can further license intact GSDMD to undergo membrane insertion and pore formation independent of proteolytic processing[22].

In contrast, apoptosis is a relatively "silent" form of PCD. Apoptosis proceeds mainly through the following three pathways: intrinsic; extrinsic; and endoplasmic reticulum (ER) stress-mediated. The intrinsic pathway is initiated by mitochondrial cytochrome c release, leading to caspase-9 activation and subsequent cleavage of executioner caspases-3, -6, and -7. The extrinsic pathway is mediated by death receptors (Fas or TNFR1), which recruit the adaptor protein, TRADD. TRADD displays dual signaling functions. Specifically, TRADD recruits molecules, such as TRAF2 and RIPK1, to activate pro-survival pathways, like NF-κB. Alternatively, TRADD associates with FADD, RIPK1, and caspase-8 to form the death-inducing signaling complex (Complex II). The ER stress pathway primarily involves IRE1, PERK, and ATF6 signaling during the unfolded protein response (UPR), triggering ER-mitochondria crosstalk that ultimately promotes apoptosis. In this setting, caspase-4/12 acts as an initiator caspase that is activated under ER stress and further engages caspase-9 of the mitochondrial pathway, leading to cleavage of executioner caspases, such as caspase-3 and -7[23,24].

Necroptosis, in contrast, is a form of inflammatory necrosis. The core mechanism revolves around the RIPK1–RIPK3 signaling axis, which drives phosphorylation and oligomerization of the MLKL pseudokinase. RIPK1 and RIPK3 assemble into the necrosome when caspase-8 activity is inhibited or absent, resulting in MLKL phosphorylation and oligomerization. Oligomerized MLKL then translocates to the plasma membrane and forms pores, causing cytolysis. Conversely, active caspase-8 suppresses necroptosis by cleaving RIPK1 and RIPK3, thereby diverting the cell toward apoptosis[25] (**Figure 1**).

PANoptosis and PANoptosome

PANoptosis is an inflammatory PCD pathway regulated by the multiprotein complex termed the PANoptosome, rather than the coincidental simultaneous activation of three independent pathways: pyroptosis; apoptosis; and necroptosis. Distinguishing PANoptosis from simultaneous multi-pathway activation primarily relies on two key criteria: physical assembly evidence; and genetic epistasis analysis.

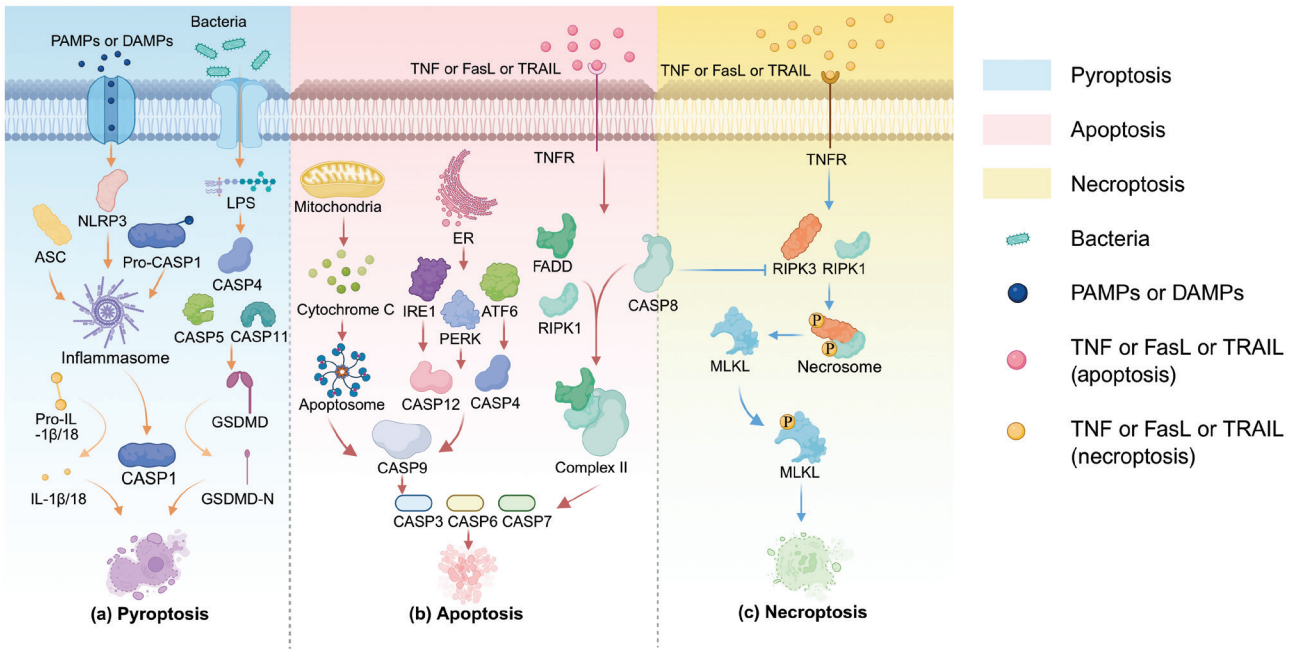


Figure 1 Molecular mechanisms and pyroptosis, apoptosis, and necroptosis signaling pathways. This schematic comprehensively illustrates the distinct biochemical cascades and key molecular executioners governing three major forms of programmed cell death, highlighting the specific intracellular signaling networks triggered by diverse extracellular and intracellular stimuli. **(a) Pyroptosis:** This panel depicts the activation of inflammasomes leading to inflammatory, lytic cell death. Extracellular PAMPs or DAMPs bind to membrane receptors, triggering the canonical pathway in which NLRP3 recruits ASC and Pro-CASP1 to assemble the inflammasome. This complex activates CASP1, which subsequently cleaves pro-IL-1β/18 into mature, secretable IL-1β/18 and processes GSDMD into the active N-terminal fragment GSDMD-N. In parallel, the non-canonical pathway is initiated when intracellular bacteria release LPS, which is directly sensed by CASP4, CASP5, or CASP11, also lead to GSDMD cleavage. GSDMD-N translocates to and forms pores within the plasma membrane, resulting in the extracellular release of IL-1β/18 and characteristic cell rupture. **(b) Apoptosis:** This panel illustrates the highly regulated, non-inflammatory cell death driven by three converging pathways. Death ligands in the extrinsic pathway, including TNF, FasL, or TRAIL, bind to the specific membrane receptor (TNFR), recruiting FADD and RIPK1 to form Complex II, which effectively activates CASP8. Intracellular stress prompts the mitochondria in the intrinsic pathway to release cytochrome C, leading to the formation of the apoptosome and activation of CASP9. Concurrently, the ER stress pathway is governed by sensors, including IRE1, PERK, and ATF6, which trigger the activation of CASP12 and CASP4. All three upstream signaling routes converge to activate the executioner caspases, CASP3, CASP6, and CASP7, culminating in orderly cellular shrinkage and apoptotic body formation. **(c) Necroptosis:** This panel details the pathway of programmed necrosis, that is typically engaged when apoptosis is blocked. Binding of TNF, FasL, or TRAIL to TNFR initiates the cascade. Under conditions in which CASP8 activity is explicitly inhibited, RIPK1 and RIPK3 accumulate and undergo mutual phosphorylation (P) to form the functional necrosome. This complex subsequently phosphorylates the effector protein, MLKL. Phosphorylated MLKL oligomerizes and translocates to the plasma membrane, driving irreversible membrane destabilization and necroptotic cell rupture. ASC, apoptosis-associated speck-like protein containing a CARD; ATF6, activating transcription factor 6; CASP, caspase; DAMPs, damage-associated molecular patterns; ER, endoplasmic reticulum; FADD, Fas-associated protein with death domain; FasL, Fas ligand; GSDMD, gasdermin D; GSDMD-N, gasdermin D N-terminal domain; IL-1β/18, interleukin-1β/18; IRE1, inositol-requiring enzyme 1; LPS, lipopolysaccharide; MLKL, mixed lineage kinase domain-like protein; NLRP3, NOD-like receptor protein 3; P, phosphorylation; PAMPs, pathogen-associated molecular patterns; PERK, protein kinase RNA-like endoplasmic reticulum kinase; RIPK1/3, receptor-interacting serine/threonine-protein kinase 1/3; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; TRAIL, TNF-related apoptosis-inducing ligand (figure created with BioRender.com).

Cells frequently exhibit the molecular hallmarks of pyroptosis, apoptosis, and necroptosis concurrently during pathogen infection (e.g., influenza virus). Malireddi et al.[26] addressed this phenomenon and demonstrated based on genetic analysis that deletion of the upstream sensor, ZBP1, alone completely abrogated all cell death phenotypes induced by infection or inflammatory stimuli. This finding indicated that the multiple death outcomes are not activated in an independent, parallel manner but are driven by a unified upstream signaling hub. Furthermore, Christgen et al.[11] confirmed *via* co-immunoprecipitation that ZBP1 simultaneously recruits RIPK1, RIPK3, caspase-8, and NLRP3 to assemble

into a high-molecular-weight multiprotein complex (the PANoptosome). This finding structurally established the existence of an integrated signaling platform.

In the context of simultaneous multi-pathway activation, inhibiting a single executioner molecule typically only blocks the corresponding pathway, thereby partially mitigating tissue damage. However, targeting a single downstream effector molecule frequently fails to halt pathologic progression in PANoptosis due to compensatory pathway switching within the complex. For example, Karki et al.[27] showed that isolated inhibition of caspase-8 paradoxically exacerbates tissue damage by triggering RIPK3-mediated necroptosis in a cytokine shock model. Conversely, genetic knockout of upstream master regulators, such as ZBP1 or AIM2, completely blocks the entire cell death spectrum and rescues the host from lethality. This finding proves the existence of extensive molecular crosstalk and compensatory mechanisms within PANoptosis, rendering single blockade of downstream executioner molecules generally ineffective.

The collective evidence supports that the PANoptosome constitutes a unified signaling integration platform that regulates the activation of pyroptosis, apoptosis, and necroptosis in a coordinated fashion, thereby establishing PANoptosis as an integrated inflammatory PCD modality. PANoptosome exhibits the following "sensor–adaptor–catalytic" triad architecture: sensor proteins recognize PAMPs or DAMPs; adaptor proteins serve as scaffolding components that bridge sensors and downstream effector molecules; and catalytic effectors cooperate to activate executioner proteins, collectively driving the induction of PANoptosis[28] (**Figure 2**).

ZBP1-PANoptosome

ZBP1, an innate immune receptor, functions as a prototypical PANoptosome sensor protein that was initially identified during influenza A virus (IAV) infection. ZBP1 contains two Zα, an RHIM, and a C-terminal domain, enabling ZBP1 to recognize Z-DNA/Z-RNA and initiate cell death and inflammatory responses in infected cells[6]. Upon sensing an IAV infection, ZBP1 recruits RIPK3 and caspase-8 to assemble the ZBP1-PANoptosome, a complex comprised of RIPK3, RIPK1, caspase-8, FADD, ASC, NLRP3, and caspase-1, which consequently induces PANoptosis[29,30]. Within this complex, ZBP1 interacts with RIPK3 *via* the RHIM domain to activate caspase-8 and promote RIPK3-MLKL phosphorylation, thereby triggering apoptotic and necroptotic pathways. Simultaneously, ZBP1 engages the NLRP3 inflammasome through the FADD- and caspase-8-containing death-inducing signaling complex (DISC), activating the pyroptotic pathway. Furthermore, interferon regulatory factor 1 (IRF1) acts as a positive regulator of ZBP1 expression during viral infections, consequently enhancing ZBP1-mediated PANoptosome activation and PANoptosis[31].

In addition to core components, PANoptosis engages in extensive crosstalk with other cell death pathways. Autophagy exhibits bidirectional regulation of PANoptosis. Specifically, protective mitophagy (e.g., PINK1/Parkin) eliminates dysfunctional mitochondria, thereby reducing the production of mitochondrial reactive oxygen species (mtROS) and leakage of mitochondrial DNA (mtDNA) to suppress PANoptosome sensor activation[32]. Conversely, autophagy deficiency leads to the accumulation of damaged mitochondria, triggering ROS bursts that activate RIPK3-MLKL and caspase-8 signalling, as well as upregulating ZBP1 expression. This process creates a positive feedback loop that amplifies PANoptosis[33]. Core autophagy proteins also interact directly with PANoptosome components. ATG5 binds to FADD to enhance the co-localization of caspase-8 and RIPK3, while Beclin-1 inhibits assembly of the NLRP3 inflammasome[34].

Ferroptosis synergises with PANoptosis through iron-dependent lipid peroxidation and ROS production, inducing conformational changes in ZBP1 and NLRP3 and promoting PANoptosome assembly. This mediates the transition from relatively non-inflammatory ferroptosis to highly inflammatory PANoptosis[35]. Mitochondria serve as the central hub that integrates these signals, linking mitochondrial dysfunction to both pathways and amplifying cellular injury in pathologic contexts, including cancer and neurodegenerative diseases.

AIM2-PANoptosome

AIM2 is a sensor protein within the PANoptosome complex that recognizes pathogenic and endogenous double-stranded DNA (dsDNA)[36,37]. AIM2 undergoes a conformational change upon binding to dsDNA that exposes the N-terminal pyrin domain (PYD), which enables interaction with the PYD of ASC. The CARD domain of ASC subsequently recruits pro-caspase-1, facilitating autoproteolytic cleavage into active caspase-1. These steps lead to the formation of a functional AIM2 inflammasome comprising AIM2, ASC, and caspase-1[38]. Furthermore, AIM2 collaborates with proteins, such as ZBP1, RIPK1, and RIPK3, to assemble the AIM2-PANoptosome complex, thereby driving PANoptosis[8,38,39]. Like the ZBP1-PANoptosome, genetic deletion of AIM2 suppresses PANoptosis[37]. It is noteworthy that complete loss of AIM2 abolishes inflammatory cell death entirely, whereas deficiency in pyrin or ZBP1 only leads to partial reduction, indicating that the AIM2 inflammasome acts upstream of pyrin- or ZBP1-mediated PANoptotic signaling.

RIPK1-PANoptosome

RIPK1 is a key regulator of TNFR1 signaling that promotes the transcription of inflammatory cytokines and has a critical role in the modulation of cell death. Previous studies have shown that upon *Yersinia* infection in macrophages, transforming

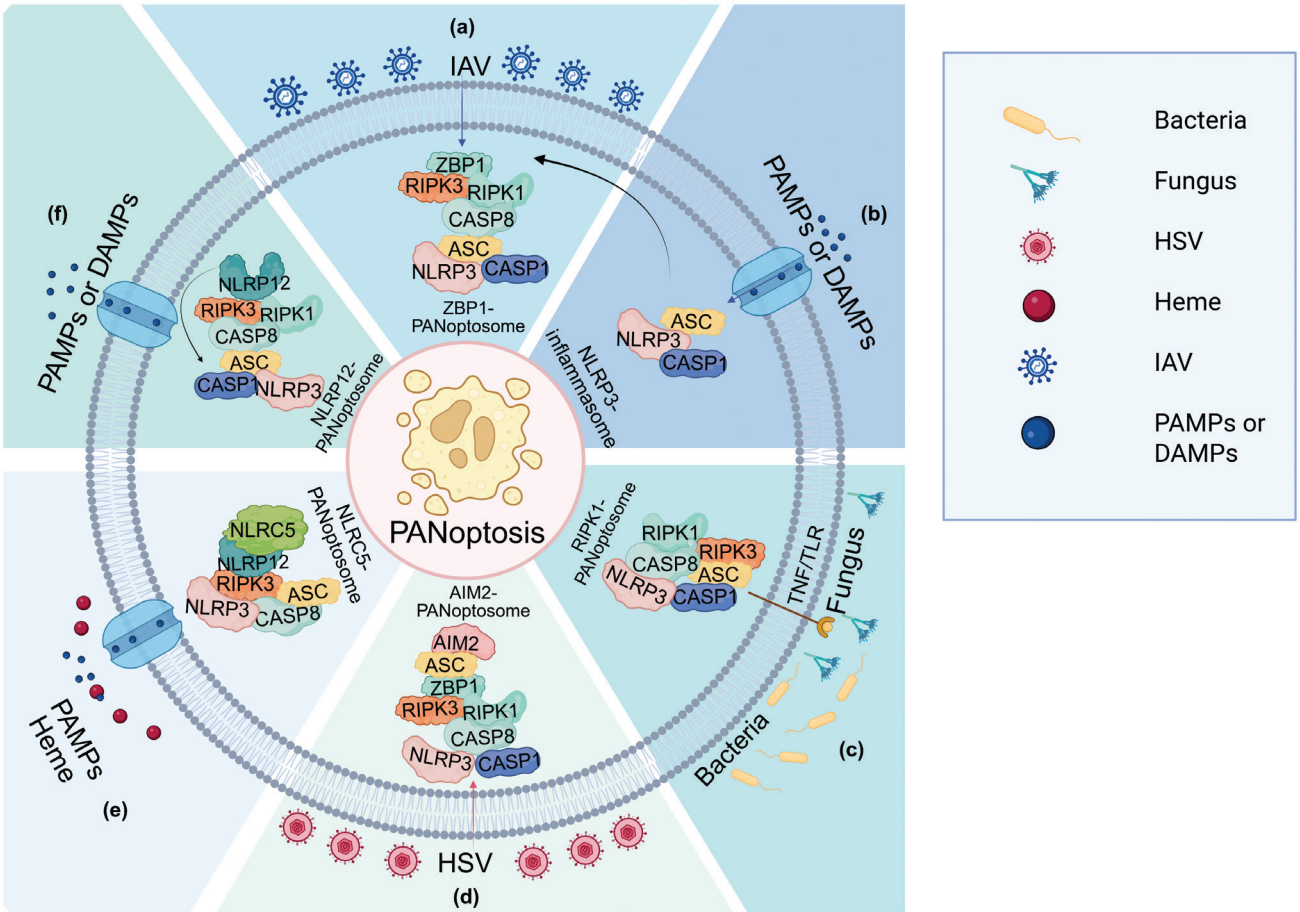


Figure 2 Molecular composition and activation mechanisms underlying the PANoptosome. This schematic comprehensively delineates the diverse molecular assemblies of PANoptosome complexes and the NLRP3-Inflammasome, illustrating how specific pathogens and sterile danger signals trigger distinct sensor proteins to orchestrate the unified cell death response of PANoptosis. The central core of the figure depicts a dying cell undergoing PANoptosis, which is characterized by massive membrane rupture. The surrounding panels detail six distinct activation contexts: **(a) ZBP1-PANoptosome**: Infection by the IAV is sensed intracellularly, prompting the primary sensor ZBP1 to recruit a multifaceted complex comprising RIPK3, RIPK1, CASP8, ASC, NLRP3, and CASP1. **(b) NLRP3-inflammasome**: Extracellular PAMPs or DAMPs enter the cytoplasm via membrane channels, triggering the assembly of the canonical inflammasome, which consists of the NLRP3 sensor, the ASC adaptor, and the effector CASP1. **(c) RIPK1-PANoptosome**: Extracellular fungus and bacteria engage surface TNF or TLRs, initiating a receptor-mediated signaling cascade that scaffolds the RIPK1-PANoptosome, integrating RIPK1, CASP8, RIPK3, ASC, NLRP3, and CASP1. **(d) AIM2-PANoptosome**: The intracellular presence of HSV activates the AIM2 sensor, leading to the formation of a complex that incorporates AIM2, ASC, ZBP1, RIPK3, RIPK1, CASP8, NLRP3, and CASP1. **(e) NLRC5-PANoptosome**: Sterile triggers, such as heme and microbial PAMPs, traverse the plasma membrane to stimulate a unique complex formed by the dual sensors (NLRC5 and NLRP12) with RIPK3, ASC, CASP8, NLRP3, and CASP1. **(f) NLRP12-PANoptosome**: Cytosolic delivery of PAMPs or DAMPs activates the NLRP12 sensor, which subsequently recruits RIPK3, RIPK1, CASP8, ASC, CASP1, and NLRP3 to form the active executioner complex. AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a CARD; CASP, caspase; DAMPs, damage-associated molecular patterns; HSV, herpes simplex virus; IAV, influenza A virus; NLRC5, NOD-like receptor family CARD domain containing 5; NLRP3/12, NOD-like receptor protein 3/12; PAMPs, pathogen-associated molecular patterns; RIPK1/3, receptor-interacting serine/threonine-protein kinase 1/3; TLR, Toll-like receptor; TNF, tumor necrosis factor; ZBP1, Z-DNA-binding protein 1 (figure created with BioRender.com).

growth factor-β-activated kinase 1 (TAK1) activity is inhibited, leading to subsequent activation of RIPK1. The activated RIPK1 then nucleates the assembly of the PANoptosome by recruiting components, such as NLRP3, RIPK3, ASC, caspase-1, and caspase-8, thereby inducing PANoptosis[40]. Further research indicates that TAK1 suppresses RIPK1 phosphorylation, thereby restraining activation and preventing spontaneous PANoptosis. Conversely, genetic deletion of

RIPK1 can rescue cell death in TAK1-deficient macrophages[6,41]. However, studies by Malireddi et al.[26] revealed that cells have evolved a mechanism to sense TAK1 inactivation independent of RIPK1 kinase activity. Specifically, TLR priming can bypass the requirement for RIPK1 kinase function and induce PANoptosis, even in TAK1-deficient cells. Nevertheless, unlike ZBP1-PANoptosome-mediated PANoptosis, RIPK1 deficiency does not completely abolish cell death.

NLRP12-PANoptosome

NLRP12, a member of the NLR family, is closely associated with innate immunity and inflammatory diseases. Previous studies have shown that NLRP12 recognizes pathogen-derived signals during *Yersinia pestis* infection and functions as an inflammasome sensor to drive pyroptosis[42]. NLRP12 facilitates assembly of the NLRP12-PANoptosome upon stimulation by heme and PAMPs through an interaction with TLR2/4, which includes NLRP3, ASC, caspase-1/8, and RIPK3, thereby promoting PANoptosis[43]. In this process, IRF1 acts as an upstream regulator by controlling the expression of NLRP12, RIPK1, AIM2, and ZBP1, which mediates formation of the NLRP12-PANoptosome and subsequent induction of PANoptosis[43]. Notably, NLRC5 can interact with NLRP12 under stimulation by heme and PAMPs to form the NLRC5-PANoptosome, a complex comprised of NLRC5, caspase-8, ASC, RIPK3, and NLRP3, which drives inflammatory cell death, including PANoptosis[44]. It is noteworthy that NLRC5 does not regulate caspase-1 activation or the release of inflammatory cytokines, whereas NLRP12 participates in these processes, highlighting the functional distinction between the two molecules.

NLRP3-inflammasome

NLRP3 serves as a core sensor within the PANoptosome, leveraging the three functional domains (PYD, NACHT, and LRR) to have a central role in inflammasome and PANoptosome assembly[45,46]. The allosteric activation of NLRP3 is initiated by the cellular perception of upstream danger signals, leading to a conformational change that relieves NACHT autoinhibition. The NACHT domain then binds ATP, facilitating oligomerization of NLRP3 monomers into a multimeric complex and exposing the PYD domain for recruitment of ASC. Upon recruitment, ASC spontaneously undergoes prion-like polymerization, serving as a signal amplifier that recruits caspase-1 and ultimately leads to the formation of a functional NLRP3 inflammasome[47-49]. Under specific conditions, ZBP1 is also activated and assembles into a ZBP1-containing complex. This complex, through BH3 domain-mediated interactions with caspase-8, bridges with the NLRP3 inflammasome to form the NLRP3-PANoptosome[50]. Furthermore, caspase-1 contributes to the activation of caspase-8-mediated apoptosis *via* signal crosstalk and facilitates RIPK3-dependent phosphorylation of MLKL, leading to necroptosis. Together, these processes orchestrate the integrated cell death pathway, which is known as PANoptosis[6,26].

Differential signaling preferences of PANoptosomes

Notably, the five currently identified PANoptosomes exhibit significant differences in driving the relative contributions of pyroptosis, apoptosis, and necroptosis, which are primarily determined by the inherent signaling preferences of the core sensor proteins. First, the AIM2- and NLRP12-driven complexes demonstrate a strong pyroptotic bias. The AIM2- and NLRP12-driven complexes rely predominantly on the caspase-1/GSDMD axis for execution. Caspase-8-mediated apoptosis and MLKL-mediated necroptosis act as fail-safe mechanisms that are only initiated when the pyroptotic pathway is obstructed[51]. Second, the RIPK1 and NLRC5-driven PANoptosomes are highly biased toward apoptosis and necroptosis. Within these complexes, canonical NLRP3 inflammasome-mediated pyroptosis functions more as a secondary amplification response downstream of the RIPK1/RIPK3 signaling cascade[26,44]. Finally, ZBP1 exhibits a balanced synergistic pattern. ZBP1 concurrently drives robust apoptosis and necroptosis through the RHIM domain, while efficiently bridging the pyroptosis pathway[29]. This sensor-dependent cell death allocation pattern provides a critical mechanistic framework for designing precision therapies targeting specific PANoptosomes in complex diseases.

Contextual regulation of PANoptosome assembly

The assembly of the PANoptosome is a "contextual integration" that is highly dependent on cell lineage and the tissue microenvironment. The intrinsic transcriptional profile of a cell determines the "sensitization threshold" for PANoptosis. For example, myeloid cells primed by IFN significantly upregulate ZBP1 to establish a "primed state" ready to assemble the ZBP1-RIPK3-caspase-8 complex, whereas such molecular reservoirs typically remain silenced or exhibit low expression in fibroblasts or specific epithelial cells[29].

Building upon this finding, the tissue microenvironment acts as a decisive gating mechanism. A local cytokine storm, particularly the synergistic action of TNF-α and IFN-γ[27], provides the requisite upstream activation signals and is frequently accompanied by metabolic reprogramming. This mechanism includes ROS accumulation driven by enhanced glycolysis or fluctuations in tricarboxylic acid (TCA) cycle metabolites, such as itaconate[52,53]. These metabolic signals directly interfere with the conformational stability of caspase-8 or NLRP3 *via* alkylation modifications or redox states.

Furthermore, post-translational modifications (PTMs), such as the palmitoylation of GSDMD or the phosphorylation state of RIPK1, spatially restrict membrane translocation efficiency of effector molecules[21]. This heterogeneity at the assembly level directly reshapes the downstream signaling flux. The caspase-1/GSDMD axis dominates in some microenvironments, leading to severe inflammatory necrosis, whereas under conditions in which RIPK3 activity is suppressed, signaling may skew toward caspase-8-mediated immune-silent apoptosis. Consequently, identical pathogen stimulation may trigger explosive PANoptosis in alveolar macrophages but elicit only mild apoptosis or survival signals in surrounding lung epithelial cells[51]. This heterogeneity ultimately shapes distinct pathologic injury patterns.

Mitochondria: the core signaling hub of PANoptosis

Mitochondria, as central organelles in cellular energy metabolism and signaling regulation, are key participants in PCD, such as apoptosis and pyroptosis. Mitochondria also serve as a hub where multiple death pathways converge during PANoptosis[54]. Mitochondria precisely regulate the initiation and progression of PANoptosis by controlling MOMP, mtROS production, and mtDNA release. Dysfunction of these organelles is closely linked to the assembly and activation of the PANoptosome complex. BCL-2 family proteins are core regulators of mitochondrial apoptosis and determine cell fate by maintaining a dynamic balance between pro- and anti-apoptotic members[55]. Activation of pro-apoptotic members promotes MOMP, a hallmark of mitochondrial damage. This effect releases cytochrome c to initiate intrinsic apoptosis and enhances MLKL phosphorylation and oligomerisation *via* the RIPK1–RIPK3 axis, thereby driving necroptosis synergistically. Excessive mtROS generation, as the primary source of ROS, creates an oxidative stress microenvironment that directly triggers conformational changes in PANoptosome sensors, such as ZBP1, NLRP3, and AIM2. The conformational changes promote assembly with adaptor proteins (ASC and FADD) and effectors (caspase-8 and RIPK3). Concurrently, mtDNA leaks into the cytoplasm where mtDNA is recognized by AIM2 and NLRP3 inflammasomes as a mitochondrial-derived DAMP, directly inducing the formation of AIM2- and NLRP3-PANoptosomes and activating the pyroptotic pathway. In summary, mitochondria act as a central signaling platform that links mitochondrial damage to PANoptosome activation *via* MOMP, mtROS, and mtDNA release. In pathologic states, such as myocardial infarction (MI), atherosclerosis, and neurodegenerative diseases, excessive PANoptosis driven by mitochondrial dysfunction is a key mechanism underlying tissue injury and disease progression.

Role of PANoptosis in disease

PANoptosis has a pivotal role in the onset and progression of various diseases. Notably, PANoptosis exhibits a characteristic "dual effect" in host defense, as follows: 1. Functionally, as a form of PCD integrating apoptosis, pyroptosis, and necrosis, inhibiting any single functional molecule fails to suppress cell death. For example, IAV induces PANoptosis by activating caspase-1 and GSDMD, caspase-8, -3, and -7, and MLKL. Inhibiting any single molecule fails to suppress IAV-induced cell death. 2. Therapeutically, targeting a single PCD pathway may yield limited efficacy due to compensatory activation of alternative death mechanisms. In contrast, modulating PANoptosis holds promise for coordinating multiple death pathways, thereby enhancing the effectiveness of single-target therapies. This distinction is particularly critical in cancer treatment. Leveraging PANoptosis as a "dual process" can amplify anti-tumor immunity, while excessive activation must be avoided in chronic inflammation to prevent systemic inflammatory damage[56] (**Figure 3**).

Infectious diseases

PANoptosis has been characterized in multiple pathogen infection models, including viral, bacterial, and parasitic diseases. SARS-CoV-2 triggers inflammatory PCD in alveolar type II epithelial cells in COVID-19 with TNF-α acting as a key inducer[57]. Building on earlier work, it is proposed that TNF-α and IFN-γ synergistically activate the JAK/STAT1/IRF1 axis, upregulating death receptors and inflammatory genes to initiate PANoptosis *via* the caspase-8/FADD complex[58]. Moreover, the role of PANoptosis in host defense has been demonstrated in HSV-1 infection. HSV-1 promotes caspase-1 cleavage in an AIM2-dependent manner, facilitating assembly of the PANoptosome and subsequent induction of PANoptosis, which confers protection against HSV-1 infection[10].

In the context of bacterial infections, the *Salmonella* effector SopF has been identified as a regulator of PANoptosis in intestinal epithelial cells (IECs), modulating host defense and systemic infection severity. Studies have revealed that upon translocation into IECs, SopF activates the RSK signaling pathway, downregulates caspase-8 expression, and thereby suppresses PANoptosis. This finding implies that pathogens may strategically target core components of the PANoptosis pathway to evade host PCD responses and enhance survival[59]. AIM2 assembles a PANoptosome complex with pyrin and ZBP1 in *Francisella novicida* models, thereby inducing PANoptosis in infected macrophages, restricting bacterial dissemination, and bolstering host defense[37].

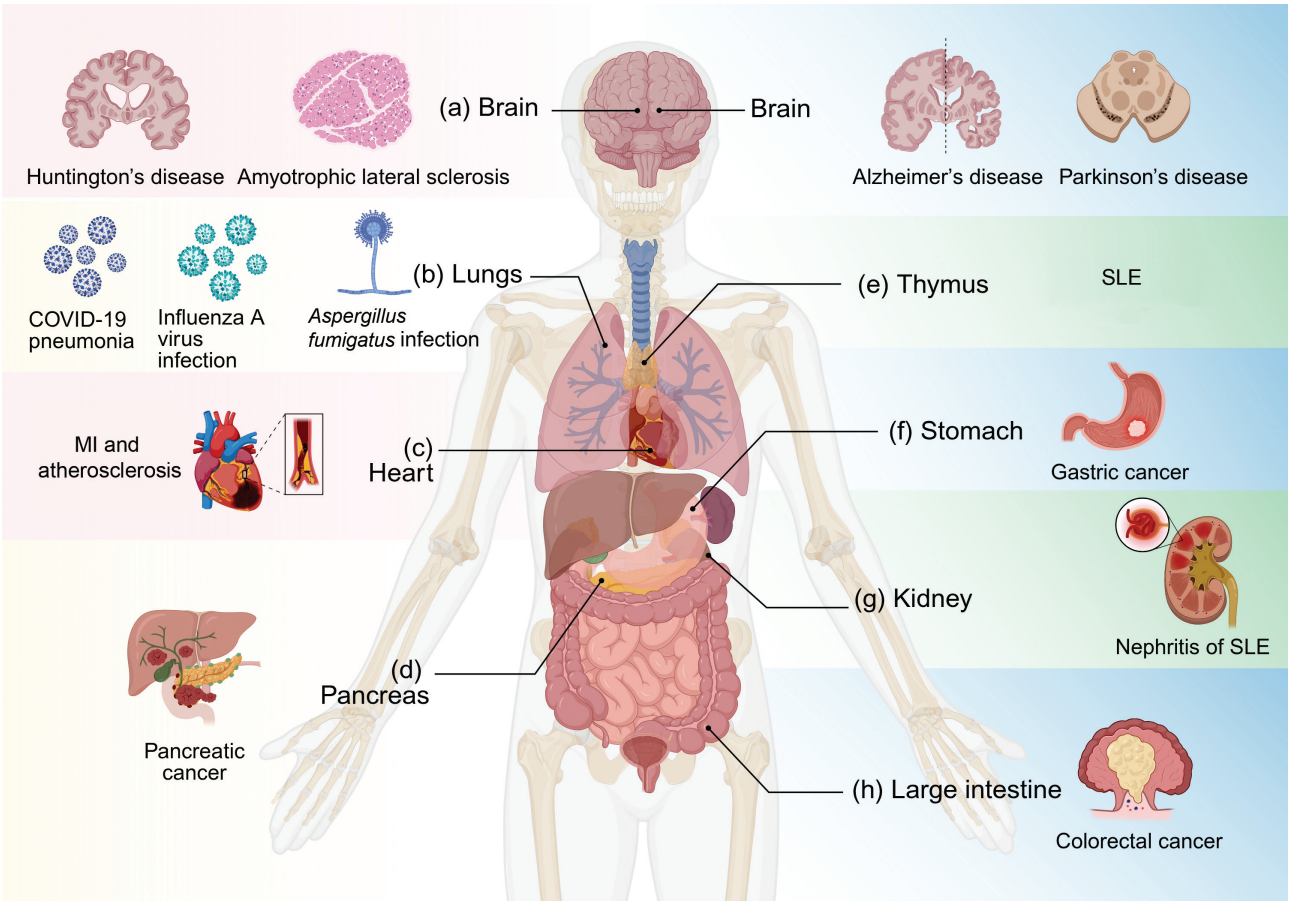


Figure 3 Systemic overview of diseases associated with PANoptosis. This schematic maps the broad pathophysiologic involvement of PANoptosis across multiple human organ systems, illustrating the dual role in mediating inflammatory tissue damage and host defense. **(a) Brain**: Highlights neurodegenerative conditions, specifically Huntington's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and Parkinson's disease, in which dysregulated inflammatory cell death contributes to progressive neuronal loss. **(b) Lungs**: Depicts severe respiratory infections driven by viral and fungal pathogens, including COVID-19 pneumonia, influenza A virus infection, and Aspergillus fumigatus infection, which trigger lethal pulmonary PANoptosis. **(c) Heart**: Illustrates cardiovascular pathologies, pointing to the structural and vascular damage inherent in MI and atherosclerosis. **(d) Pancreas**: Highlights the involvement of PANoptosis in the progression of pancreatic cancer. **(e) Thymus**: Points to central immune compartments involved in systemic autoimmune disorders, represented here by SLE. **(f) Stomach**: Connects PANoptotic pathways to the development of gastric cancer. **(g) Kidney**: Depicts nephritis of SLE, showcasing a specific complication in which auto-immune-driven PANoptosis leads to severe renal tissue injury. **(h) Large intestine**: Illustrates colorectal cancer, in which intestinal inflammation and cell death dynamics heavily influence localized tumorigenesis. COVID-19, coronavirus disease 2019; MI, myocardial infarction; SLE, systemic lupus erythematosus (figure created with BioRender.com).

Tumors

The role and mechanisms underlying PANoptosis in various tumors have gradually attracted increasing attention, including pancreatic cancer (PC), thyroid cancer, breast cancer (BC), gastric cancer (GC), and colorectal cancer (CRC)[60]. This increased research interest suggests that PANoptosis is a multi-mechanistic cell death modality with therapeutic potential against highly invasive and metastatic malignancies (**Figure 4**).

PANoptosis and the tumor microenvironment (TME)

The interaction between tumors and the TME is a complex and dynamic process that is shaped by the continuous exchange of cytokines, metabolites, and death signals that influence tumor progression[61]. PANoptosis in tumor cells releases DAMPs and inflammatory mediators that can activate dendritic cells (DCs) and promote T-cell infiltration, fostering anti-tumor immunity and thereby inducing anti-tumor immunity[62]. However, excessive PANoptosis may also trigger cytokine storms, recruit immunosuppressive M2

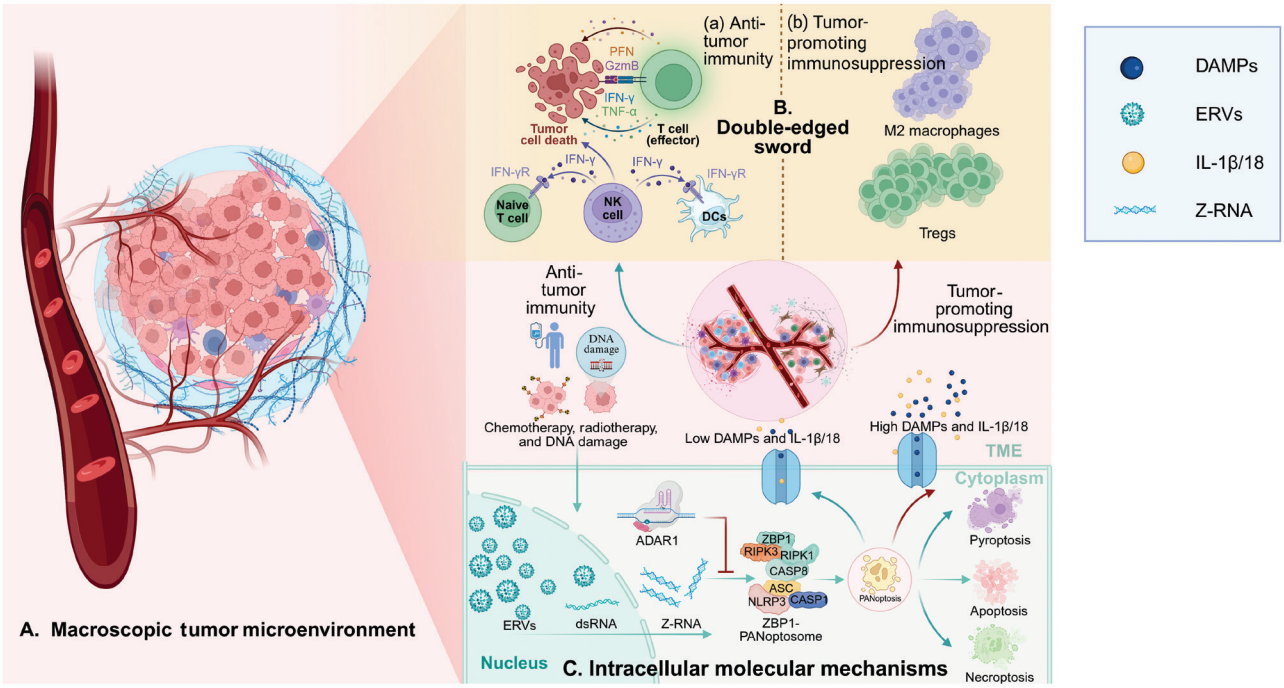


Figure 4 The dual role of PANoptosis in the TME. This schematic comprehensively illustrates how the magnitude and context of PANoptosis dictate opposing immunologic outcomes within the TME. A. **Macroscopic tumor microenvironment**: Depicts a solid tumor mass, highlighting the complex cellular milieu including tumor cells, neovascularization, and the surrounding extracellular matrix. B. **Dual role**: Elucidates the divergent immune responses triggered by PANoptosis. **(a) Anti-tumor immunity**: A robust PANoptotic response releases high levels of DAMPs and interleukins (IL-1β/18). These factors activate DCs and NK cells. DCs present antigens to naive T cells, which along with NK cells, secrete IFN-γ. IFN-γ binds to the IFN-γR on T cells, promoting differentiation into effector T cells. These effector T cells secrete PFN, GzmB, IFN-γ, and TNF-α, directly executing targeted tumor cell death. **(b) Tumor-promoting immunosuppression**: Conversely, a weak PANoptotic response producing low levels of DAMPs and IL-1β/18 fosters an immunosuppressive niche dominated by Tregs and M2 macrophages, allowing tumor immune evasion. C. **Intracellular molecular mechanisms**: Details the upstream signaling driving PANoptosis. Cellular stress from chemotherapy, radiotherapy, and DNA damage induces the transcription of ERVs in the nucleus. This generates dsRNA and Z-RNA. While ADAR1 typically suppresses Z-RNA, the uninhibited accumulation in the cytoplasm triggers the ZBP1 sensor. ZBP1 subsequently recruits RIPK3, RIPK1, CASP8, ASC, NLRP3, and CASP1 to assemble the ZBP1-PANoptosome, culminating in PANoptosis, a coordinated execution of pyroptosis, apoptosis, and necroptosis. ADAR1, adenosine deaminase acting on RNA 1; ASC, apoptosis-associated speck-like protein containing a CARD; CASP, caspase; DAMPs, damage-associated molecular patterns; DCs, dendritic cells; dsRNA, double-stranded RNA; ERVs, endogenous retroviruses; GzmB, granzyme B; IFN-γ, interferon-gamma; IFN-γR, interferon-gamma receptor; IL-1β/18, interleukin-1β/18; NK, natural killer; NLRP3, NOD-like receptor protein 3; PFN, perforin; RIPK1/3, receptor-interacting serine/threonine-protein kinase 1/3; TME, tumor microenvironment; TNF-α, tumor necrosis factor-alpha; Tregs, regulatory T cells; ZBP1, Z-DNA binding protein 1; Z-RNA, Z-form RNA (figure created with BioRender.com).

macrophages and regulatory T cells (Tregs), and promote immune evasion[63].

Endogenous retrovirus (ERV) elements can be activated upon DNA damage and the transcripts are recognized by ZBP1, which subsequently triggers PANoptosis and induces immunogenic cell death[64]. Conversely, adenosine deaminase acting on RNA 1 (ADAR1) modifies RNA molecules to weaken ZBP1 signaling, thereby reducing necroptosis and PANoptosis and ultimately diminishing sensitivity to immunotherapy[65]. Thus, targeting the ADAR1–ZBP1 axis may represent a potential strategy to enhance the efficacy of immune checkpoint inhibitors (ICIs). However, the expression of ADAR1, ZBP1, and related caspases or nucleotide-binding oligomerization domain-like receptors (NLRs) varies considerably across tumor models[66]. For example, based on The Cancer Genome Atlas (TCGA) transcriptomic data, the classification of glioma, renal carcinoma, and melanoma into "PANoptosis-high" and "PANoptosis-low" subtypes revealed significant differences in survival, immune cell infiltration, and key signaling pathway activity, further supporting the tumor-type specificity of PANoptosis function[67].

The "dual prole effect" of PANoptosis in tumor biology is essentially the result of a dynamic balance between cell

death clearance mechanisms and immune microenvironment remodeling. In solid tumors, such as melanoma, therapy-induced acute PANoptosis can exert a tumor-suppressive function as a cell death clearance mechanism[68]. Because many tumor cells evade apoptosis by downregulating caspase-8 or overexpressing anti-apoptotic proteins, such as the Bcl-2 family, PANoptosis provides a crucial alternative death pathway. For example, IFNs and TNF can activate ZBP1, which subsequently assembles the PANoptosome containing RIPK3 and caspase-8, inducing robust lytic death of tumor cells. This mode of death not only directly reduces tumor burden but is also accompanied by the massive release of DAMPs, which effectively activate antigen-presenting cells, thereby enhancing the CD8+T cell-mediated anti-tumor immune response. In this context, inducing PANoptosis is an effective strategy to overcome tumor drug resistance.

Conversely, in chronic inflammation-driven tumor types, endogenous, sustained, low-level PANoptosis acts as a tumor promoter. The persistent activation of PANoptosis and the upstream signaling pathways may promote tumorigenesis in colitis-associated cancer (CAC) or hepatocellular carcinoma in the clinical setting of chronic hepatitis[69]. This negative effect primarily stems from the vicious cycle of necroinflammation. When cells within the TME undergo continuous PANoptosis, the released pro-inflammatory cytokines (IL-1β, IL-18, and TNF-α) recruit myeloid-derived suppressor cells (MDSCs) and TAMs, thereby constructing an immunosuppressive stromal environment. Furthermore, persistent PANoptosis can lead to tissue barrier disruption and the reactive release of growth factors, such as EGF or Wnt signaling. This environment not only promotes tumorigenesis *via* immunosuppression but also directly accelerates malignant clonal evolution and metastasis by providing mitogenic signals. Moreover, in some tumors, like breast cancer, transcriptomic data indicate that high expression of PANoptosis-related genes correlates with a poor prognosis, which likely reflects the formation of an inflammation-driven tumor niche rather than merely enhanced tumor cell death[70]. Therefore, in these specific cancer types or disease stages, PANoptosis is no longer a means of eradicating tumors but becomes a driver for tumors to utilize the inflammatory microenvironment for immune evasion and invasion. This tissue specificity and environment dependency suggest that when designing therapeutic strategies targeting PANoptosis, the specific immune state of the TME must be precisely evaluated.

Tumor drug resistance

PC is a highly invasive and lethal tumor characterized by limited treatment options and resistance to standard therapies[71]. PANoptosis holds promise for overcoming the resistance of PC cells to single death pathways by orchestrating multiple molecular mechanisms, thereby enhancing tumor cell killing and improving chemosensitivity. Researchers have identified 24 PANoptosis-related genes (PANRGs), based on which patients were stratified into 2 distinct PANclusters, exhibiting differential drug sensitivity profiles. Furthermore, a prognostic PANoptosis model consisting of CXCL10 and ITGB6 was developed, demonstrating excellent predictive performance. This evidence confirms the involvement of PANoptosis in PC regulation and provides valuable guidance for tailoring individualized therapeutic strategies[72].

Studies have revealed that upregulation of upstream PANoptosis mediators in GC and CRC can activate the NLRP3 inflammasome and caspase-1 to induce pyroptosis. In addition, activation of RIPK3 and MLKL drives necroptosis, thereby suppressing tumor proliferation and metastasis[18]. Moreover, a bioinformatics analysis of GC samples identified three distinct PANoptosis expression patterns and developed a PANscore classification system, as follows: a low PANscore phenotype was associated with improved survival outcomes and better responses to immunotherapy, whereas a high PANscore correlated with immunosuppressive features, such as low immune checkpoint expression, elevated TGF-β levels, and infiltration of cancer-associated fibroblasts (CAFs) and M2 macrophages[73]. Upregulation of IRF1 in CRC was shown to promote PANoptosis by modulating pro-inflammatory cytokines, such as TNF and IFN, thereby activating multiple cell death pathways[72].

Importantly, PANoptosis not only circumvents tumor resistance to single death pathways but also reshapes the immune microenvironment *via* inflammatory signaling, providing a novel therapeutic strategy[74]. Moving forward, further investigation is needed to elucidate the specific mechanisms underlying PANoptosis across different tumor types and develop targeted regulatory strategies.

Neurodegenerative diseases

With the emergence of the PANoptosis concept and ongoing elucidation of the underlying molecular mechanisms, growing evidence indicates that PANoptosome-associated components overlap with key mediators of neurodegenerative pathologies.

Alzheimer's disease (AD) is pathologically characterized by amyloid-β (Aβ) deposition and hyperphosphorylated tau accumulation[75,76]. Importantly, neuronal death in AD does not merely represent a combination of distinct PCD pathways but rather reflects a PANoptosis-mediated death paradigm. For example, NLRP3 inflammasome deficiency has been shown to reduce tau hyperphosphorylation and aggregation, ameliorating neurologic deficits in AD models and highlighting the potential as a therapeutic target[77]. Parkinson's disease (PD) represents the second most common neurodegenerative disorder after AD[78,79]. Accumulating evidence suggests that neuronal death in PD involves interconnected PCD mechanisms, reflecting a PANoptosis-like process. For example, GSDMD is significantly upregulated in PD, promoting microglial hyperactivation and inflammatory cytokine release,

which accelerates dopaminergic neurodegeneration in the substantia nigra[80].

Glaucoma, a common neurodegenerative disease, is characterized by progressive retinal ganglion cell (RGC) loss and visual field defects[81]. NLRP3 activation is accompanied by significant upregulation of caspase-1 and its cleavage products in both patients and animal models, highlighting the importance of inflammatory PCD in disease progression[82]. Huntington's disease (HD) is a fatal autosomal dominant neurodegenerative disorder. Mutant huntingtin protein aggregates disrupt mitochondrial function and cellular metabolism, activate the NLRP3 inflammasome, and induce pyroptosis, thereby exacerbating neuronal damage[83,84]. Amyotrophic lateral sclerosis (ALS) is another progressive neurodegenerative disorder that primarily affects motor neurons[85]. Both ALS patients and mouse models exhibit upregulation and activation of NLRP3, caspase-1, and IL-1β[86]. Inhibition of NLRP3 has been shown to mitigate neuroinflammation and neuronal injury in ALS models, delaying disease progression[87].

Autoimmune diseases

Autoimmune diseases comprise a spectrum of chronic inflammatory disorders characterized by dysregulated immune function and loss of self-tolerance[88,89]. Crohn's disease (CD) is a chronic relapsing transmural inflammatory bowel disease[90,91]. Yang et al.[92] identified 10 pivotal PANoptosis-related genes (PRGs) through integration of multi-omics datasets and machine learning approaches and constructed regulatory networks that classified CD into 2 distinct PANoptosis subtypes based on hub differentially expressed PRGs (DE-PRGs). A subsequent study on inflammatory bowel disease (encompassing CD and ulcerative colitis)[93] corroborated 12 DE-PRGs significantly associated with immune cell infiltration and inflammatory pathways, such as NF-κB and TNF signaling, while also identifying promising drug candidates. Collectively, these findings position PRGs as potential biomarkers for precision stratification and personalized therapy in CD.

Systemic lupus erythematosus (SLE) arises from aberrant immune activation against self-tissues[94], manifesting clinically as a highly heterogeneous syndrome that includes multi-organ involvement, such as lupus nephritis and neuropsychiatric symptoms. Evidence indicates significant upregulation of NLRP3 in peripheral blood mononuclear cells (PBMCs) from SLE patients, correlating with disease activity[95]. Transcriptomic profiling has further identified five key DE-PRGs in PBMCs from SLE patients compared to healthy controls. These genes correlate with altered abundances of memory B cells, neutrophils, and CD8+ T cells. Functional enrichment analyses revealed involvement in type I interferon responses and the IL-6–JAK–STAT3 signaling pathway, implying that PANoptosis may exacerbate immune dysregulation and tissue damage *via* interferon-driven inflammation and JAK–STAT overactivation[96]. Although the mechanistic landscape of PANoptosis in SLE remains incompletely mapped, current evidence supports a role as a critical integrator of immune dysfunction and multi-organ injury, highlighting the potential as a therapeutic target.

Cardiovascular diseases

MI is a severe clinical condition resulting from acute coronary artery occlusion[97,98]. Emerging evidence underscores the critical role of PANoptosis-associated PCD in the pathophysiology of MI. For example, cleavage of GSDMD and activation of caspase-1, which are hallmarks of pyroptosis, are prominently observed in cardiomyocytes following MI[99]. Pharmacologic inhibition of RIPK1 with necrostatin-1 attenuates infarct size and cardiomyocyte death, conferring cardioprotection in experimental I/R models[100]. As a core mediator of necroptosis within the PANoptosis network, RIPK1 inhibition not only preserves myocardial structure but also mitigates reactive fibrosis post-I/R injury[101]. Targeted intervention against key molecules within these interconnected cell death pathways may offer promising strategies for the prevention and treatment of MI.

Atherosclerosis is the most prevalent and clinically significant form of arteriosclerotic vascular disease[102]. The NLRP3 inflammasome has been shown to have a pivotal role in the process of vascular inflammation and atherogenesis[103]. Within atherosclerotic plaques, macrophages undergo PANoptosis in response to oxidized low-density lipoprotein (ox-LDL) and cholesterol crystals. These stimuli activate the NLRP3 inflammasome and other sensors, such as AIM2, integrating caspase and RIPK-mediated signaling to induce synergistic cell death[104]. Collectively, oxidative stress and signaling crosstalk among PANoptosis components create a vicious cycle that perpetuates atherosclerotic progression[105,106].

Targeting PANoptosis as a therapeutic strategy for disease

PANoptosis has been established as a critical regulator in the pathogenesis of inflammatory diseases and tumors. While suppressing PANoptosis ameliorates inflammatory disorders, the targeted induction of PANoptosis represents an emerging anti-tumor strategy. Notably, multiple preclinical studies have demonstrated that candidate drugs directly modulating PANoptosis demonstrate substantial therapeutic potential across multiple diseases, positioning the drugs as promising next-generation precision therapeutics (**Figure 5**).

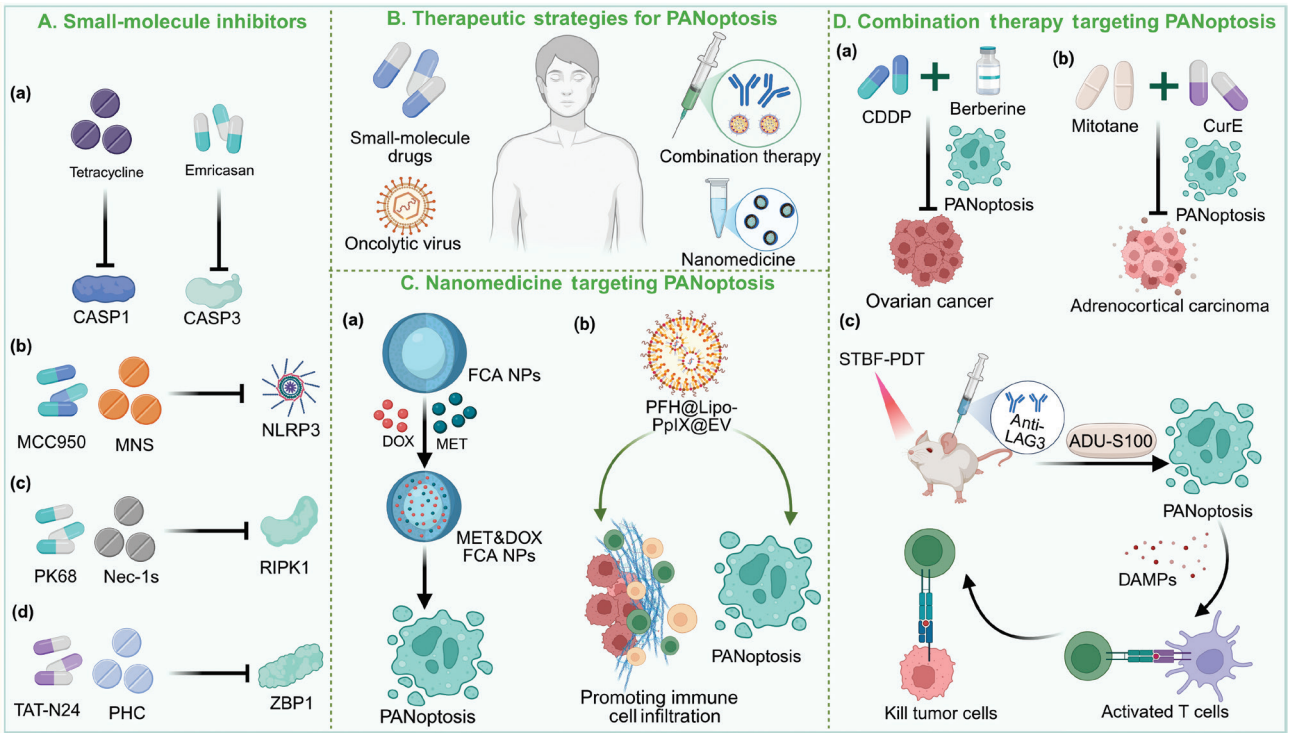


Figure 5 Therapeutic strategies targeting PANoptosis. This schematic summarizes the diverse pharmacologic and nanomedicine interventions designed to inhibit or induce PANoptosis for targeted disease management. A. **Small-molecule inhibitors:** Details specific drugs targeting individual components of the PANoptosome. **(a)** Tetracycline and emricasan inhibit the effector caspases, CASP1 and CASP3, respectively. **(b)** MCC950 and MNS specifically block the NLRP3 sensor. **(c)** PK68 and Nec-1s suppress the kinase activity of RIPK1. **(d)** TAT-N24 and PHC target the upstream sensor, ZBP1. B. **Therapeutic strategies for PANoptosis:** Provides a general overview of the four primary clinical modalities utilized: Small-molecule drugs, oncolytic virus therapy, combination therapy, and nanomedicine. C. **Nanomedicine targeting PANoptosis:** Illustrates advanced delivery systems designed to induce regulated cell death. **(a)** FCA NPs are co-loaded with DOX and MET to form MET&DOX FCA NPs, which effectively induce PANoptosis in target cells. **(b)** The complex nanoplatform, PFH@Lipo-PpIX@EV, simultaneously induces PANoptosis and functions in promoting immune cell infiltration into the tumor bed. D. **Combination therapy targeting PANoptosis:** Highlights synergistic drug regimens. **(a)** The combination of CDDP and berberine suppresses PANoptosis to mitigate toxicity in ovarian cancer. **(b)** Similarly, mitotane combined with CurE inhibits PANoptosis in adrenocortical carcinoma. **(c)** Conversely, a pro-death strategy employing STBF-PDT alongside anti-LAG3 antibodies and the STING agonist, ADU-S100, robustly induces PANoptosis. This triggers the extensive release of DAMPs, which sequentially generates activated T cells that proceed to kill tumor cells in a positive feedback loop. ADU-S100, a STING pathway activator; CASP, caspase; CDDP, cisplatin; CurE, curcumin analog; DAMPs, damage-associated molecular patterns; DOX, doxorubicin; EV, extracellular vesicle; FCA, specific nanoparticle material formulation; LAG3, lymphocyte-activation gene 3; Lipo, liposome; MET, metformin; MNS, 3,4-methylenedioxy-beta-nitrostyrene; NLRP3, NOD-like receptor protein 3; NPs, nanoparticles; PDT, photodynamic therapy; PFH, perfluorohexane; PpIX, protoporphyrin IX; RIPK1, receptor-interacting serine/threonine-protein kinase 1; STBF, specific therapeutic formulation; ZBP1, Z-DNA binding protein 1 (figure created with BioRender.com).

Small-molecule inhibitors

The key molecular components, including ZBP1, NLRP3, RIPK1, and caspase-8, collectively mediate the assembly of the PANoptosome and have an indispensable regulatory role in PANoptosis. Targeting these molecules constitutes a novel therapeutic strategy for treating diseases through precision modulation of PANoptosis. Uysal et al.[107] reported that pretreatment with 3,4-methylenedioxy-β-nitrostyrene (MNS), a specific NLRP3 inhibitor, in a rat renal ischemia-reperfusion (RIR) model can provide significant renal protective effects against RIR injury by blocking NLRP3 inflammasome-dependent PANoptosis. MCC950 was shown to directly inhibit the NLRP3 inflammasome in an AD model and reduce neuroinflammation and neuronal damage, while ameliorating cognitive deficits in APP/PS1 mice[108]. In addition, MCC950 alleviated cerebral injury in an ischemia-reperfusion model and improved neurologic function after ischemic stroke[109].

These studies provide experimental evidence that targeting NLRP3 exerts therapeutic potential for multi-organ ischemia-reperfusion injuries and neurodegenerative diseases through the regulation of PANoptosis.

RIPK1 has a pivotal role in the regulation of PANoptosis as a crucial component of the RIPK1-PANoptosome complex by modulating intrinsic protein functions. The small-molecule inhibitor, PK68, can directly inhibit RIPK1 kinase activity and pretreatment with PK68 has been shown to significantly suppress the metastatic potential of murine melanoma and lung cancer cells[110]. The highly selective RIPK1 inhibitor, Nec-1s, specifically blocks RIPK1-mediated neuroinflammation and PANoptosis in animal models, thereby markedly improving motor dysfunction in MPTP-induced mouse models of PD, highlighting the potential therapeutic utility[111].

Emerging evidence indicates that ZBP1 serves as a precise target for modulating PANoptosis. Penehyclidine hydrochloride attenuates myocardial injury, reduces cardiac enzyme release, and improves cardiac function by inhibiting ZBP1-mediated PANoptosis[112]. CurE regulates PANoptosis through ZBP1-dependent CDK1 inhibition in adrenocortical carcinoma (ACC)[113]. Baicalin disrupts ZBP1-PANoptosome assembly, which mitigates inflammatory diseases[114]. Notably, TAT-N24 protects neurons from inflammatory damage in acute glaucoma models by suppressing PANoptosis in RGCs through disruption of the ZBP1-PANoptosome[115]. Given that caspase activation is an integral executioner component within the PANoptosis pathway, the pan-caspase inhibitor, emricasan, targets caspase-3, -8, and -9 to inhibit neuronal apoptosis[116]. Tetracycline alleviated pulmonary inflammation by suppressing caspase-1-dependent cytokine production[117]. Collectively, these findings underscore the importance of elucidating PANoptosome composition and function for advancing therapeutic development.

Nanomedicine

Nanocarriers achieve site-specific targeting, enhancing bioavailability while minimizing off-target toxicity. Emerging evidence has demonstrated that nanoparticles (NPs) trigger PANoptosis to potentiate therapeutic efficacy. For example, Song et al.[118] developed folic acid-cholesterol-sodium alginate (FCA) NPs co-encapsulating metformin (MET) and doxorubicin (DOX). This nanosystem induced PANoptosis in melanoma by regulating the expression of N-GSDMD, MLKL, and caspase-7, thereby enhancing anti-tumor efficacy[118]. Similarly, Zhou et al.[119] engineered extracellular vesicle-based PFH@Lipo-PpIX@EV NPs, which induce PANoptosis and activate the STING pathway. This approach enhanced the infiltration of $CD4^+$ and CD8+ T cells into tumors *via* PANoptosis-mediated immunomodulation, demonstrating significant therapeutic efficacy in triple-negative breast cancer (TNBC) models[119]. In another study, hydrazided hyaluronic acid (HHA)-modified Zn-CuO_2 (HZCO) NPs trigger AIM2-PANoptosome assembly and activate PANoptosis, eliciting anti-tumor immunity and suppressing tumor growth. Furthermore, HZCO converts immunologically cold tumors into hot tumors, enhancing susceptibility to immune surveillance. When combined with anti-PD-1 therapy, HZCO potently inhibits primary tumor progression[120]. In addition, FePTX@CM NPs co-assembled with proanthocyanidin (PYD) and pentoxifylline (PTX) exert dual therapeutic actions in severe acute pancreatitis (SAP). PYD mitigates mitochondrial ROS-mediated Golgi stress, whereas PTX inhibits ZBP1-driven PANoptosis in SAP-associated macrophages. This synergistic suppression of pro-inflammatory mediator release significantly ameliorates SAP pathology and inflammatory progression[121]. Together, these collective findings demonstrated that PANoptosis induced by nanoengineering exhibits distinct therapeutic potential for diverse diseases, with a marked advantage particularly in the context of enhanced anti-tumor efficacy.

Combination therapy

Combination therapies have shown superior efficacy over monotherapies in various diseases. Cisplatin, as a foundational chemotherapeutic agent, promotes tumor cell apoptosis and pyroptosis. When combined with berberine (BBR) in ovarian cancer cells, this regimen synergistically enhances caspase-8 activation by concurrently upregulating extrinsic apoptosis and necroptosis effector proteins[122]. CDK1 governs ZBP1-dependent PANoptosis regulation in ACC. Mitotane and the CDK1 inhibitor, cucurbitacin E (CurE), combined therapy effectively eliminates ACC tumors, providing novel molecular targets and translational strategies for precision combination therapy[113]. Furthermore, clinical antibiotic overuse fuels the emergence of drug-resistant strains, severely compromising treatment efficacy. Chlorogenic acid (CGA), the active component of Yinhua Pingwei granules, exerts dual antioxidant and anti-inflammatory effects. By suppressing inflammatory mediators, ROS, and PANoptosis-associated proteins, CGA mitigates macrophage damage induced by cefotaxime-resistant *E. coli* infection[123]. This study substantiated the synergistic benefit of "antibiotic-natural product" combination therapy against resistant infections and clinical outcome improvement.

Similarly, combining nanotechnology with photodynamic therapy (PDT) has emerged as a novel approach to induce potent cell death. The aggregation-induced emission (AIE)-based photosensitizer, T-T, exhibits precise mitochondrial targeting capability and potent ROS generation capacity, concurrently inducing PANoptosis and ferroptosis. This dual cell death mechanism significantly enhances PDT efficacy. The integration of nanotechnology with PDT establishes a novel paradigm to overcome limitations of single-pathway targeted PDT[124].

Oncolytic virotherapy represents a promising anti-cancer strategy. Vesicular stomatitis virus-S (VSV-S) induces PANoptosis in head and neck squamous cell carcinoma (HNSCC) through caspase-1/GSDMD signaling, while concomitantly downregulating PD-L1 expression. VSV-S exhibits superior synergistic tumor control compared to monotherapies when combined with anti-PD-1 blockade, thereby establishing this combination approach as a novel therapeutic paradigm for HNSCC[125]. Oncolytic herpes simplex virus (oHSV) induces ZBP1-mediated PANoptosis, while *Fusobacterium nucleatum*-derived outer membrane vesicle (Fn-OMV) upregulates the expression of GSDMD/E and MLKL by disrupting the ubiquitination process. This combination therapy reprograms the immunosuppressive TME and exhibits a robust synergistic anti-tumor immune effect[126]. Combination therapeutic strategies overcome the limitations of monotherapies through synergistic effects across multiple pathways, establishing novel paradigms for refractory diseases.

In summary, as an emerging frontier, in-depth investigation into PANoptosome-associated genes and key protein regulation will yield additional relevant molecular targets to facilitate precision therapeutics for diverse conditions, including inflammation-associated diseases and malignancies.

Clinical translation of PANoptosis in disease therapy

In recent years several small-molecule inhibitors capable of directly modulating PANoptosis and implicated in the pathogenesis of various diseases have advanced into clinical trials. Pre-clinical studies have demonstrated that tetracyclines confer anti-inflammatory properties by directly inhibiting caspase-1 for ARDS, thereby blocking the inflammasome-caspase-1 pathway. A related clinical trial is currently underway (NCT04079426)[18,117].

In the context of COVID-19 treatment, one clinical trial (NCT04492475) evaluated the efficacy of IFN-β-1a in combination with remdesivir versus remdesivir monotherapy in hospitalized COVID-19 patients. The results indicated that the combination therapy was not superior to monotherapy and patients receiving IFN-β-1a exhibited worse outcomes compared to the placebo group[127]. Conversely, another trial (NCT04385095) demonstrated that the nebulized recombinant IFN-β formulation SNG001 was effectively delivered to infected sites. Patients receiving SNG001 showed better tolerance and superior therapeutic responses relative to those receiving placebo[128].

Notably, Ventyx Biosciences reported positive outcomes for VTX3232, a novel central nervous system penetrant NLRP3 inhibitor, in early-stage PD patients (NCT06556173) in 2025. The compound exhibited favorable pharmacokinetics, was safe, and well-tolerated over 28 d of treatment, and significantly reduced levels of NLRP3 inhibition-related biomarkers, thereby attenuating neuroinflammatory responses.

Concurrently, RIPK1 inhibitors are being explored across autoimmune disorders, cancers, infections, and neurologic diseases. For example, SAR443122 is under investigation for cutaneous lupus erythematosus [CLE] (NCT04781816) and is currently in phase II trials. Two clinical trials (NCT03757325 and NCT03757351) evaluating DNL747 in AD and ALS have progressed to the Ib stage[129]. To date, only GSK3145095, a kinase-specific RIPK1 inhibitor, has been investigated in oncology. A trial assessing GSK3145095 efficacy alone or in combination with pembrolizumab in pancreatic ductal adenocarcinoma (PDAC) (NCT03681951) was terminated following internal review[130]. Furthermore, as indicated on ClinicalTrials.gov, studies numbered NCT05237284, NCT05570006, and NCT05848258 have all entered phase II.

Although small-molecule inhibitors targeting PANoptosis show clinical potential, clinical translation faces severe challenges with the core bottlenecks being signal pathway redundancy and inflammatory toxicity. The extensive molecular crosstalk and shared components of PANoptosis endow cells with robust compensatory capabilities. When a single death branch (e.g., pyroptosis) is pharmacologically inhibited, cells can rapidly switch to apoptosis or necroptosis *via* "fail-safe" mechanisms. This pathway redundancy causes single-target inhibitors to be highly susceptible to resistance or failure in clinical applications. In contrast, the robust activation of PANoptosis is accompanied by the explosive release of DAMPs and cytokines. Lacking precise tissue selectivity, systemic administration can trigger severe off-target toxicity and cytokine storms, severely narrowing the safe therapeutic window of the drugs.

Clinical application requires balancing the pro-death and anti-inflammatory effects to avoid treatment-related adverse effects, such as tissue fibrosis. To overcome these challenges, combination therapeutic strategies can be used, such as co-administering ICIs with PANoptosis inducers to synergistically enhance anti-cancer efficacy. Furthermore, future translational research urgently needs to focus on developing multi-target modulators directed at upstream PANoptosome sensors to overcome network redundancy. This research should be deeply integrated with nanomedicine delivery systems to achieve local, precise intervention of PANoptosis through site-specific targeting. Building on this research, leveraging multi-omics integration and interdisciplinary collaboration with artificial intelligence (AI) predictive modeling, holds promise for identifying more effective inhibitors. This approach maximizes the reduction of systemic adverse reactions, while ensuring efficacy and substantially advancing clinical translation and precision medicine (**Table 1**).

Table 1 Clinical trials modulating PANoptosis in diverse diseases

Clinical trial ID	Drug	Target/mechanism	Disease	Phase
NCT04079426	Tetracycline	Inhibited inflammasome–caspase-1 pathway	ARDS	NA
NCT04492475	IFN-β-1a + remdesivir/ remdesivir	Activated the JAK/STAT1/IRF1 inflammatory axis, leading to the activation of caspase-8/FADD and triggering PANoptosis	COVID-19	Phase 3
NCT04385095	SNG001	Activated caspase-8/FADD and triggered PANoptosis	COVID-19	Phase 2
NCT06556173	VTX3232	Inhibited the expression of NLRP3	PD	Phase 2
NCT04781816	SAR443122	Inhibited the expression of RIPK1	CLE	Phase 2
NCT03757325	DNL747	Inhibited the expression of RIPK1	AD	Phase 1
NCT03757351	DNL747	Inhibited the expression of RIPK1	ALS	Phase 1
NCT03681951	GSK3145095/GSK3145095 + pembrolizumab	Inhibited the expression of RIPK1	PDAC	Phase 2
NCT05237284	SAR443820	Inhibited the expression of RIPK1	ALS	Phase 2
NCT05570006	ABBV-668	Inhibited the expression of RIPK1	UC	Phase 2
NCT05848258	LY3871801	Inhibited the expression of RIPK1	RA	Phase 2

ARDS, acute respiratory distress syndrome; IFN-β-1a, interferon beta-1a; JAK/STAT1/IRF1, Janus kinase/signal transducer and activator of transcription 1/interferon regulatory factor 1; FADD, Fas-associated death domain protein; NLRP3, NLR family pyrin domain containing 3; PD, Parkinson's disease; CLE, cutaneous lupus erythematosus; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; PDAC, pancreatic ductal adenocarcinoma; UC, ulcerative colitis; RA, rheumatoid arthritis; RIPK1, receptor-interacting protein kinase 1.

Summary and prospect

The theoretical significance of PANoptosis as a 'super-complex' that integrates multiple modes of cell death lies in the fundamental departure from the traditional linear paradigm of independent pathways. By assembling sensors, adapters, and effectors from apoptosis, pyroptosis, and necroptosis into a unified PANoptosome platform, cells can execute multiple death programs in a coordinated manner in response to complex pathologic stresses. This integrative mechanism not only explains why single-pathway inhibitors are often ineffective in treating many diseases but also reveals a higher-order regulatory network that governs cell fate. In conditions, such as sepsis, SARS-CoV-2 infection, and cancer, viewing PANoptosis as a 'super-complex' that has malfunctioned provides deeper insights into disease pathogenesis and opens up new avenues for therapeutic intervention, from small-molecule PANoptosome modulators-to-nanotechnology-based delivery systems, paving the way for next-generation precision medicine.

Although PANoptosis has demonstrated considerable promise in the treatment of various diseases, several challenges remain. For example, the precise molecular mechanisms governing PANoptosis have not been fully elucidated. Deeper investigation into these processes may reveal potential therapeutic targets within the PANoptosome complex, thereby paving the way for the development of PANoptosis modulators. Another research priority is the development of effective targeted drugs for PANoptosis. Although several compounds have shown potential in inhibiting PANoptosis, the exact mechanisms of action need further clarification and the efficacy and safety profiles require additional validation in clinical settings. It is recognized that integrating PANoptosis-targeting strategies with nanomedicine and expanding the application to the treatment of other diseases may substantially improve clinical outcomes. Furthermore, combination therapies that merge PANoptosis-targeting approaches with existing treatment modalities have overcome the limitations of monotherapies, demonstrated superior efficacy, and opened new avenues for PANoptosis-based treatments.

Currently, there is no well-established methodology for detecting PANoptosis and the lack of specific biomarkers and effective therapeutic targets significantly hinders clinical translation. Therefore, future research on targeted modulation of PANoptosis should focus on improving detection techniques, developing highly sensitive and spatiotemporally resolved platforms for multi-component PANoptosome analysis, and identifying more specific diagnostic biomarkers and novel targets. Moreover, integrating advanced technologies, such as bioinformatics, proteomics, and single-cell transcriptomics, will facilitate the discovery of more specific biomarkers, thereby enhancing clinical decision-making and promoting the role of PANoptosis in personalized medicine. Stratifying patients based on responses to PANoptosis-targeted therapies will enable tailored treatment strategies and pave the way for precision-targeted interventions.

In summary, to fully exploit the therapeutic potential of PANoptosis, future efforts should integrate fundamental research with clinical applications, promoting investigations into nanomedicine, multi-omics technologies, and combination therapies within PANoptosis-targeted treatment paradigms to develop more effective therapeutic approaches and modalities.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Writing – review & editing, Writing – original draft, Visualization: Yi Zhu, Shengming Ou, Xuer Ye.
Writing – review & editing: Juncheng Li.
Writing – review & editing, Visualization: Xiaoya Nie.
Writing – review & editing, Supervision, Conceptualization: Jinrong Zhu, Rongxin Zhang, Hongwei Shao.

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