

PANoptosis as a Potential Therapeutic Target in Drug-Induced Liver Injury: A Narrative Review

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Abstract: PANoptosis is a recently characterized form of programmed cell death defined by the coordinated regulation of pyroptosis, apoptosis, and necroptosis mediated by the multi-protein PANoptosome complex, a phenomenon that cannot be fully explained by any individual pathway. The initiation of PANoptosis relies on the assembly and activation of the PANoptosome, a process that has been closely linked to the onset and progression of multiple disorders, including inflammatory and neurodegenerative diseases, cancer, and pulmonary conditions. However, the contribution of PANoptosis to drug-induced liver injury (DILI) has not been thoroughly evaluated. DILI is a frequently encountered clinical adverse drug reaction, and its development is strongly associated with hepatocyte death. Therefore, this review aims to summarize the molecular mechanisms underlying PANoptosis and the assembly of the PANoptosome complex, elucidate the interactions among apoptosis, necroptosis, and pyroptosis, and assess the potential involvement of PANoptosis in DILI. Furthermore, investigating natural products that inhibit PANoptosome assembly or target key regulators such as ZBP1, AIM2, and NLRP3 to modulate PANoptosis may offer promising therapeutic opportunities for the management of DILI.

Keywords: drug-induced liver injury, PANoptosis, PANoptosome, therapeutic targets

Introduction

Programmed cell death is essential for maintaining organismal homeostasis and defending against pathogenic infections, and its dysregulation is closely linked to the onset and progression of infectious diseases, cancer, and organ injury. According to the international standards established by the Nomenclature Committee on Cell Death (NCCD), programmed cell death can be categorized into several types based on morphological, biochemical, and functional features, including intrinsic and extrinsic apoptosis, necroptosis, ferroptosis, and pyroptosis.¹ In recent years, PANoptosis has emerged as a novel pro-inflammatory form of programmed cell death, characterized by the PANoptosome-mediated coordination of pyroptosis, apoptosis, and necroptosis.² Increasing evidence indicates that Z-DNA-binding protein 1 (ZBP1) functions as a key molecular sensor that initiates inflammasome activation and drives PANoptosis.³ Nearly all pathological processes of PANoptosis depend on the assembly of the PANoptosome, as it integrates diverse cell-death signals and detects danger cues, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).

PANoptosis is closely linked to the pathogenesis and progression of a wide range of diseases, including infectious, inflammatory, neurological, neoplastic, and pulmonary disorders.⁴⁻⁶ It also plays a significant role in liver diseases.^{7,8} Drug-induced liver injury (DILI) refers to hepatic damage caused by a wide range of over-the-counter and prescription medications, including herbal products, dietary supplements, anti-infective agents, nonsteroidal anti-inflammatory drugs, and chemotherapeutic agents.^{9,10} A two-year, population-based prospective study conducted in Iceland reported an incidence of 19.1 cases per 100,000 inhabitants,¹¹ whereas a retrospective study from mainland China documented an annual incidence of 23.80 cases per 100,000 individuals—higher than that reported in Iceland, France, and other Western

countries.¹² Diagnosing DILI remains challenging due to the lack of specific biomarkers, resulting in substantial underdiagnosis and misdiagnosis, as differentiation from other liver diseases often relies on exclusion.^{13–15} Moreover, some primary diseases requiring pharmacological treatment may themselves induce hepatic dysfunction, further complicating causal inference.¹⁴ Hepatocyte death is one of the defining features of DILI. The underlying mechanisms involve well-characterized forms of cell death, including apoptosis, necroptosis, autophagy, and necrosis, as well as more recently identified processes such as inflammatory cell death and ferroptosis.¹⁶ The specific cell death subroutine activated largely depends on the primary drug.¹⁷ However, in certain cases, targeting a single pathway of pyroptosis, apoptosis, or necroptosis fails to ameliorate DILI.^{18–20} Given the pivotal roles of apoptosis, necroptosis, and pyroptosis in DILI, we propose that PANoptosis is critically involved in the onset and progression of this condition. Nevertheless, the molecular mechanisms regulating PANoptosis in DILI remain poorly understood. Accordingly, this review summarizes the mechanisms and recent advances related to PANoptosis, highlights the distinctions and interconnections among these three forms of programmed cell death, and discusses the role of PANoptosis in DILI and potential therapeutic targets, thereby providing new strategies and theoretical frameworks for targeted intervention.

Apoptosis

Apoptosis is a normal biological process within organisms and is commonly referred to as programmed cell death. It constitutes a critical component of cellular self-regulation, guiding cells toward an orchestrated form of death through the activation of defined signaling pathways. Mechanistically, the release of cytochrome c from mitochondria initiates two primary downstream pathways: the intrinsic (mitochondrial) pathway and the extrinsic (death receptor-mediated) pathway (Figure 1).

The intrinsic pathway is triggered by diverse intracellular stressors—such as DNA damage, nutrient deprivation, cytosolic Ca^{2+} overload, reactive oxygen species (ROS), and the accumulation of misfolded or unfolded proteins,²¹ and is tightly regulated by pro- and anti-apoptotic members of the Bcl-2 family.^{22,23} As a central organelle responsible for cellular energy production, mitochondria play a pivotal role in maintaining intracellular homeostasis and are major targets of oxidative stress.²⁴ Bcl-2 family proteins localize to the outer mitochondrial membrane, where they modulate membrane permeability, thereby governing cytochrome c release and subsequent activation of the caspase cascade.^{25,26} Upon release into the cytosol, cytochrome c associates with the C-terminal WD-40 domains of Apaf-1 in an ATP/dATP-dependent manner to assemble the apoptosome, which facilitates the homotypic interaction and autoactivation of pro-caspase-9,²⁷ ultimately activating downstream caspase-3/7 to execute apoptosis.²⁸ Mitochondrial stress, such as the accumulation of misfolded proteins, can further disrupt membrane permeability, leading to excessive ATP depletion, increased production of ROS, and perturbations in calcium homeostasis.²⁹ Elevated mitochondrial calcium exacerbates oxidative stress and facilitates cytochrome c release, while aberrant calcium signaling may induce endoplasmic reticulum stress, activate calpains, and initiate caspase-dependent apoptosis.²¹

In the extrinsic pathway, ligand engagement with death receptors—including TNFR, FAS (CD95), DR3, and TRAIL-R1/R2—recruits adaptor proteins such as FADD, thereby activating caspase-8, which in turn cleaves and activates downstream caspase-3/7 to execute apoptotic signaling.³⁰

Necroptosis

Necroptosis is a recently defined form of regulated cell death. RIPK1 and RIPK3 function as key regulators of both apoptosis and necroptosis. Activated caspase-8 degrades RIPK1 and RIPK3, which suppresses the necroptotic signaling pathway and promotes apoptosis.^{31,32} When caspase-8 activity is inhibited, RIPK1 recruits and phosphorylates RIPK3, resulting in its activation and oligomerization and ultimately leading to the formation of the necrosome.^{33–35} In addition to RIPK1 and RIPK3, the mixed lineage kinase domain-like protein MLKL also participates in necroptosis, and phosphorylation of RIPK3 at Ser 232 enhances the recruitment of MLKL.³⁶ RIPK3 subsequently recruits and phosphorylates MLKL, promoting its oligomerization and conformational changes that enable its translocation to the plasma membrane, where it increases membrane permeability and initiates inflammatory responses.^{37,38}

ROS are key mediators of necroptosis and enhance TNF α -induced necroptosis by activating RIPK1 and RIPK3 through promoting RIPK1 autophosphorylation at the S161 site.^{39,40} However, the functional role of ROS in necroptosis remains a subject of debate. Studies have shown that mitochondrial depletion suppresses TNF-induced ROS production

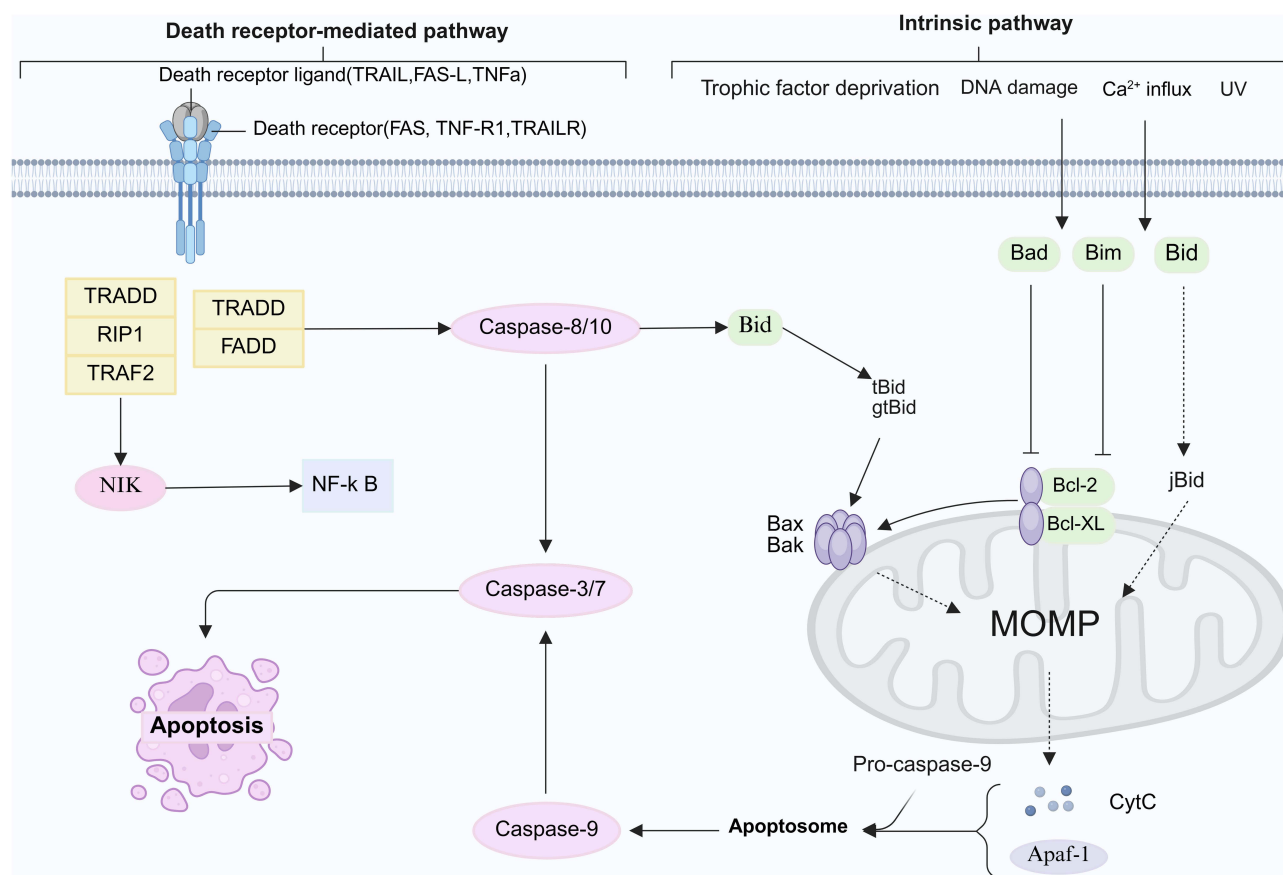


Figure 1 Apoptosis pathway. The apoptosis pathway comprises both the intrinsic and extrinsic pathways. In the intrinsic pathway, cellular stressors such as DNA damage, hypoxia, elevated cytosolic Ca²⁺ levels, or metabolic stress initiate the translocation and oligomerization of Bax and Bak in the mitochondrial outer membrane. This process forms membrane pores that enable the release of pro-apoptotic factors—such as cytochrome c, Smac, and endonuclease G—from the mitochondrial intermembrane space. Cytochrome c subsequently binds to the scaffold protein Apaf-1, inducing conformational changes that drive the formation of a seven-spoked apoptosome. The apoptosome subsequently recruits and activates pro-caspase-9, which then triggers the activation of downstream effector caspases to execute apoptosis. In the extrinsic pathway, engagement of death receptors—including TNFR, FAS (CD95), DR3, and TRAIL-R1/R2—by their respective ligands recruits adaptor proteins such as FADD, ultimately resulting in effector caspase activation and the induction of apoptotic cell death. By BioRender (<https://BioRender.com/y09b871>).

but does not alter the progression of necroptosis.⁴¹ Furthermore, even when mitochondria are impaired, activated RIPK3 can still induce necroptosis independently of ROS.⁴¹ These findings underscore the need for further study of the interactions and underlying mechanisms involving ROS and RIPKs across various cell death pathways. In addition, pattern recognition receptor-mediated necroptosis represents an important mode of cell death, and Toll-like receptors together with ZBP1 function as essential mediators in this process. TLR3 recognizes viral double-stranded RNA and TLR4 recognizes lipopolysaccharide, and upon activation, both receptors recruit TRIF and interact with RIPK3 to initiate necroptosis (Figure 2).⁴² Overall, the induction and regulation of necroptosis constitute highly complex processes that depend on the coordinated activities of multiple signaling molecules.

Pyroptosis

Pyroptosis is an inflammatory form of programmed cell death that was initially recognized to eliminate intracellular pathogens through caspase-1 activation, which promotes plasma membrane pore formation and results in membrane rupture or lysis.⁴³ Recent studies have shown that in addition to caspase-1, other cysteine proteases, including caspase-4, caspase-5, caspase-12, caspase-11 in mice, and caspase-8, also participate in this process.^{44,45} Activated inflammatory caspases cleave Gasdermin D (GSDMD) and release it from its inhibitory state. The activated GSDMD subsequently translocates to the plasma membrane, binds to phospholipids, and initiates pore formation, which disrupts membrane integrity, causes cytoplasmic swelling, and promotes the release of intracellular contents, ultimately leading to cell death.^{45–47}

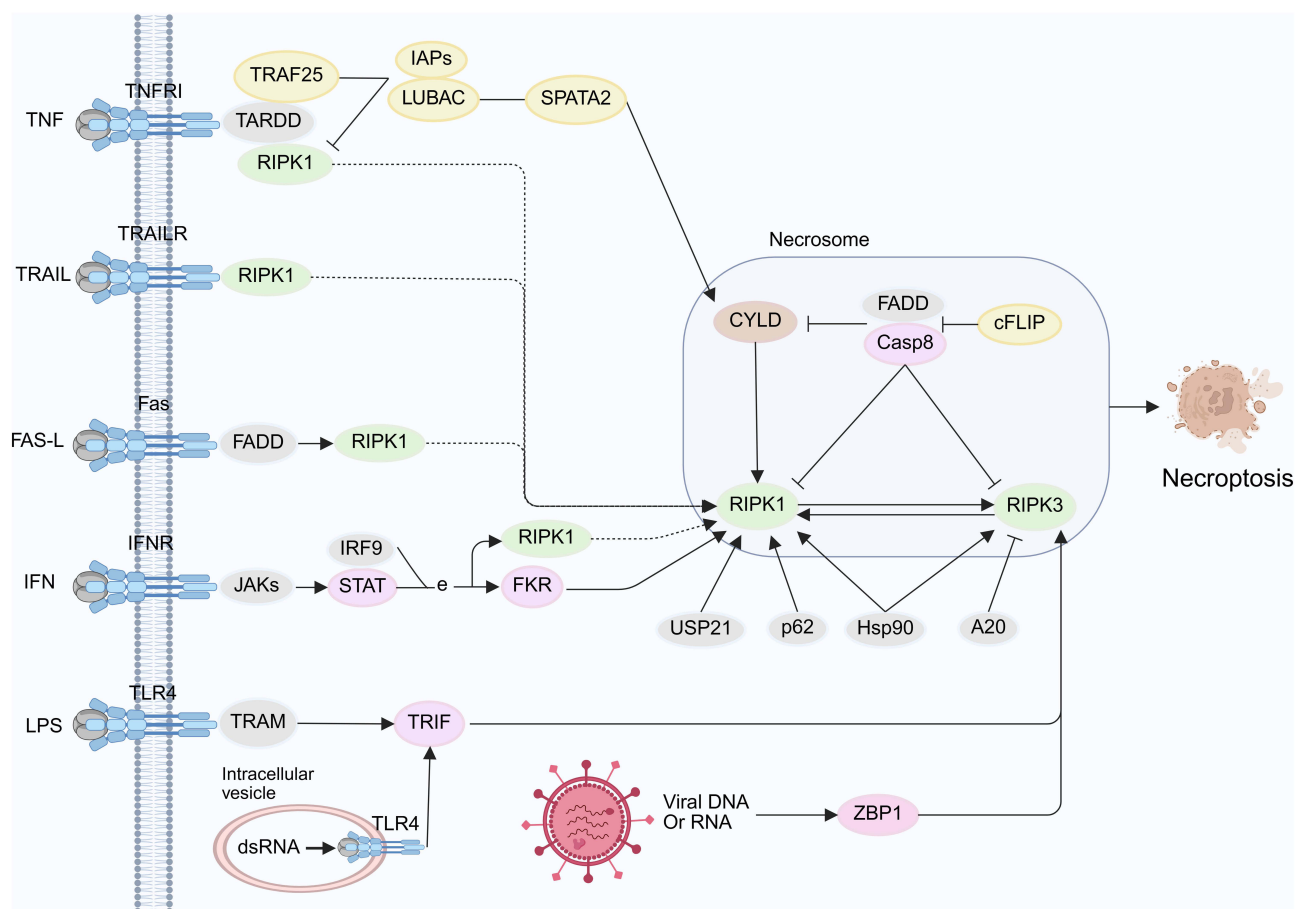


Figure 2 Necroptosis pathway. The necroptotic pathway is initiated upon activation of TNFR1 by TNF α . Activation of additional cellular receptors can also induce necroptosis, including death receptors such as Fas, Toll-like receptors such as TLR4, tumor necrosis factor-related apoptosis-inducing ligand receptors such as TRAIL-R, and interferon receptors such as IFNR. Downstream of these receptors, activated RIPK1 is recruited into a complex that includes FADD, caspase-8, and caspase-10. In the absence of caspase-8 activity, RIPK1 recruits and phosphorylates RIPK3, which leads to the formation of the necrosome. By BioRender (<https://BioRender.com/n56j719>).

Inflammasomes, such as absent in melanoma 2 (AIM2) and NLR family pyrin domain containing 3 (NLRP3), can activate caspase-8 and caspase-1, thereby inducing apoptosis and promoting the classical pyroptotic pathway.⁴⁸ In contrast, the non-classical pathway occurs when cytosolic lipopolysaccharide forms an inflammasome complex that activates caspase-4, caspase-5, and caspase-11, which induce pyroptosis through GSDMD cleavage (Figure 3).⁴⁹ Activation of caspase-1 under non-classical stimulation requires NLRP3 and apoptosis-associated speck-like protein containing a CARD (ASC), whereas caspase-11-mediated activation and the resulting cell death proceed independently of these components.⁵⁰ As research progresses, additional insights into the roles and interactions of caspases in pyroptosis are anticipated.

PANoptosis

PANoptosis is a recently identified form of programmed cell death that integrates the defining features of pyroptosis, apoptosis and necroptosis, and the cell death processes mediated by these pathways are not completely independent. A study conducted in 2016 first reported the simultaneous activation of these three forms of cell death in macrophages infected with influenza A virus, demonstrating close molecular interactions among the different programmed cell death pathways.⁵¹ Current research in this field mainly centers on pathogen infection models, where the core regulatory mechanism involves a multiprotein complex termed the PANoptosome. This complex plays a central role in recognizing danger signals, including DAMPs and PAMPs, and in initiating the cell death process.^{52–55} The molecular composition of the PANoptosome displays substantial plasticity, with its components changing in response to different activating signals

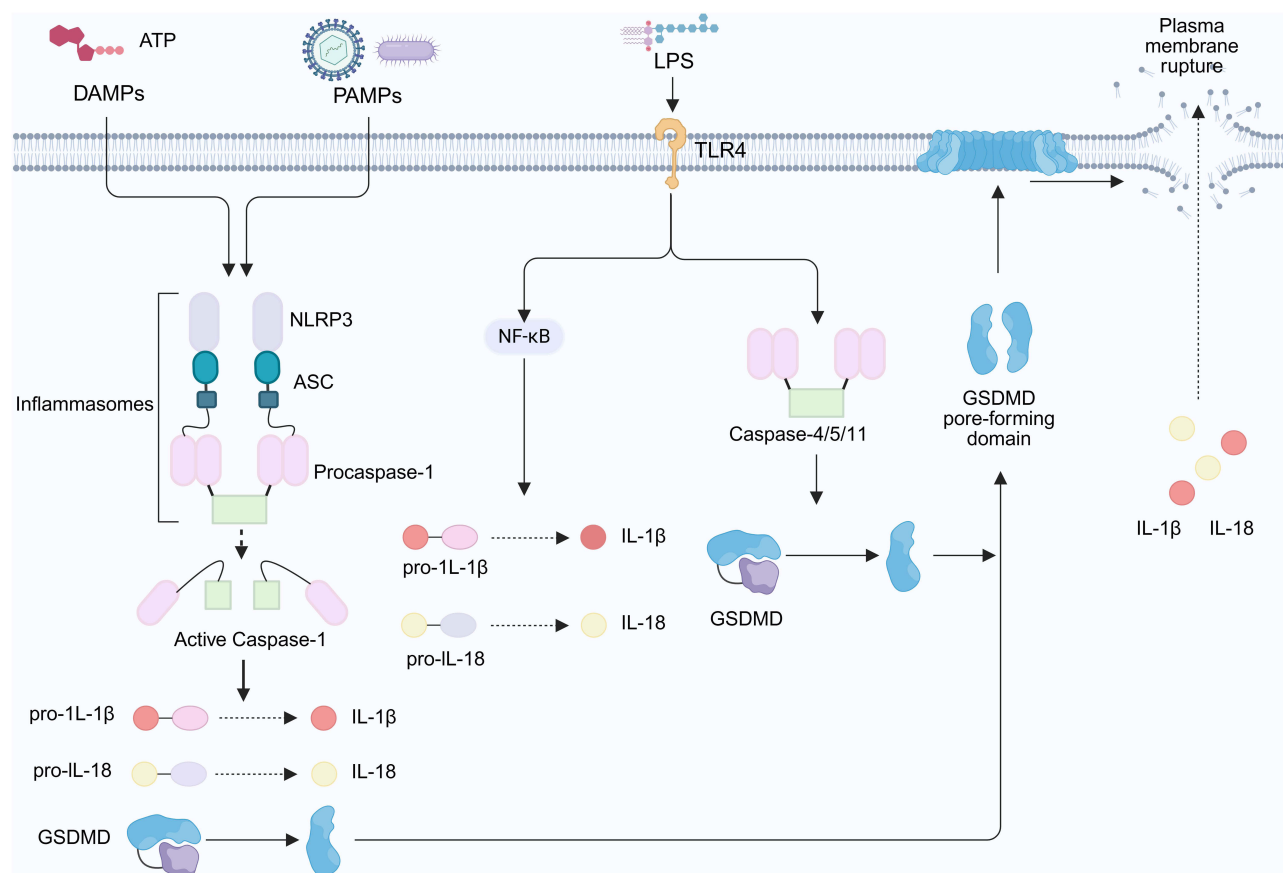


Figure 3 Pyroptosis pathway. DAMPs and PAMPs activate inflammasomes, such as AIM2 and NLRP3, which initiate the classical pyroptotic pathway through the activation of caspase-8 and caspase-1. In the non-classical pathway, cytosolic lipopolysaccharide forms an inflammasome complex that activates caspase-4, caspase-5, and caspase-11. These enzymes induce pyroptosis by cleaving GSDMD and generating its activated form, which subsequently translocates to the plasma membrane, associates with phospholipids, and initiates pore formation. This series of events compromises membrane integrity, induces cytoplasmic swelling, and promotes the release of intracellular contents, ultimately resulting in cell death. By BioRender (<https://BioRender.com/h37i302>).

and comprising cytosolic innate immune sensors such as ZBP1, AIM2, RIPK3, RIPK1, ASC, FADD, members of the caspase family, and key effector molecules that execute pyroptosis, apoptosis, and necroptosis.^{53,54,56,57} Activation of these sensor molecules induces inflammatory responses and regulated forms of cell death, including apoptosis, inflammatory cell death, necroptosis, and PANoptosis (Figure 4).⁵⁸

In recent years, several PANoptosome complexes have been identified, among which the ZBP1 PANoptosome is considered the most representative. Following activation by influenza A virus, ZBP1 interacts with RIPK1 to form the ZBP1 RIPK1 complex, which subsequently promotes the assembly of the ZBP1 PANoptosome composed of ZBP1, RIPK3, RIPK1, FADD, and caspase-8.^{59,60} The formation of this complex initiates downstream molecular events, including the activation of GSDMD and GSDME, which promotes the secretion of IL-1β and IL-18, and the activation of caspase-3/7 and the MLKL pathway.^{58,59} These events collectively induce pyroptosis, apoptosis, and necroptosis, ultimately resulting in the execution of PANoptosis (Figure 4).^{58,59} Wang et al developed an expansion microscopy approach that enables visualization of the spatial organization of ASC, caspase-8, and RIPK3 within the PANoptosome. This optimized protocol exhibits broad applicability because it validates PANoptosome assembly at the single-cell level and facilitates the study of other multiprotein complexes and cell death inducers, indicating considerable potential for future research.⁶¹ To date, the molecular features of AIM2, RIPK1, and NLRP12 associated PANoptosomes have also been elucidated (Figure 4).^{53,54,57} In summary, the concept of PANoptosis is expected to continue expanding and advancing with ongoing scientific investigation. In the following sections, we outline the distinctions and interrelationships among PANoptosis, apoptosis, necroptosis, and pyroptosis.

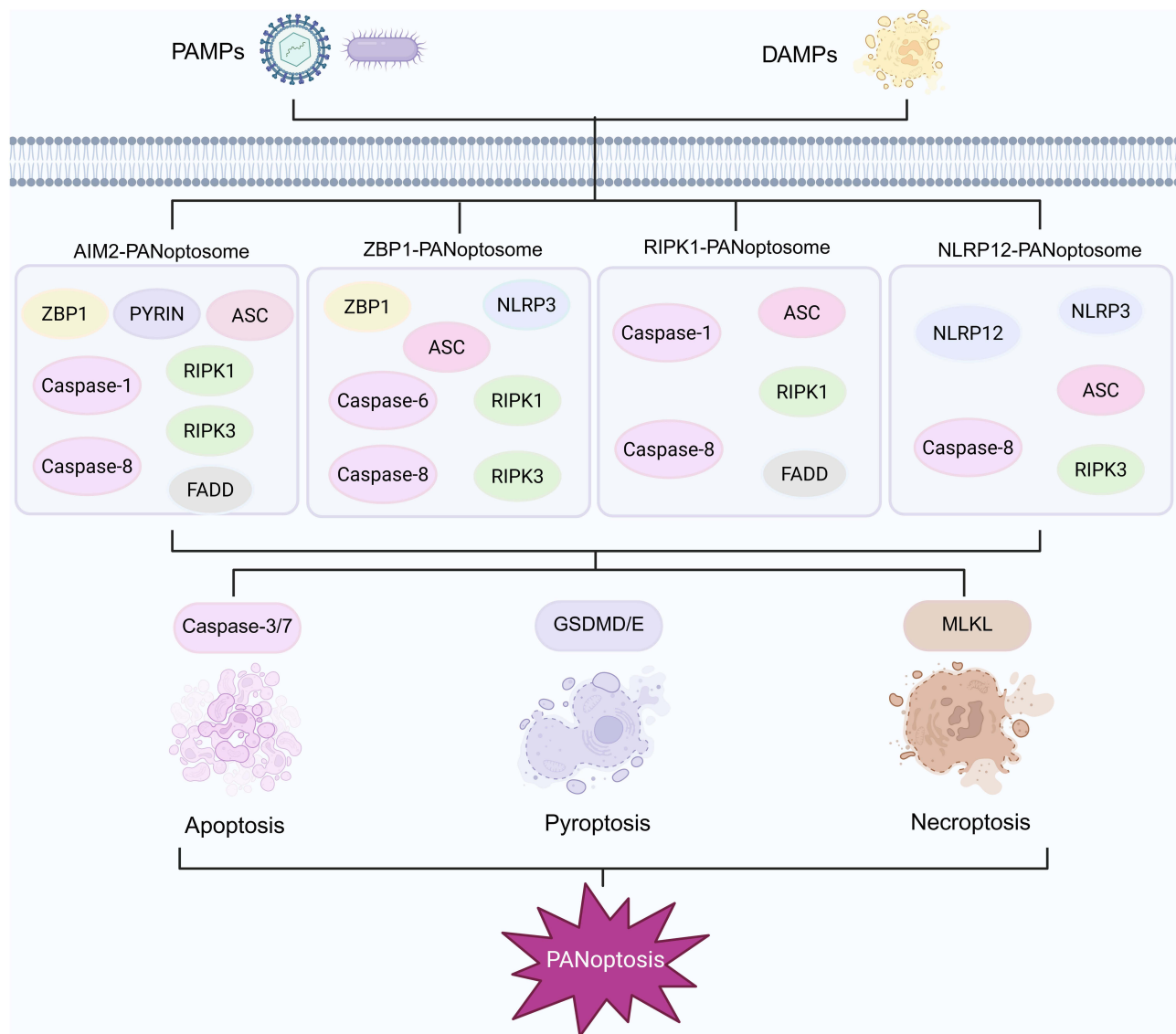


Figure 4 Assembly of different PANoptosome complexes. Upon activation by PAMPs or DAMPs, sensor proteins interact with adaptor proteins to form specific PANoptosome complexes, such as the AIM2 PANoptosome composed of ZBP1, PYRIN, ASC, caspase-1, caspase-8, RIPK1, RIPK3, and FADD, the ZBP1 PANoptosome consisting of ZBP1, NLRP3, ASC, caspase-6, caspase-8, RIPK1 and RIPK3, the RIPK1 PANoptosome containing RIPK1, caspase-1, caspase-8, ASC and FADD, and the NLRP12 PANoptosome comprising NLRP12, NLRP3, ASC, caspase-8 and RIPK3. These complexes integrate the essential signaling pathways that mediate apoptosis, pyroptosis, and necroptosis. Caspase-1 activates GSDMD or GSDME to initiate pyroptosis, while RIPK3 interacts with MLKL to promote necroptosis. In addition, caspase-8, together with caspase-3 or caspase-7, mediates apoptosis, and the integration of these pathways culminates in the coordinated cell death modality termed PANoptosis. By BioRender (<https://BioRender.com/yks3w20>).

The Interactions Between Apoptosis, Necroptosis, and Pyroptosis

ZBP1 has been identified as a sensor of double-stranded DNA and functions as both a key initiator of innate immune responses and a central regulatory hub within the PANoptosis signaling network. Its mechanism of action involves the recognition of the NP and PB1 proteins of influenza A virus and the Z nucleic acids produced during viral replication, thereby initiating downstream signaling cascades.^{51,62} This recognition event primarily activates the RIPK1-RIPK3-caspase-8 axis, which mediates both cell death and inflammatory responses. Through the regulation of RIPK3, caspase-8, and the NLRP3 inflammasome, this pathway concurrently induces pyroptosis, necroptosis, and apoptosis and enhances inflammatory responses.^{51,63} The Za2 domain of ZBP1 is critical for inflammasome assembly and for initiating PANoptosis.³ Evidence from influenza A virus infection models indicates that deletion of the Za2 domain abolishes influenza A virus-induced PANoptosis and activation of the NLRP3 inflammasome.⁶³ In these models, interferon

regulatory factor one functions as an upstream regulatory element. It promotes PANoptosome activation by transcriptionally regulating the expression of key molecules, including ZBP1, AIM2, RIPK1, and NLRP12.^{64,65} Loss of interferon regulatory factor one markedly reduces ZBP1 expression, suppresses activation of the NLRP3 inflammasome, diminishes the execution of apoptosis and necroptosis, and ultimately compromises viral clearance.⁶⁴

The ZBP1 PANoptosome complex is composed of the sensor molecules ZBP1, NLRP3, caspase-8, caspase-6, ASC, RIPK1, and RIPK3.^{52,56,66} Its assembly is linked to the activation of TNFR or TLR4 signaling and the suppression of MAPK and NF-kappa-B pathways. Notably, ZBP1 interacts with the NLRP3 inflammasome to form the ZBP1 NLRP3 complex, which functions as a central structural unit essential for PANoptosome assembly.⁶² Additional evidence indicates that ASC, caspase-8, and RIPK1 colocalize in a ZBP1-dependent manner during PANoptosis.⁶¹ Moreover, the lack of ASC speck formation in ZBP1-deficient cells underscores the essential role of ZBP1 in this process.⁶¹ AIM2 acts as a cytosolic sensor of double-stranded DNA originating from pathogens or damaged organelles. By recruiting ASC and caspase-1 to assemble the AIM2 inflammasome, AIM2 activates caspase-1 and triggers inflammatory responses through cytokine maturation and pyroptosis.⁶⁷ Activation of AIM2 and NLRP3 promotes the formation of a shared cytosolic inflammasome platform that contains the adaptor ASC along with caspase-1 and caspase-8, thereby establishing a dual cytosolic surveillance system.⁶⁸ AIM2 also modulates the innate immune sensors Pyrin and ZBP1 to promote inflammatory signaling and PANoptosis.⁵³ AIM2, Pyrin, and ZBP1 interact with ASC to form a multiprotein complex that includes ASC, caspase-1, caspase-8, RIPK3, RIPK1, and FADD, which collectively mediate inflammatory cell death (Figure 4).⁵³ Activation of this cooperative cell death mechanism depends on both the direct detection of viral components and the sensing of cellular stress conditions, although the specific mechanisms and functions of AIM2 in PANoptosis have yet to be fully elucidated. Although the composition of PANoptosomes varies depending on the stimulus, all forms ultimately induce necroptosis, apoptosis, and pyroptosis.

The caspase family coordinates the crosstalk among apoptosis, pyroptosis, and necroptosis during PANoptosis. Initiator caspases, including caspase-2, caspase-8, caspase-9, and caspase-10, act as proteolytic signal amplifiers that activate effector caspases, while effector caspases such as caspase-3, caspase-6, and caspase-7 cleave specific cellular substrates to promote apoptosis.⁶⁹ Among these enzymes, caspase-8 serves as a molecular switch that regulates apoptosis, necroptosis, and pyroptosis.⁷⁰ Following viral infection, RIPK1 and caspase-8 are recruited to the retinoic acid-inducible gene I (RIG-I) signaling complex, where ubiquitination of RIPK1 promotes complex assembly and enhances phosphorylation of interferon regulatory factor 3 (IRF3).⁷¹ This modification also exposes the RIPK1 cleavage site, allowing caspase-8 to process it into an inhibitory fragment.⁷¹ Caspase-8 additionally suppresses type I interferon production by inhibiting the RIPK1-TBK1 axis, and its loss or functional impairment enhances RIPK1-TBK1 interaction, markedly elevates interferon levels, and exacerbates inflammatory injury.⁷² Enzymatically inactive caspase-8 induces embryonic lethality and inflammatory damage in mice by triggering necroptosis and pyroptosis, while activated caspase-8 mediates intrinsic apoptosis and cleaves GSDMD and GSDME to induce macrophage pyroptosis.^{73,74} Furthermore, the scaffold functions of caspase-8 and MLKL contribute to the regulation of NLRP3 inflammasome activation downstream of TLR3.⁷⁵ Caspase-1-mediated apoptosis proceeds through the Bid caspase-9/3 axis and may subsequently transition into GSDME-dependent secondary necrosis or pyroptosis.⁷⁶ Caspase-1 induces pyroptosis when GSDMD is present, yet in GSDMD-deficient cells, it promotes apoptosis by activating caspase-3/7.⁷⁷ Caspase-3 also cleaves GSDME to generate a pore-forming fragment that induces pyroptosis,⁷⁸ and restrains excessive cytokine production by processing cyclic GMP-AMP synthase (cGAS), mitochondrial antiviral signaling protein (MAVS), and IRF3.⁷⁹ Caspase-6 plays a central role in host defense against influenza A virus by promoting RHIM-dependent binding between RIPK3 and ZBP1, which leads to inflammasome activation and coordination of PANoptosis.⁵⁹ Additionally, apoptosis mediated by Bak and Bax promotes interferon production through mitochondrial DNA release and activation of the cGAS/STING pathway, while the caspase-9/3/7 cascade restricts interferon beta secretion by suppressing this pathway.⁸⁰ Collectively, apoptosis, pyroptosis, and necroptosis all depend on the activation of caspase family members, indicating that these cell death programs are interdependent rather than isolated processes.

RIPK1 is a central regulator of innate immune signaling, and its activation state governs TNF-mediated apoptosis, necroptosis, and inflammatory responses.⁸¹ RIPK1 undergoes post-translational regulation through ubiquitination, phosphorylation, and caspase-8-mediated cleavage.⁸² FADD and caspase-8 may cooperate to suppress RIPK1 by promoting

its cleavage and inactivation, thereby inhibiting RIPK1-mediated necroptosis.⁸³ In the absence of RIPK1, cells exhibit increased sensitivity to TNF-induced TNFR1-FADD-caspase-8-mediated apoptosis and to TLR ligation or interferon-induced RIPK3-dependent necrosis.⁸⁴ RIPK3 functions as a critical regulator of apoptosis and necroptosis and redirects TNF-triggered cell death from apoptosis to necroptosis in a kinase-dependent manner.⁸⁵ Therefore, RIPK1 and RIPK3 are essential mediators of PANoptosis and host defense. TAK1 functions as a regulatory switch that governs PANoptosome assembly. In the absence of TAK1, macrophages undergo spontaneous activation of the NLRP3 inflammasome, and RIPK1 recruits NLRP3 and ASC to form a death-inducing complex that activates the inflammasome, caspase-8, and GSDMD, thereby promoting pyroptosis and apoptosis.^{86,87} The RIPK1-mediated PANoptosome primarily consists of RIPK1, ASC, caspase-1, caspase-8, and FADD, and it was initially described by the Malireddi group.⁵⁷ Moreover, the RIPK3-MLKL pathway can be activated independently of RIPK1 kinase activity.^{85,88} Collectively, these mechanisms highlight the central roles of RIPKs in the regulation of PANoptosis and in the coordination of cell death and inflammatory processes.

Activation of the NLRP3 inflammasome and GSDMD-mediated pyroptosis plays a central role in regulating apoptosis and necroptosis. Both pyroptotic and necroptotic pathways can activate the NLRP3/IL-1 β signaling axis. During necroptosis, RIPK3-MLKL activates the NLRP3 inflammasome to induce caspase-1-mediated IL-1 β maturation, and the cytokine is released through membrane pores formed by GSDMD and MLKL, thereby establishing a positive inflammatory feedback loop.⁸⁹ The MLKL inhibitor necrosulfonamide targets GSDMD to suppress pyroptosis, highlighting the MLKL-GSDMD interaction as a critical regulatory node that links pyroptosis and necroptosis.⁹⁰ In addition, GSDMD disrupts mitochondrial membrane permeability, which enhances apoptosis-related caspase-3 activation and inflammasome signaling to promote cooperation between pyroptosis and apoptosis.⁹¹ Beyond the canonical NLRP3 inflammasome, the NLRC4 inflammasome also plays a significant role in PANoptosis. Upon sensing T3SS proteins, NAIP binds to NLRC4 to activate the NAIP-NLRC4 inflammasome, which subsequently activates caspase-1 and induces GSDMD-mediated pyroptosis.⁹² NLRC4 also activates caspase-8, which subsequently activates caspase-3/7 to trigger apoptosis.⁹² During *Pseudomonas aeruginosa* infection, MLKL-dependent cell death is enhanced in NLRC4-deficient cells, which promotes necroptosis, and inhibition of pyroptosis does not fully prevent cell death.⁹³ It is suggested that this pathogen induces PANoptosis and activates MLKL as a compensatory mechanism when inflammasome signaling is impaired. The sensor NLRP12 is associated with infectious and inflammatory diseases and interacts with cell death molecules to assemble a protein PANoptosome that promotes inflammatory cell death.⁵⁴ By coordinating a PANoptosome composed of ASC, NLRP3, caspase-8, and RIPK3, NLRP12 induces caspase-1, caspase-8, and RIPK3-dependent PANoptosis, thereby promoting inflammatory cell death (Figure 4).⁵⁴ Notably, during coronavirus infection, impaired NLRP3 inflammasome activation and reduced pyroptosis lead to pronounced inflammatory cell death mediated by caspase-8 and RIPK3.⁹⁴ Further studies are required to determine whether NLRP12-mediated cell death pathways operate in non-immune cells such as epithelial cells and to define the breadth of their biological functions.

Mitochondrial reactive oxygen species have long been recognized as essential signaling molecules in pyroptosis.⁹⁵ GSDMD rapidly disrupts the inner and outer mitochondrial membranes, leading to reduced mitochondrial abundance, increased mitophagy, and elevated ROS production. GSDMD-mediated mitochondrial permeabilization facilitates cytochrome c release and activates caspase-3, thereby establishing extensive crosstalk between pyroptosis and mitochondrial apoptosis.⁹¹ Furthermore, GSDMD pores formed on the mitochondrial membrane promote the release of mitochondrial reactive oxygen species, thereby shifting cell death toward RIPK1, RIPK3, and MLKL-dependent necroptosis.⁹⁶ These findings indicate that oxidative stress modulates mitochondrial membrane permeability and signal transduction to regulate the activation and interaction among pyroptosis, apoptosis, and necroptosis. As a key initiator of mitochondrial death pathways, oxidative stress has been shown to contribute to PANoptosis in models of hepatic and toxic injury. Excessive acetaminophen-induced liver injury stimulates mitochondrial reactive oxygen species production and mitochondrial DNA leakage, and mitochondrial DNA subsequently activates the TLR9 pathway to promote neutrophil extracellular trap formation, thereby inducing PANoptosis.⁹⁷ HDN attenuates deoxynivalenol-induced liver injury and associated PANoptosis by inhibiting mitochondrial damage mediated through the ROS-P53-PGC-1 α pathway and by reducing excessive mitochondrial reactive oxygen species production.⁹⁸ Similarly, oxidative stress triggered by SiO₂

exposure leads to mitochondrial dysfunction and mitochondrial DNA leakage, which activates ZBP1-mediated PANoptosis, whereas quercetin suppresses this process by modulating the Nrf2/ROS/Drp1 axis.⁹⁹

PANoptosis in Drug-Induced Liver Injury

Acetaminophen

Excessive administration of acetaminophen (APAP) can cause severe liver injury, and nearly half of DILI cases are associated with its use. Previous investigations have shown that APAP-induced hepatotoxicity is characterized by extensive hepatocellular necrosis and pronounced inflammatory responses. However, the specific mode of cell death triggered by APAP remains a subject of debate. Although a small number of studies have suggested the involvement of apoptosis, the absence of detectable caspase activation raises questions regarding whether APAP truly induces apoptotic cell death.¹⁰⁰

A recent study reported that APAP promotes caspase-1-mediated pyroptosis by activating the NLRP3 inflammasome. Mice with hepatocyte-specific deletion of NLRP3 exhibited reduced liver injury and lower mortality after APAP exposure, accompanied by diminished inflammatory cell infiltration and attenuated inflammatory responses. Pharmacological inhibition of NLRP3 or GSDMD using MCC950 or disulfiram substantially ameliorated liver injury and reduced hepatocyte death.¹⁰¹ Pyroptosis is characterized by activation of the NLRP3 inflammasome, which leads to the generation of caspase-1.¹⁰² However, several findings challenge the concept that APAP induces acute liver injury through pyroptosis. Treatment of C57BL/6 mice with a pan-caspase inhibitor to suppress caspase-1-mediated IL-1 β maturation during APAP overdose did not modify APAP-induced liver injury or neutrophil infiltration.¹⁰³ Moreover, genetic deletion of GSDMD or GSDME did not prevent APAP-induced liver injury.¹⁰⁴ Necroptosis, also known as receptor-interacting protein kinase-dependent necrosis, is regulated by RIPK1 and RIPK3. Although activation of RIPK1 and RIPK3 has been observed in APAP-induced liver injury and inhibition of either kinase attenuates liver injury,^{105–107} other studies show that deletion of RIPK3 or MLKL does not provide protection.¹⁰⁸ These observations suggest that MLKL is not required for APAP-induced acute liver injury.

Based on the available evidence, Dr. Hartmut Jaeschke proposed that APAP-induced hepatocyte death does not occur through apoptosis, pyroptosis, or necroptosis, and that morphological observations instead support a necrotic pattern of cell death.¹⁰⁰ However, recent studies indicate that hepatocellular injury induced by excessive APAP involves several forms of programmed cell death, including pyroptosis, apoptosis, and necroptosis.

Cells can die in multiple ways, but does it matter which way they die? The occurrence of PANoptosis may reflect the coordinated effects of various stimuli acting on the cell. Shi et al reported that the mode of cell death is determined by three major factors, including the nature of the stimulus, the cellular state, and the expression of cell death-related genes.¹⁹ Different stimuli can activate distinct intracellular signaling pathways, thereby inducing multiple forms of programmed cell death. For example, in the APAP-induced liver injury model, loss of GSDMD leads to differential upregulation of apoptosis and necroptosis.¹⁰⁹ The severity of necrosis may further influence the choice of death modality, with necroptosis occurring only when the injury is more severe. Caspase-8, a central regulator of apoptosis and necroptosis, also plays an essential role in PANoptosis. Activated caspase-8 mediates intrinsic apoptosis and also cleaves GSDMD and GSDME to trigger pyroptosis in macrophages.^{73,74} Moreover, APAP exposure has revealed an alternative pathway in which GSDMD modulates caspase-8, as caspase-8 is elevated in the absence of GSDMD and subsequently regulates apoptosis and necroptosis.¹⁰⁹ As previously noted, cells under stress may preferentially initiate faster forms of death such as pyroptosis. Ultimately, the choice of a specific death pathway is also influenced by the expression of genes associated with programmed cell death.¹⁹ Based on these observations, we speculate that during APAP-induced liver injury, APAP may regulate the interactions among apoptosis, necroptosis, and pyroptosis by modulating the activity and expression of key molecules such as GSDMD and caspase-8, thereby contributing to the regulation of PANoptosis.

Studies have shown that in mouse models of APAP-induced acute liver injury, markers of neutrophil extracellular traps in both liver tissue and serum are markedly elevated, along with activation of GSDMD, caspase-3, and MLKL, which collectively initiate PANoptosis.⁹⁷ Administration of DNase1 significantly suppresses the formation of neutrophil extracellular traps, decreases PANoptotic cell death and mitigates APAP-induced liver injury in this model.⁹⁷

Furthermore, mice deficient in AIM2 exhibit markedly attenuated hepatic injury after APAP exposure and show a reduced occurrence of PANoptosis.⁹⁷ These findings suggest that PANoptosis contributes to APAP-induced liver injury through a mechanism in which DNA contained within neutrophil extracellular traps activates the DNA sensor AIM2 in hepatocytes, leading to AIM2-dependent assembly of the PANoptosome. Human umbilical cord mesenchymal stromal cells (hucMSCs) and hucMSCs-exosomes (MSCs-Exo) also markedly ameliorate APAP-induced acute liver failure in mice. Mechanistic analyses reveal that miR-423-5p enriched in these extracellular vesicles exerts anti-inflammatory effects by targeting and suppressing ZBP1, a key component of the ZBP1-associated PANoptosome complex that is essential for the execution of PANoptosis.¹¹⁰

However, another study reported that deletion of the AIM2 gene exacerbates APAP-induced acute liver injury in mice, which is characterized by impaired mitochondrial stability, increased glutathione depletion and diminished autophagy, although AIM2 expression is modulated in an age-dependent manner.¹¹¹ AIM2 expression in the liver progressively increases with age, and AIM2 facilitates autophagy and confers protection during APAP-induced hepatic injury. Nevertheless, AIM2 serves as a critical component of the AIM2 PANoptosome and plays a central role in the pathogenesis of APAP-induced liver injury.

Overall, current evidence suggests that PANoptosis may participate in the progression of APAP-induced liver injury. Therefore, the specific regulatory mechanisms underlying PANoptosis require further in-depth investigation and refinement, particularly in relation to its potential as a therapeutic target.

Triptolide

Triptolide is an active diterpenoid lactone isolated from *Tripterygium wilfordii* and exhibits distinct immunomodulatory and antitumor pharmacological properties, although its clinical application is limited by adverse reactions. It shows substantial cytotoxicity toward macrophages and is capable of inducing multiple forms of regulated cell death. Notably, inhibitors that target individual cell death pathways are unable to fully suppress triptolide-induced cytotoxicity. Studies by Zhang et al showed that triptolide induces PANoptosis, as demonstrated by the simultaneous activation of pyroptotic, apoptotic, and necroptotic markers, as well as ASC specks that colocalize with RIPK3 or caspase-8 and interact with these proteins, suggesting the formation of a PANoptosome.¹⁸ The study further indicated that triptolide-induced renal and hepatic injuries may be associated with its capacity to trigger PANoptosis. Mechanistically, triptolide binds to the VAL27 site of caspase-3 and promotes its cleavage, and the cleaved enzyme subsequently induces pyroptosis in Kupffer cells through GSDME cleavage.¹¹² Yuan et al reported that mice treated with triptolide exhibited liver injury and NLRP3 inflammasome activation accompanied by increased neutrophil infiltration, further supporting the contribution of pyroptosis to triptolide mediated hepatic injury.¹¹³ Notably, deletion of GSDMD in Kupffer cells suppresses triptolide-induced pyroptosis, suggesting that triptolide acts primarily on caspase-3 rather than GSDMD and may impair cellular viability through additional signaling pathways.¹¹² Moreover, triptolide-induced liver injury may also involve apoptotic signaling and is associated with altered expression of apoptosis related genes including Bcl-2, Bax, caspase-9, and caspase-3.¹¹⁴

Caspase-8, caspase-3, NLRP3, and GSDMD constitute essential components of the PANoptosome. These findings suggest that triptolide-induced liver injury may be associated with several modes of cell death, including apoptosis, pyroptosis, and necroptosis. Although the presence of the PANoptosome has not yet been clearly established in liver injury models, further studies are needed to clarify whether triptolide can induce its formation in the liver and to identify the key molecules that regulate PANoptosis.

Isoniazid/Rifampicin

Tuberculosis continues to represent a significant global health burden. Although anti-tuberculosis drugs provide therapeutic benefits, they are accompanied by various toxic side effects, most notably DILI. However, the precise mechanisms underlying these hepatic injuries remain incompletely understood. Previous studies have demonstrated that antituberculosis drugs can induce hepatocyte apoptosis in liver tissue. For example, treatment with isoniazid and rifampicin downregulates the antiapoptotic protein Bcl-2 and enhances the expression of the proapoptotic protein Bax.¹¹⁵ In a zebrafish larval model of isoniazid-induced hepatotoxicity, increased expression of apoptosis-related genes, including caspase-3, caspase-8, and caspase-9, has also been observed.¹¹⁶ Notably, isoniazid and rifampicin

provoke a marked inflammatory response in rat liver tissue through activation of the NLRP3 inflammasome, whereas treatment with inflammasome inhibitors such as INF39 or CP-456773 significantly attenuates the hepatotoxicity induced by these agents.¹¹⁷ Caspase-3, caspase-8, and NLRP3 represent essential components of the PANoptosome. Although hepatic PANoptosome formation has not yet been demonstrated in response to isoniazid or rifampicin, the current evidence provides a foundational basis for the potential involvement of PANoptosis and PANoptosome-associated mechanisms in this process.

Methotrexate

Methotrexate (MTX) is an effective chemotherapeutic and immunosuppressive agent, although its clinical application is limited by significant hepatotoxicity. Pronounced hepatocyte apoptosis has been consistently observed in animal models of MTX-induced toxicity. MTX-induced liver injury is characterized by increased immunoexpression of Bax, elevated levels of Bax and caspase-3, and decreased expression of Bcl-2.¹¹⁸ The metabolite MTX polyglutamate activates caspase-3 through the intrinsic apoptotic pathway and thereby initiates the classical apoptotic cascade.¹¹⁹ Moreover, MTX triggers inflammatory responses by upregulating the TLR4/NF- κ B signaling pathway and subsequently activates the downstream NLRP3caspase-1 inflammasome axis, which further exacerbates hepatotoxicity.¹²⁰ MTX also activates caspase-3 and GSDME through the TLR4/NF- κ B pathway, thereby promoting pyroptosis.¹²¹ Notably, AIM2 expression is elevated in MTX-induced liver injury models and shows a positive correlation with the expression of caspase-1 and IL-1 β .¹²² As a key component of the AIM2 PANoptosome, AIM2 may contribute to the inflammatory processes associated with MTX-induced liver injury. Collectively, these findings indicate that MTX-induced liver injury may involve PANoptosis, a recently recognized form of programmed cell death, although its precise mechanisms require further elucidation.

Cisplatin

Cisplatin-induced hepatotoxicity is closely associated with apoptosis. Evidence indicates that cisplatin markedly increases the expression of P53 and Bax in liver tissue while reducing Bcl-2 expression, thereby promoting apoptotic progression.¹²³ Consistent with these observations, cisplatin significantly activates caspase-8 and caspase-9.¹²³ Moreover, exposure to cisplatin results in a dose-dependent increase in the expression of NLRP3, caspase-1, and IL-1 β .¹²⁴ Additional studies have shown that cisplatin promotes GSDME activation in vivo and in vitro and induces Bax-mediated caspase-3 cleavage, suggesting that caspase-3 and GSDME-dependent pyroptosis also contributes to cisplatin-induced liver injury.¹²⁵ Although direct evidence linking cisplatin-induced hepatotoxicity to PANoptosis is still lacking, existing data suggest that PANoptosis may play a potential role in this process.

Aurantio-Obtusin

Previous studies have shown that aurantio-obtusin, a major anthraquinone component derived from *Cassia obtusifolia* seeds, exhibits diverse biological activities in preclinical research and clinical practice. However, this compound can also induce hepatotoxicity, which is characterized by reduced hepatocyte viability and impaired biochemical functions. Its hepatotoxic effects are associated with apoptosis, as indicated by increased expression of caspase-3 and cleaved caspase-3, enhanced cytochrome c release, elevated Bax expression, and reduced Bcl-2 expression.¹²⁶ Furthermore, aurantio-obtusin has been reported to induce hepatic inflammation in zebrafish larvae and in female mice. In female mice, it activates the NOD-like receptor signaling pathway, resulting in increased expression of NLRP3, caspase-1, pro-IL-1 β , IL-1 β , and IL-18, which suggests that pyroptosis may contribute to its hepatotoxicity.¹²⁷ Given that multiple cell death pathways may jointly contribute to aurantio-obtusin-induced liver injury, identifying key targets related to PANoptosis may offer new strategies for the treatment of DILI. The drugs, components, and mechanisms of the PANoptosome involved in DILI are summarized in Table 1.

Inhibit PANoptosis and Alleviate Liver Damage

Baicalin is a natural flavonoid compound isolated from the root of *Scutellaria baicalensis*, and it possesses anti-inflammatory, antioxidant, and antimicrobial properties. It is one of the major active constituents of this traditional medicinal herb and is widely used in herbal formulations and modern drug development. Numerous studies have demonstrated that baicalin inhibits

Table 1 Components and Mechanisms of the PANoptosome Involved in DILI

Drugs	Involved PANoptosome Component	Mechanisms	References
Acetaminophen	NLRP3	Inhibit the NLRP3 inflammatory inflammasome can reduce hepatocyte pyroptosis.	[101]
	RIPK3	Activate the level of RIPK3, and influence the regulation of mitochondrial dysfunction and oxidative stress.	[105]
	RIPK1	Activate the RIPK-dependent necroptosis pathway	[106]
	Caspase-8/GSDMD	Caspase-8 increases in the absence of GSDMD and regulates apoptosis and necroptosis.	[109]
	GSDMD/caspase-3/MLKL/AIM2	In mice with AIM2 gene knockout, excessive APAP-related liver damage was significantly reduced, and the frequency of PANoptosis was lower.	[97]
Triptolide	ZBP1	miR-423-5p targets ZBP1 to induce hepatocyte pyroptosis.	[110]
	RIPK3/caspase-8	Activate markers of pyroptosis, apoptosis, and necrosis, accompanied by ASC specks that colocalize with either RIPK3 or caspase-8 and their interactions, as well as the formation of PANoptosome.	[18]
	Caspase-3/GSDME	Binding to the VAL27 site of caspase-3 promotes the cleavage of caspase-3, and cleaved caspase-3, through GSDME cleavage, induces pyroptosis in Kupffer cells.	[112]
Isoniazid/Rifampicin	NLRP3	Activate the TLR4-MyD88-NF- κ B signaling axis to induce the NLRP3 inflammatory inflammasome, and activate the caspase-1/GSDMD pyroptosis pathway.	[113]
	Caspase-3	Activate Bcl-2, Bax, caspase-9, and caspase-3, inducing apoptosis.	[114]
	Caspase-3/8/9	Increase the mRNA levels of caspase-3, caspase-8 and caspase-9, and induce apoptosis.	[116]
Methotrexate	NLRP3	Activate the NLRP3 inflammatory body, drive the oligomerization of ASC adaptor protein, and the autocleavage activation of caspase-1.	[117]
	Caspase-3	The immunoexpression of Bax was upregulated, the levels of Bax and caspase-3 increased, the level of Bcl-2 decreased, and apoptosis was induced.	[118,119]
Cisplatin	NLRP3/caspase-1/GSDME	Activate the TLR4/NF- κ B pathway and NLRP3/caspase-1 or NLRP3/GSDME, inducing pyroptosis.	[120,121]
	AIM2	Activate AIM2 inflammasome.	[122]
	Caspase-8/3	Upregulate Bax, downregulate caspase-8, caspase-9, and caspase-3, and downregulate Bcl-2, thereby inducing apoptosis.	[123]
	NLRP3/caspase-1	In a dose-dependent manner, it significantly activates the NLRP3 inflammasome pathway, accompanied by the activation of caspase-1 and the release of IL-1 β .	[123,124]
Aurantio-obtusin	Caspase-3/GSDME	Increase the expression of GSDME and promote the caspase-3 cleavage-mediated by Bax to induce pyroptosis.	[125]
	Caspase-3	Increase the expression of caspase-3, cytochrome c, and Bax, reduce the expression of Bcl-2, and induce apoptosis.	[126]
	NLRP3, caspase-1	Activation of the NLRP3 inflammasome signaling pathway induces hepatotoxicity.	[127]

multiple forms of regulated cell death, including apoptosis-associated secondary necrosis, pyroptosis, and necroptosis, thereby mitigating inflammatory responses. Additional evidence indicates that baicalin alleviates liver injury by suppressing PANoptosis. Specifically, baicalin inhibits the formation of mitochondrial Z-DNA and the assembly of the ZBP1 PANoptosome complex, thereby suppressing PANoptosis in macrophages.¹²⁸ In a mouse model of hemophagocytic lymphohistiocytosis, baicalin markedly reduced hepatic injury and the expression of PANoptosis markers in Kupffer cells, suggesting that its hepatoprotective effects are mediated through modulation of the PANoptosis pathway.¹²⁸ Hesperidin similarly mitigates deoxynivalenol (DON)-induced liver injury in mice, and this protective effect is closely associated with its ability to attenuate oxidative stress and PANoptosis-related cell death. Mechanistic studies show that hesperidin inhibits ROS-induced DNA damage and decreases p53 expression, which leads to increased PGC-1 α levels, improved mitochondrial dynamics, reduced mitochondrial ROS, and suppression of PANoptosis, ultimately mitigating DON-induced liver injury.⁹⁸

Moreover, the development of therapeutic agents targeting PANoptosome sensors and other components of the PANoptosis pathway may provide important opportunities for the treatment of DILI.¹²⁹

Summary and Outlook

PANoptosis is a recently identified mode of cell death that arises from the coordinated action of multiple factors and underscores the close interconnections and reciprocal regulation among pyroptosis, apoptosis, and necroptosis. Various stimuli can activate distinct intracellular signaling pathways, ultimately initiating specific cell death programs. Under stress conditions, cells often preferentially activate rapid death mechanisms, and the specific pathway adopted is largely determined by the expression profile of death-related genes. In DILI models, activation of GSDMD, caspase-3, and MLKL has been observed, along with the colocalization of ASC specks with RIPK3 or caspase-8, thereby providing additional evidence supporting the involvement of PANoptosis. Moreover, miR-423-5p enriched in hucMSCs-Exo attenuates hepatocellular inflammation and cell death by suppressing ZBP1 expression and disrupting ZBP1 PANoptosome assembly, suggesting a promising therapeutic strategy based on exosomal miRNA-mediated targeting of ZBP1. Interventions targeting various nodes within the PANoptosis pathway, such as NETs, AIM2, and ZBP1, demonstrate considerable therapeutic potential.

However, it should be noted that current insights into the mechanisms of DILI remain largely speculative and are predominantly based on experimental observations, whereas direct evidence demonstrating that specific drugs activate the PANoptosome complex in vivo and regulate multiple cell death pathways remains limited. Consequently, critical questions, including whether PANoptosomes are present in DILI-induced by different drugs and how to rationally select appropriate inhibitors or inducers, require further investigation. Comprehensive investigation of natural compounds capable of inhibiting PANoptosome assembly, along with the development of therapeutic agents that target PANoptosome sensors and other components of the PANoptosis pathway, may offer substantial opportunities for advancing the treatment of DILI.

In summary, PANoptosis, as a newly identified form of programmed cell death, plays a pivotal role in the initiation and progression of DILI. Therefore, elucidating the regulatory mechanisms that govern PANoptosis in DILI is essential for deepening our understanding of drug-induced hepatotoxicity and provides new opportunities for the development of targeted therapeutic strategies.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

Zhang Xinru: Conceptualization, Writing – original draft.

Zhou Zhipin: Conceptualization, Supervision, Writing – review & editing.

Xie Zhuohua, Chen Jieyi, Deng Yanting: Methodology.

Fang Yibin, Deng Jiasheng, Ye Xiaoxue: Investigation, Resources.

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

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Disclosure

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