

PANoptosis: A novel therapeutic target in kidney disease (Review)

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Abstract. The global prevalence of kidney diseases continues to rise annually, posing a serious public health challenge, and notably contributing to morbidity and mortality rates worldwide. In affected individuals, kidney function progressively declines, ultimately resulting in renal failure. Therefore, elucidating the pathophysiological mechanisms underlying kidney diseases and identifying novel therapeutic targets is of paramount importance. Among these, the regulation of cell death pathways has emerged as a pivotal factor in disease progression. PANoptosis, a recently characterized form of programmed cell death, is activated by diverse stimuli, and involves the integrated activation of pyroptosis, apoptosis and necroptosis, coordinated through the PANoptosome complex. Increasing evidence has suggested that PANoptosis serves an important role in the development of kidney diseases, and further investigation into its regulatory mechanisms may provide valuable insights into disease modulation. The present review summarizes current knowledge regarding the mechanisms of PANoptosis and its involvement in various kidney diseases, offering perspectives for future diagnostic and therapeutic strategies.

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1. Introduction

Programmed cell death (PCD) is a tightly regulated biological process influenced by various external stimuli and intracellular conditions. PCD encompasses several distinct forms of cell death, including apoptosis, pyroptosis, necroptosis, ferroptosis and autophagy, each mediated through specific genetic and molecular mechanisms (1). These forms of cell death are essential for embryonic development, the maintenance of tissue homeostasis and the clearance of intracellular pathogens, and are regarded as fundamental processes for preserving physiological stability (1,2). PCD pathways can be categorized into lytic and non-lytic forms of cell death. Lytic cell death, such as pyroptosis and necroptosis, involves membrane potential loss and cellular swelling, resulting in disrupted cell integrity and ultimately leading to cell rupture, releasing a large amount of inflammatory mediators (2). Comparatively, non-lytic forms of PCD, such as apoptosis, involve the coordinated breakdown of dying cells into smaller fragments for the isolation of cellular contents, which limits the release of cytokines and damage-associated molecular patterns (DAMPs), typically in a silent manner without triggering a pronounced immune response (1).

PANoptosis is a recently identified form of PCD that is initiated by innate immune signaling, and integrates key features of pyroptosis, apoptosis and necroptosis. Notably, its biological effects cannot be fully explained by any of these pathways alone. The concept of PANoptosis was first introduced by Malireddi *et al* in 2019 (3) (Fig. 1). Mechanistically, PANoptosis is mediated through the assembly of a multiprotein complex known as the PANoptosome, which incorporates essential components from the pyroptotic, apoptotic and necroptotic pathways. This complex enables cross-talk and coordinated activation among the three pathways, resulting in a unified mode of cell death (4,5). Due to the regulatory role of the PANoptosome, inhibition of a single form of cell death is insufficient to prevent PANoptosis. Instead, effective blockade

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requires targeting components within the PANoptosome complex.

Emerging evidence has revealed that PANoptosis contributes to the pathogenesis of several kidney diseases, including both acute and chronic forms (6-12). Although the role of PANoptosis has been extensively studied in cancer, infections and inflammatory conditions, its function in renal pathology remains insufficiently characterized. The present review summarizes the molecular mechanisms underlying PANoptosis activation and explores its potential involvement in acute kidney injury (AKI), chronic kidney disease (CKD), diabetic kidney disease (DKD), renal cell carcinoma (RCC) and drug-induced kidney injury, aiming to provide a theoretical foundation for PANoptosis-targeted therapeutic strategies in kidney disease.

2. Literature search, and cross-regulation of apoptosis, pyroptosis and necroptosis

A comprehensive search for studies published up to May 2025 was performed on platforms including PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Google Scholar (<https://scholar.google.com/>), Web of Science (<https://webofscience.com/WOS/>), ScienceDirect (<https://www.sciencedirect.com/>) and CNKI (<https://www.cnki.net/>). The search adopted a combination of subject terms and free terms, and was appropriately adjusted according to the rules of the different databases. The key terms included 'Kidney disease', 'Kidney failure', 'Renal insufficiency', 'Renal failure', 'Nephropathy', 'Renal disease' and 'PANoptosome' or 'PANoptosis'. Notably, low-quality articles and papers with incomplete information were excluded. The main inclusion criteria for the literature were original research or comprehensive reports. The research content clearly involved the mechanism or therapeutic significance of PANoptosis in kidney diseases, and the research subjects included humans and mammals. The screening was independently conducted by two researchers, and any disputes arising during the process were resolved through mutual discussion or arbitration by a third-party senior researcher.

Apoptosis. Apoptosis, pyroptosis and necroptosis represent the three primary forms of PCD, each characterized by distinct initiators, signaling mediators and execution mechanisms. Among them, apoptosis is the most extensively studied and was first described by Kerr *et al* in 1972 (13) (Fig. 1). Apoptosis depends on the involvement of caspases. Morphologically, apoptosis is defined by characteristic features including cell shrinkage, cytoplasmic condensation, membrane blebbing and nuclear chromatin condensation (13,14). Apoptosis occurs through two main pathways: The intrinsic (mitochondrial) pathway and the extrinsic (death receptor-mediated) pathway (Fig. 2A). The intrinsic pathway is activated in response to intracellular stressors such as DNA damage, oxidative stress or toxic insults. In this context, key stress-sensing proteins, such as the tumor suppressor protein 53 (P53), serve a central regulatory role by transcriptionally activating pro-apoptotic members of the Bcl-2 family, such as BAK and BAX, while concurrently suppressing anti-apoptotic proteins, such as Bcl-2 and Bcl-XL (15-17). Activated BAK and BAX oligomerize on the mitochondrial outer membrane, resulting in mitochondrial

outer membrane permeabilization and the release of cytochrome *c* (Cyt *c*) into the cytosol (18). Cyt *c* subsequently binds to apoptotic protease-activating factor 1, promoting the formation of the apoptosome complex, which leads to the activation of caspase-9 (19,20). Caspase-9 then cleaves and activates downstream effector caspases, including caspase-3 and caspase-7, ultimately executing the apoptotic process (21). The extrinsic pathway is initiated by the binding of death ligands to their corresponding receptors. Fas and tumor necrosis factor receptor (TNFR) recruit adaptor proteins, such as TNFR-associated death domain protein (TRADD) and Fas-associated death domain protein (FADD), forming the death-inducing signaling complex, which activates caspase-8 and caspase-10 (22-24). Active caspase-8/10 cleaves and activates the effector caspases, including caspase-3, caspase-7 and caspase-6, leading to apoptosis (25,26). Caspase-8 also cleaves BID, which activates the intrinsic pathway and further promotes apoptosis (27).

Necroptosis. Necroptosis was first reported by Degterev *et al* (28) in 2005 as a distinct form of PCD (Fig. 1). It is morphologically characterized by organelle swelling, plasma membrane rupture and leakage of cellular contents (29,30) and is regulated through the formation of the necrosome, a signaling complex composed of receptor-interacting protein kinase 1/3 (RIPK1/3) and mixed-lineage kinase domain-like protein (MLKL) (31,32) (Fig. 2B). Upon stimulation or injury, death receptors such as TNFR1, Fas, TNF and TNF-related apoptosis-inducing ligand (TRAIL) receptor bind to their respective ligands, initiating downstream signaling cascades. These interactions recruit kinases and adaptor proteins that assemble the necrosome complex (33-36). Within the necrosome, RIPK1 activates RIPK3 through phosphorylation (37), and this activation frequently leads to NF- κ B-mediated pro-inflammatory and pro-survival signaling (35,38,39). When caspase-8 is active, it forms a complex with RIPK1 and FADD to initiate apoptosis. However, when caspase-8 is inhibited, RIPK1 engages and phosphorylates RIPK3 via the RIP homotypic interaction motif (RHIM) domain. Activated RIPK3 subsequently phosphorylates MLKL, which oligomerizes and translocates to the plasma membrane. MLKL is the terminal effector of necroptosis (40-43). Oligomerized MLKL disrupts membrane integrity by forming pores, leading to ion imbalance and water influx, which cause cell swelling and rupture (44,45). This facilitates the release of DAMPs into the extracellular space, activating the innate immune response, and amplifying inflammation and tissue injury (46).

Pyroptosis. Pyroptosis was first observed in 1992 when macrophages infected with *Shigella flexneri* exhibited cell death characterized by features initially mistaken for apoptosis (47). Subsequent studies revealed that this process was distinct from apoptosis and relied on caspase-1 activation rather than the classical apoptotic molecule caspase-3 (48). In 2001, Cookson and Brennan (49) introduced the term 'pyroptosis' to describe this caspase-1-dependent form of PCD (Fig. 1).

Pyroptosis is an inflammation-associated form of PCD that occurs through the classical or non-classical pathways. While this process shares some morphological features with apoptosis, such as nuclear condensation and DNA fragmentation, its

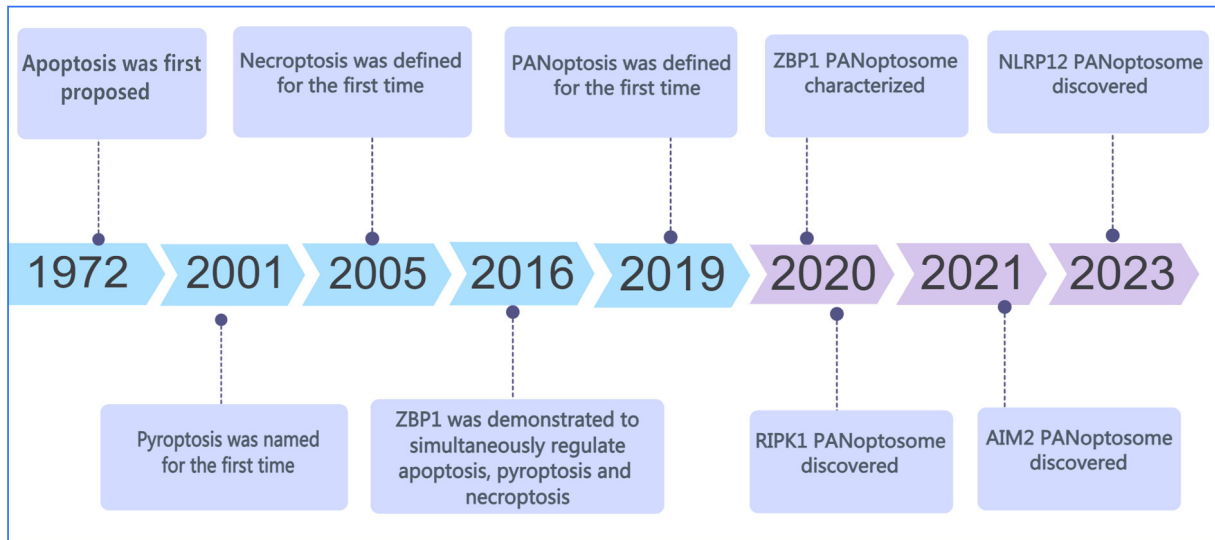


Figure 1. Timeline of the discovery of apoptosis, necroptosis, pyroptosis and PANoptosis. In 2019, PANoptosis was first named, and four types of PANoptosomes have since been characterized. Created with MedPeer (medpeer.cn). NLRP12, Nod-like receptor pyrin domain-containing protein 12; RIPK1, receptor-interacting protein kinase 1; ZBP1, Z-DNA binding protein 1.

hallmark characteristics include pore formation in the plasma membrane, cell swelling, membrane rupture and the release of pro-inflammatory intracellular contents; these events trigger a robust inflammatory response (49-51). Upon exposure to toxic stimuli, intracellular and extracellular danger signals induce the formation of inflammasome complexes in the cytoplasm through the classical caspase-1-dependent pathway or the non-classical caspase-4/5/11-dependent pathway; these inflammasome complexes are composed of Nod-like receptor family pyrin domain containing (NLRP)3/NLRP1, apoptosis-related speck-like protein (ASC) and pro-caspase-1 (Fig. 2C). Inflammasomes promote the production of caspase-1, and the maturation and secretion of IL-1 β and IL-18, and induce cleavage of the pyroptosis executioner protein gasdermin D (GSDMD). The N-terminal fragment of GSDMD forms pores in the membrane, initiating pyroptosis (51-54).

Interaction and cross-regulation among apoptosis, pyroptosis, and necroptosis. For a long time, different cell death modalities were examined in isolation due to their regulation by distinct molecular mechanisms. However, the identification of PANoptosis has revealed that these pathways are interconnected at multiple levels and can be activated simultaneously or sequentially within the same cell. Rather than acting independently, these forms of cell death can switch from one to another under specific conditions, highlighting their close association and mutual regulation (3,4).

Among the key mediators linking these pathways, caspases have a central role. Caspase-8, classically recognized as the initiator enzyme of the extrinsic apoptotic pathway, promotes the cleavage of BID to tBID, which subsequently activates BAX and BAK, and initiates apoptotic signaling. However, increasing evidence (22,55-60) has indicated that caspase-8 also participates in necroptosis and pyroptosis (Fig. 2B and C); it can trigger necroptosis mediated by RIPK3 and MLKL, and also contributes to pyroptotic regulation (55-58). Caspase-8 forms an oligomeric complex with

RIPK1 and FADD, which facilitates the activation of downstream effector caspases-3/7 and promotes apoptosis (59,60). Additionally, caspase-8 can directly cleave RIPK1 and RIPK3, thereby suppressing necroptosis. When caspase-8 activity is inhibited, this suppression is lifted, allowing RIPK3 activation and promoting necroptotic cell death (61,62). RIPK1 also contributes to FADD/caspase-8-dependent apoptosis. Upon TNFR1 engagement, the TNFR1 signaling complex recruits TRADD, which subsequently recruits FADD. FADD then binds pro-caspase-8, facilitates its dimerization and activation, and initiates apoptosis (63). Dillon *et al* (64) demonstrated through both *in vitro* and *in vivo* studies that RIPK1 can regulate FADD/caspase-8-mediated apoptosis as well as RIPK3/MLKL-induced necroptosis, thereby preventing perinatal mortality in mice (Fig. 2A and B). Caspase-8 also has a regulatory role in pyroptosis by facilitating activation of the NLRP3 inflammasome, promoting ASC complex formation and caspase-1 activation, which in turn induces IL-1 β secretion and pyroptosis (55,62). In the context of *Yersinia* infection, inhibition or deletion of transforming growth factor- β -activated kinase 1 (TAK1) has been shown to enhance caspase-8-mediated GSDMD cleavage, thereby favoring pyroptosis while reducing apoptosis (65) (Fig. 2A and C). Furthermore, caspase-8 can act on other GSDM family members, such as GSDMC, which is specifically cleaved under TNF α stimulation to generate the N-terminal domain of GSDMC, leading to pore formation in the plasma membrane and the induction of pyroptosis (66,67). During influenza virus infection, caspase-8 activates caspase-3, which cleaves GSDMD into an inactive form, thereby reducing IL-1 β and IL-18 release, and suppressing pyroptosis (68). These findings collectively indicate that caspase-8 is a pivotal regulator linking apoptosis, necroptosis and pyroptosis.

Caspase-3, a key executioner of apoptosis, also contributes to pyroptosis. Upon activation, it cleaves GSDME, generating the GSDME-N fragment that induces pyroptotic membrane disruption (69,70). Similarly, caspase-1, the terminal effector

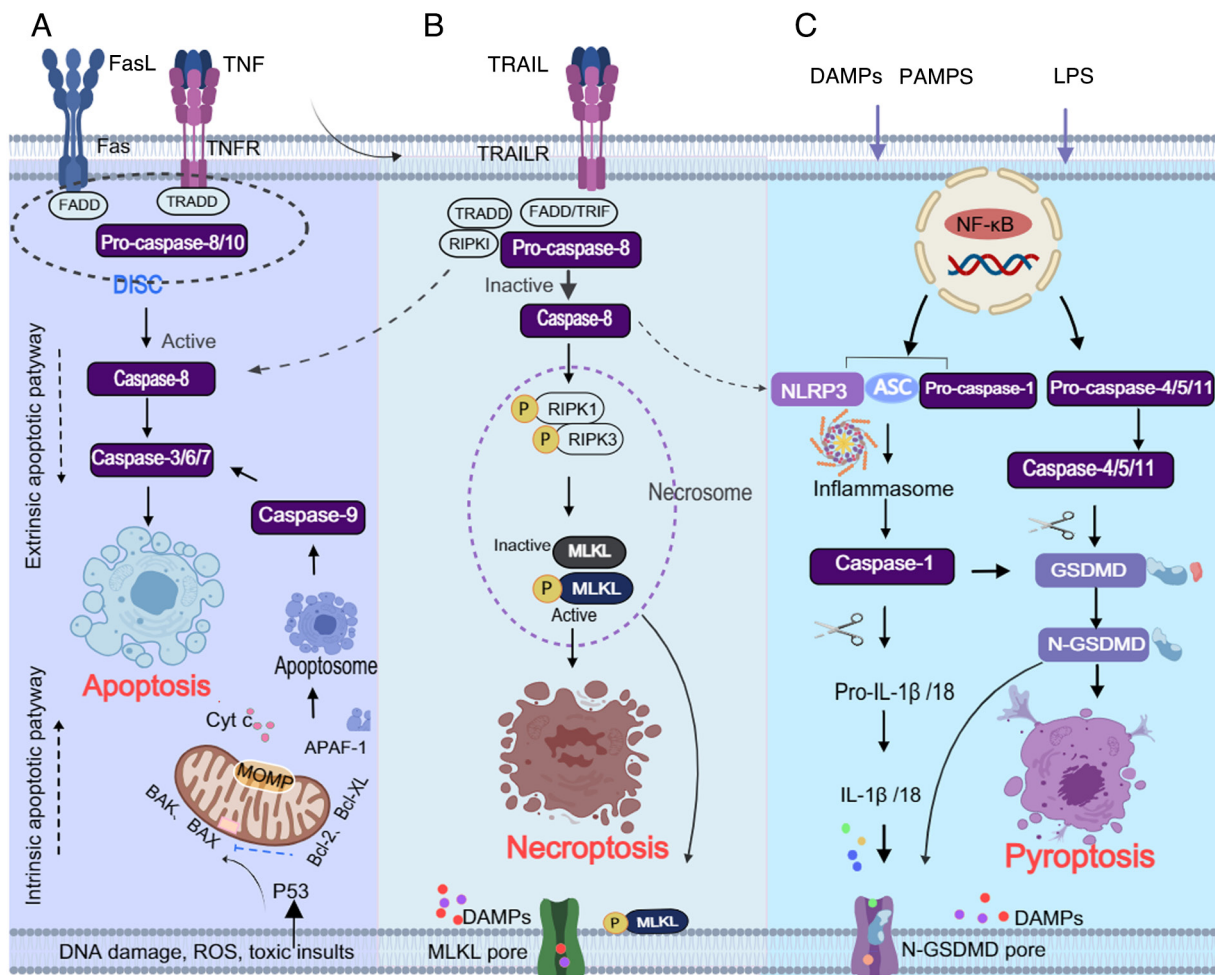


Figure 2. Mechanisms of apoptosis, necroptosis and pyroptosis. (A) Apoptosis depends on the involvement and regulation of caspases, and is divided into intrinsic (dependent on caspase-9) and extrinsic (dependent on caspase-8/10) pathways, which respectively cleave downstream factors dependent on caspase-3/6/7 to perform apoptosis. (B) RIPK1 recruits and phosphorylates RIPK3 in necroptosis, further activating MLKL. MLKL has pore-forming activities, leading to necroptosis. (C) Pyroptosis is divided into classical (dependent on caspase-1) and non-classical (dependent on caspase-4/5/11) pathways, which rely on the cleavage of the executive protein GSDMD, forming N-terminal GSDMD fragments that form pores in the cell membrane, inducing the release of inflammatory exudate and driving pyroptosis. The three modes of cell death are not isolated, but interact with each other, for example, caspase-8 is involved in regulating all three cell death modes simultaneously. Created with MedPeer (medpeer.cn). APAF-1, apoptotic protease-activating factor 1; ASC, apoptosis-related speck-like protein; Cyt c, cytochrome c; DAMPs, damage-associated molecular patterns; DISC, death-inducing signaling complex; FADD, Fas-associated death domain protein; GSDMD, gasdermin D; LPS, lipopolysaccharide; MLKL, mixed-lineage kinase domain-like protein; MOMP, mitochondrial outer membrane permeabilization; NLRP3, Nod-like receptor pyrin domain-containing protein 3; PAMPs, pathogen-associated molecular patterns; RIPK, receptor-interacting protein kinase; ROS, reactive oxygen species; TNF, tumor necrosis factor; TNFR, TNF receptor; TRADD, TNFR-associated death domain protein; TRAIL, TNF-related apoptosis-inducing ligand; TRAILR, TRAIL receptor.

of pyroptosis, has been shown to mediate apoptosis in the absence of GSDMD by activating the BID/caspase-9/caspase-3 axis (71,72).

In addition to caspases, multiple signaling complexes and inflammasomes contribute to the cross-talk among these cell death pathways. NLRP3, the most extensively studied inflammasome, serves a critical role in pyroptosis by promoting inflammatory responses. Potassium efflux, a known activator of NLRP3, can result from MLKL-mediated membrane disruption during necroptosis, which subsequently leads to caspase-1 activation and IL-1β maturation (73-75) (Fig. 2B and C). Moreover, upregulation of RIPK3 has been shown to trigger the RIPK3/MLKL/NLRP3/caspase-1 signaling cascade, further supporting the interconnected nature of these pathways (76).

Collectively, these findings indicate that apoptosis, pyroptosis and necroptosis constitute an interconnected network rather than three independent cell death pathways, with

key regulators, such as caspase-8, exerting multiple functions, including promoting apoptosis through activation of caspase-3/7, suppressing necroptosis by cleaving RIPK1 and RIPK3, and participating in NLRP3 inflammasome-dependent pyroptosis. Similarly, RIPK1 is involved in apoptosis and pyroptosis. These pathways are not isolated but rather interdependent, with key molecules functioning as receptors for initiating and recognizing death signals, as adapters for recruiting downstream mediators, and as effectors that execute the final cell death program.

3. Mechanism and key molecules involved in PANoptosis

The concept of PANoptosis emerged from studies investigating the molecular overlap among pyroptosis, apoptosis and necroptosis. Increasing evidence has suggested that these three forms of PCD can occur simultaneously and

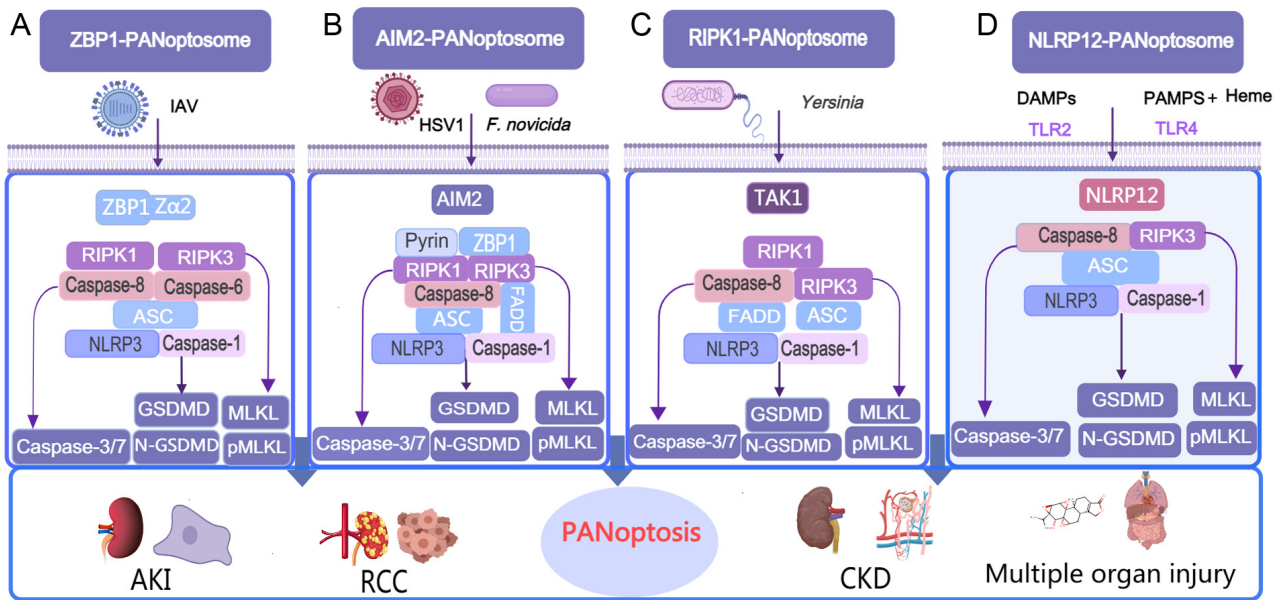


Figure 3. Molecular compositions and mechanisms of the PANoptosome complexes. (A) ZBP1-PANoptosome consists of RIPK3, caspase-8, caspase-6, caspase-1, RIPK1, ZBP1, ASC and NLRP3. (B) AIM2-PANoptosome is assembled by combining molecules such as AIM2, ZBP1, pyrin, ASC, caspase-8, caspase-1, RIPK3, RIPK1, NLRP3 and FADD. (C) RIPK1-PANoptosome contains molecules such as caspase-8, caspase-1, FADD, NLRP3, ASC, RIPK1 and RIPK3. (D) NLRP12-PANoptosome consists of NLRP12, caspase-1, caspase-8, RIPK3, NLRP3 and ASC. The four PANoptosomes all contain key factors for three cell death modes, caspase-3/7, MLKL and GSDMD, which induce apoptosis, necroptosis and pyroptosis, respectively. Created with MedPeer (medpeer.cn). AKI, acute kidney injury; ASC, apoptosis-related speck-like protein; CKD, chronic kidney disease; DAMPs, damage-associated molecular patterns; FADD, Fas-associated death domain protein; GSDMD, gasdermin D; HSV1, herpes simplex virus 1; IAV, influenza A virus; MLKL, mixed-lineage kinase domain-like protein; NLRP, Nod-like receptor family pyrin domain containing; PAMPs, pathogen-associated molecular patterns; RCC, renal cell carcinoma; RIPK, receptor-interacting protein kinase; TAK1, transforming growth factor- β -activated kinase 1; TLR, Toll-like receptor; ZBP1, Z-DNA binding protein 1.

are interconnected through a complex molecular network, rather than acting as isolated pathways (77-80), leading to the recognition of PANoptosis as a distinct, coordinated form of cell death. PANoptosis is a newly characterized PCD pathway regulated by innate immune responses and mediated through the assembly of a multiprotein complex known as the PANoptosome. It is initiated by innate immune sensors and executed via caspases and RIPKs. The PANoptosome integrates components from the pyroptotic, apoptotic and necroptotic machinery, enabling their coordinated activation. Regulation of the PANoptosome allows simultaneous control of all three death pathways, while also providing a molecular scaffold that facilitates interaction among key signaling molecules, thereby driving PANoptosis (81,82).

Activation of PANoptosis involves upstream receptors and signaling cascades that lead to the formation of the PANoptosome. These complexes serve as platforms for cross-talk among the three PCD pathways and are essential for their integration (83). The PANoptosome typically comprises three categories of components (5,8,11,80,83): i) Pattern recognition receptors or sensors that detect pathogen-associated molecular patterns (PAMPs) and DAMPs, including Z-DNA binding protein 1 (ZBP1), NLRP12, AIM2, RIPK1, pyrin and NLRP3; ii) adaptor proteins such as ASC and FADD; and iii) catalytic effectors, including RIPK1, RIPK3, caspase-1 and caspase-8. The composition of the PANoptosome is context-dependent and varies according to the nature of the stimulus or pathological condition. In general, the sensors recognize PAMPs or DAMPs and initiate PANoptosome assembly through homotypic or heterotypic interactions among adaptor domains. This assembly provides a structural platform

for the convergence of apoptotic, pyroptotic and necroptotic effectors. The resulting complex enables the coordinated activation of caspases and RIPKs, thereby inducing pyroptosis, apoptosis and necroptosis in a synchronized manner (80,83).

The PANoptosome complexes characterized to date include the ZBP1-PANoptosome (84-86), AIM2-PANoptosome (82), RIPK1-PANoptosome (87) and NLRP12-PANoptosome (88) (Figs. 1 and 3). Among them, ZBP1 is a critical innate immune sensor involved in host defense that serves as a key initiator of PANoptosis. Structurally, ZBP1 contains two N-terminal $Z\alpha$ domains ($Z\alpha1$ and $Z\alpha2$), two RHIMs (RHIM1 and RHIM2) and a C-terminal domain. The expression of ZBP1 is typically induced by interferons (IFNs), and ZBP1 is also activated in response to pathogens or cellular stress (3,86,89). In 2016, Kuriakose *et al* (89) identified ZBP1 as a shared regulator of apoptosis, pyroptosis, and necroptosis. Later, in 2019, the same group demonstrated that ZBP1 and TAK1 can initiate the assembly of PANoptosome complexes (3). In 2020, the ZBP1-PANoptosome was further characterized (84,85). This complex orchestrates the induction of cytokine release along with the activation of apoptosis, pyroptosis and necroptosis, contributing to pathogen clearance and the maintenance of immune homeostasis (3). The ZBP1-PANoptosome is composed of RIPK3, caspase-8, caspase-6, caspase-1, RIPK1, ZBP1, ASC and NLRP3 (84-86) (Fig. 3A). During influenza A virus (IAV) infection, the RHIM domain of ZBP1 engages in homotypic interactions with the RHIM domains of RIPK1 and RIPK3, facilitating the recruitment of caspase-6 and/or caspase-8, and activating ASC, NLRP3 and caspase-1 to assemble the PANoptosome (85). This complex promotes necroptosis via the RIPK3/MLKL axis, induces pyroptosis

through NLRP3 inflammasome-mediated GSDMD cleavage, and activates apoptosis through caspase-8 and downstream effectors, such as caspase-3 and caspase-7 (90-93). Additionally, caspase-6 enhances the ZBP1-RIPK3 interaction during IAV infection and contributes to NLRP3 inflammasome activation, further facilitating PANoptosome assembly (78,94). The Za2 domain of ZBP1 serves a vital role in sensing Z-RNAs within infected cells and mediating inflammasome activation during IAV infection, thereby promoting PANoptosis (85,93). Similar mechanisms have been observed in infections caused by coronaviruses and mouse hepatitis virus, where ZBP1 activation contributes to cytokine storm and PANoptosis (86). Deletion of ZBP1 in β -coronavirus-infected mice has been shown to reduce lung injury, and to markedly suppresses cytokine storm and PANoptosis (86,95). Beyond viral infections, ZBP1 is also critical in PANoptosis induced by fungal and bacterial pathogens. It acts as an upstream sensor during fungal infections and initiates PANoptosis (84). In *Francisella novicida* infection, ZBP1 contributes to the assembly of the AIM2-PANoptosome, interacting with AIM2, pyrin, ASC and other components (82). However, in *Yersinia*-induced PANoptosis, ZBP1 is not essential, as this process is instead dependent on RIPK1, highlighting the involvement of distinct innate immune sensors under different pathological conditions (87).

AIM2 is an inflammasome sensor belonging to the PYHIN protein family that recognizes cytoplasmic double-stranded DNA (dsDNA). Structurally, AIM2 contains an N-terminal pyrin domain and a C-terminal HIN200 domain, and is primarily localized in the cytoplasm (96-98). Upon detection of pathogen-derived dsDNA, AIM2 initiates the formation of the AIM2-PANoptosome complex. This assembly activates the inflammasome pathway, leading to the secretion of IL-1 β and IL-18, and inducing pyroptosis (99,100). In bone marrow-derived macrophage models infected with herpes simplex virus 1 and *Francisella novicida*, AIM2 has been shown to regulate other innate immune sensors, including pyrin and ZBP1. Together with ASC, caspase-1, caspase-8, RIPK3, RIPK1, NLRP3 and FADD, these components assemble to form the AIM2-PANoptosome, driving PANoptosis (82) (Fig. 3B). During infection, AIM2 deficiency markedly reduces inflammation and cell death, whereas the absence of pyrin or ZBP1 produces a partial reduction in these responses. These observations suggest that AIM2 functions as an upstream regulator controlling the assembly and activation of the AIM2-PANoptosome (82).

RIPK1 is another RHIM-containing protein that serves a central role in inflammation, cell death and the regulation of PANoptosis. It can activate necroptosis by promoting the phosphorylation of RIPK3, which interacts with MLKL to induce cell death through the RIPK3/MLKL axis (40,89,101). Dillon *et al.* (64) reported that RIPK1 also contributes to FADD/caspase-8-mediated apoptosis and RIPK3-dependent necroptosis. TAK1 serves as a key upstream regulator of RIPK1, controlling the formation and activation of PANoptosomes (3,102,103). Under normal physiological conditions, TAK1 inhibits TNF-mediated autocrine signaling by suppressing TNF production and RIPK1 phosphorylation, thereby preventing PANoptosis activation (28,79). In *Yersinia*-infected cells, TAK1 inhibition or knockout promotes the assembly of the RIPK1-PANoptosome, which includes

RIPK1, caspase-8, caspase-1, FADD, NLRP3, ASC and RIPK3 (Fig. 3C). This complex activates FADD-Caspase-8-mediated apoptosis, RIPK3-MLKL-dependent necroptosis, and NLRP3 inflammasome-mediated pyroptosis (79,87). Moreover, in the absence of TAK1, microbial signals can activate PANoptosis through the RIPK3/MLKL axis independent of RIPK1 kinase activity (3). Using models specifically lacking TAK1, studies have demonstrated that inhibition of RIPK1 kinase activity in TAK1-deficient bone marrow-derived macrophages can suppress PANoptosis and inflammation, infection and myeloid proliferation (77,79,104,105).

NLRP12 is a member of the NLR family and contains an N-terminal pyrin domain, a central nucleotide-binding domain and a C-terminal leucine-rich repeat region. It functions as an innate immune sensor that modulates inflammatory signaling in response to infection and cellular stress (106). It has been demonstrated that heme, in conjunction with PAMPs, activates the Toll-like receptor 2/4 signaling axis, which induces the expression of NLRP12 (88). This induction promotes the assembly of a PANoptosome complex composed of NLRP12, NLRP3, ASC, caspase-1, caspase-8 and RIPK3, collectively referred to as the NLRP12-PANoptosome (Fig. 3D). Activation of this complex leads to PANoptosis, characterized by caspase-1, caspase-8 and caspase-3 activation, MLKL phosphorylation, and cleavage of GSDMD or GSDME. A functional study further revealed that NLRP12 deficiency confers protection against heme-induced AKI and mortality in mice, underscoring its critical role in disease pathogenesis (88). This finding suggests that NLRP12 and associated PANoptotic components may represent promising therapeutic targets for hemolytic and inflammation-related disorders (88).

4. The role of PANoptosis in kidney diseases

AKI. AKI is a clinical syndrome characterized by a sudden decline in renal function, and is associated with a high incidence and poor clinical outcomes (107,108). The incidence of AKI affects ~20% of hospitalized patients and exceeds 50% among those in intensive care units, making it a major contributor to in-hospital mortality (109). Emerging evidence (8,110-112) has indicated that PANoptosis serves an important role in various AKI models, including those induced by sepsis, ischemia/reperfusion (I/R) injury and exposure to nephrotoxic agents, such as chemicals and certain traditional Chinese medicines.

Cell death and inflammation are central events in the pathogenesis of AKI, with I/R injury being a primary cause. Previous studies have demonstrated that apoptosis, pyroptosis and necroptosis coexist in models of middle cerebral artery occlusion, oxygen-glucose deprivation/recovery and retinal I/R injury (113,114). Another study, by collecting data from animal and cell experiments, reported that PANoptosis is observed in ischemic brain injury (115). These findings suggest that PANoptosis may represent a promising therapeutic target for diseases associated with I/R injury. In I/R-induced AKI, renal tubular epithelial cells experience endoplasmic reticulum stress, oxidative stress and inflammation due to hypoxia, followed by reperfusion, leading to acute tubular cell loss. Numerous animal studies and analyses of kidney biopsies from transplant recipients have demonstrated that I/R induces

apoptosis in tubular epithelial cells (116-118). Although apoptosis was initially regarded as the principal mechanism of AKI, further studies have shown that multiple cell death pathways are involved, and inhibiting apoptosis alone is insufficient to prevent renal injury (119). In I/R-induced AKI models, NLRP3 activates caspase-1, leading to GSDMD cleavage and the release of the pro-inflammatory cytokines IL-1 β and IL-18, thereby inducing pyroptosis in renal tubular epithelial cells (120-122). Pyroptosis has also been observed in AKI models caused by cisplatin and sepsis (123). Linkermann *et al* (124,125) reported increased expression of RIPK1 and RIPK3 in I/R-induced AKI, and demonstrated that treatment with the necroptosis inhibitor necrostatin-1 (Nec-1) markedly improved renal function. Similarly, the RIPK1 inhibitor Compound-71 has been shown to alleviate cisplatin-induced AKI by suppressing necroptosis (126). In calcium oxalate-induced AKI, ZBP1 activation of the RIPK3/MLKL axis mediates necroptosis, whereas ZBP1 knockout can reduce necroptotic activity and tubular injury (127). These findings underscore the importance of simultaneously targeting apoptosis, pyroptosis and necroptosis to protect against AKI-associated kidney damage.

While previous studies have often focused on individual PCD pathways, the discovery of PANoptosis has shifted attention to the integrated role of multiple death mechanisms in AKI. In a mouse model of sepsis-induced AKI established by cecal ligation and puncture, increased AIM2 expression in kidney tissue has been shown to be associated with concurrent activation of apoptosis, pyroptosis, necroptosis and inflammatory signaling, supporting the presence of PANoptosis (110). *In vitro*, PANoptosis has been observed in lipopolysaccharide (LPS)-treated human proximal tubular epithelial HK-2 cells, and AIM2 silencing may reverse this effect, suggesting that AIM2 mediates sepsis-induced renal injury through regulation of PANoptosis (110). NLRP3, a key component of the four types of PANoptosome, has also been shown to be involved in I/R-induced AKI. The clinical agent 3,4-methylenedioxy- β -nitrostyrene has been reported to reduce apoptosis, necroptosis and pyroptosis in a renal I/R injury model by targeting NLRP3, thereby alleviating tissue damage (8). Furthermore, an aqueous extract of *Achyranthes aspera* can ameliorate cisplatin-induced AKI by inhibiting DNA damage, oxidative stress, inflammation and PANoptosis (111). In sepsis-induced AKI mouse models, elevated levels of PANoptosis-related molecules, including RIPK1, MLKL, caspase-3/7 and FADD, have been observed in renal tissue, along with marked upregulation of ZBP1, particularly in the renal interstitium, highlighting the essential role of PANoptosis in the pathogenesis of sepsis-induced AKI (112) (Table I).

RCC. PANoptosis has been increasingly linked to tumorigenesis and cancer progression (12). The boundaries between different forms of PCD have become progressively less distinct, and therapeutic strategies targeting a single form of cell death often show limited efficacy (105). The discovery of PANoptosis not only broadens the understanding of cell death pathways but also offers novel approaches for cancer therapy. RCC, characterized by the proliferation of malignant epithelial cells, relies on strategies that effectively inhibit or eliminate these cells. Inducing PANoptosis, which simultaneously activates apoptosis, pyroptosis and necroptosis, holds potential

therapeutic value for enhancing cancer cell clearance, and suppressing tumor growth and metastasis. PANoptosis has been investigated in several types of cancer, including colorectal cancer, breast cancer and low-grade glioma (12,128,129).

RCC is one of the most prevalent urological malignancies worldwide (130-132). Approximately one-third of patients present with metastatic RCC (mRCC) at the time of diagnosis, and the 5-year survival rate for mRCC remains at <30% (130,131). RCC is mainly classified into three histological subtypes: Clear cell RCC (ccRCC, also known as KIRC), papillary RCC (KIRP) and chromophobe RCC (KICH). Among these, KIRC is the most common subtype, accounting for ~70% of cases. As a highly immunogenic tumor, KIRC is treated using surgical resection and immune checkpoint inhibitors. Given its strong immunogenicity, PANoptosis may serve as a promising therapeutic target in KIRC (131,133-135).

Several studies have explored the association between PANoptosis and cancer prognosis using data from The Cancer Genome Atlas. One study reported that high expression of PANoptosis-related genes, such as AIM2, caspase-3, caspase-4 and TNFRSF10, was significantly associated with poor prognosis in KIRC (132). Conversely, in skin cutaneous melanoma, higher expression of genes including ZBP1, NLRP1, caspase-8 and GSDMD was shown to be associated with better survival outcomes (132). Further analysis has identified PANoptosis-related prognostic clusters, revealing underlying genetic mutations, distinct immune cell populations and activated oncogenic pathways that may account for differences in patient survival across tumor types (7). These findings highlight the heterogeneous nature of PANoptosis gene expression and suggest it may exert different roles depending on the cancer context.

Another study applied PANoptosis-related differentially expressed genes to predict prognosis in patients with KIRC. The high-risk PANoptosis group demonstrated an immunosuppressive tumor microenvironment, characterized by reduced infiltration of antitumor CD4⁺ T cells and natural killer cells, and elevated levels of immunosuppressive M2 macrophages and regulatory T cells. These findings suggest that PANoptosis may contribute to KIRC progression and influence immune regulation within the tumor microenvironment (9). In a separate study, Wang *et al* (133) developed a ccRCC prognostic risk model based on three specific PANoptosis-related microRNAs, revealing that patients in the high-risk group exhibited poorer outcomes and greater tumor malignancy. This group also showed enrichment of immune-related pathways and heightened immune activity, implying potential responsiveness to immunotherapy and chemotherapy. By contrast, the low-risk group demonstrated metabolic reprogramming, with increased fatty acid and amino acid metabolism. Furthermore, PANoptosis-related long non-coding RNAs have been associated with clinical outcomes, immune cell infiltration, immunosuppressive states, oncogenic signaling pathways and therapeutic responses in ccRCC. Single-cell sequencing identified LINC00944 as a potential biomarker linked to T-cell infiltration and PCD regulation, supporting its prognostic relevance (134). A recent study used bioinformatics analysis to characterize PANoptosis in the three RCC subtypes (KIRC, KIRP and KICH) and proposed a novel scoring

Table I. PANoptosis in various kidney diseases.

First author, year	Disease	Trigger	Experimental method	Damaged cells/tissues	Target/participation factors	(Refs.)
Wei, 2024	AKI	CLP	<i>In vivo/in vitro</i>	RTECs	AIM2, caspase-1, caspase-8, RIPK1, MLKL, ZBP1	(110)
Ruilian, 2023	AKI	LPS	<i>In vitro</i>	Renal cells	FADD, caspase-3, caspase-7, caspase-8, RIPK1, MLKL, ZBP1	(112)
Lin, 2024	AKI	Cisplatin	<i>In vivo</i>	Renal cells	NLRP3, caspase-1, caspase-3, NRF2, Bcl-2	(111)
Uysal, 2022	AKI	RIR	<i>In vitro</i>	RTECs	GSDMD, caspase-3, MLKL, NLRP3	(8)
Mall, 2022	KIRC	NA	Bioinformatics methods	NA	High expression of PANoptosis-related genes, such as AIM2, caspase-3, caspase-4 and TNFRSF10, is significantly associated with poor prognosis in KIRC	(132)
Mall, 2023	KIRC	NA	Bioinformatics methods	NA	Gene mutation patterns, activation of specific immune cells and oncogenic pathways are significantly different between high and low PANoptosis cluster groups	(7)
Jiang, 2024	KIRC	NA	Bioinformatics methods	NA	PANoptosis has a regulatory effect on the tumor immune microenvironment in KIRC and serves an important role in the development of KIRC	(9)
Wang, 2023	ccRCC	786-O and Caki-1 cells	Bioinformatics methods/ <i>in vitro</i>	ccRCC cells	The signal constructed based on PANoptosis-related microRNAs has clinical significance for predicting the progression of ccRCC	(133)
Liu, 2023	ccRCC	786-O and Caki-1 cells	Combining bioinformatics and <i>in vitro</i> methods	ccRCC cells	PANoptosis-related long non-coding RNAs are associated with the progression, prognosis, immune regulation and therapeutic efficacy of ccRCC	(134)
Xu, 2024	KIRC, KIRP and KICH	769-P and 786-O cells	Combining bioinformatics and <i>in vitro</i> methods	KIRC, KIRP and KICH cells	The new indicator PANII constructed based on PANoptosis-related genes (BAX, caspase-1, caspase-8 and PYCARD) can reflect the immune regulatory status and predict immune therapy response	(135)
Zhang, 2024	CKD	Adenine	Combining bioinformatics and <i>in vivo</i> methods	RTECs	FOS and PTGS2 genes may be closely related to the pathological mechanism of PANoptotic CKD	(150)
Yang, 2025	CKD	Severe burns	<i>In vivo/in vitro</i>	Macrophages and podocytes	Caspase-1, caspase-3, IL-1 β , GSDMD	(155)
Lv, 2025	DKD	STZ	<i>In vivo/in vitro</i>	Podocytes	RIPK1, tMLKL, Bcl-2, BAX, caspase-3, caspase-1	(156)

Table I. Continued.

First author, year	Disease	Trigger	Experimental method	Damaged cells/tissues	Target/participation factors	(Refs.)
Yi, 2024	Kidney damage caused by drugs	ATR	<i>In vivo</i>	Renal cells	LYC inhibits ATR exposure- induced renal PANoptosis and inflammation (AIM2, caspase 1, GSDMD, MLKL, pyrin, ZBP1)	(10)
Zhang, 2023	Renal injury caused by drugs	Triptolide	<i>In vivo/in vitro</i>	Macrophages	ASC, RIPK3, caspase-8, GSDMD, MLKL, caspase-3, caspase-1	(157)
Xu, 2024	Renal injury caused by drugs	Aristolochic acid	<i>In vivo/in vitro</i>	RTECs	RIPK3, GSDMD, MLKL, caspase-3, caspase-8, ASC	(158)
Li, 2024	Renal injury caused by drugs	CBL0137 + LPS	<i>In vivo/in vitro</i>	Macrophages	ZBP1, ASC, NLRP3, GSDMD, MLKL, caspase-1	(11)
Xie, 2024	Renal injury caused by drugs	Trichloroe- thylene	<i>In vivo/in vitro</i>	Endothelial cells	RIPK1, GSDMD, MLKL, caspase-1, caspase-3, caspase-8, ASC, RIPK3, NLRP3	(6)
Yuan, 2022	Kidney damage caused by other factors	Heatstroke	<i>In vivo/in vitro</i>	BMDMs, peritoneal macrophages and L929 mouse fibroblasts	ZBP1, GSDMD, MLKL, caspase-3, caspase-8, RIPK1, RIPK3	(159)

AKI, acute kidney injury; ATR, atrazine; BMDMs, bone marrow-derived macrophages; CKD, chronic kidney disease; CLP, cecal ligation and puncture; DKD, diabetic kidney disease; FADD, Fas-associated death domain protein; GSDMD, gasdermin D; KIRC/ccRCC, clear cell RCC; KIRC, kidney renal clear cell carcinoma; KIRP, papillary RCC; KICH, chromophobe RCC; LPS, lipopolysaccharide; MLKL, mixed-lineage kinase domain-like protein; NLRP, Nod-like receptor pyrin domain-containing protein; PANII, PANoptosis-Immunity Index; RCC, renal cell carcinoma; RIPK, receptor-interacting protein kinase; RTECs, renal tubular epithelial cells; STZ, streptozotocin; ZBP1, Z-DNA binding protein 1; ATR, atrazine; NA, not available; RIR, Renal ischemia-reperfusion; LYC, lycopenene.

system, the PANoptosis-Immunity Index (PANII). The PANII effectively reflected the immune microenvironment status across RCC subtypes and predicted response to immunotherapy. Functional validation revealed that knockout of the PYCARD gene significantly inhibited proliferation and invasion of KIRC cells *in vitro*, confirming its role in promoting tumor progression (135) (Table I).

CKD and DKD. CKD has emerged as a growing global public health concern, which markedly impairs patient quality of life. Over the past three decades, the global mortality rate associated with CKD has reached 41.5%, with ~1.2 million deaths reported in 2017. By 2040, CKD is projected to become the fifth leading cause of death worldwide (136,137). CKD is a progressive and long-term condition with diverse etiologies; however, renal fibrosis represents the common pathological hallmark driving progression to end-stage renal disease. The fibrotic process in CKD typically begins with

the gradual loss of epithelial cells, including podocytes and tubular cells, as well as endothelial cells, which is followed by progressive glomerular sclerosis, collapse of peritubular capillaries and extensive tubulointerstitial fibrosis. The development of renal fibrosis is tightly associated with sustained inflammation and various forms of cell death (138-140). Regardless of the initial cause of kidney injury, nephrons are continuously lost, and fibrotic lesions advance until end-stage renal disease becomes inevitable. Therefore, targeting cell death pathways represents a potential therapeutic strategy to prevent or slow CKD progression by limiting the loss of functional kidney cells and suppressing inflammation. Notably, apoptosis, necroptosis and pyroptosis have been recognized as central pathogenic events in CKD of different etiologies. A large number of previous studies have confirmed that the pathological mechanisms of CKD and DKD are related to renal cell apoptosis (141-144), necroptosis (138,145-147) and pyroptosis (148,149).

Recent studies have revealed that three death modes occur simultaneously in CKD and DKD, which is different from the single death mode of PCD. Zhang *et al* (150) employed bioinformatics approaches to investigate the relationship between PANoptosis and CKD, identifying two central genes, FOS and PTGS2, as potential mediators. These genes have previously been associated with tissue inflammation, cell death and renal fibrosis, suggesting that PANoptosis may contribute to the onset and progression of CKD through their regulation (151-154). In a mouse model of post-burn CKD, elevated levels of caspase-1, caspase-3 and IL-1 β have been observed in renal tissue, and apoptosis, pyroptosis and necroptosis were demonstrated to be concurrently activated (155). Sustained inflammation following burn injury led to caspase pathway activation, promoting PANoptosis, and aggravating renal injury and CKD progression. Treatment with the anti-inflammatory agent dexamethasone was able to suppress multiple forms of cell death and alleviate renal damage in this model (155) (Table I).

DKD, a major cause of end-stage kidney failure, is marked by progressive podocyte loss. Using single-cell RNA sequencing data, Lv *et al* (156) reported that TRAIL and death receptor 5 (DR5) were highly expressed in the podocytes of patients with DKD. These findings were further validated in renal biopsy samples. *In vitro* and *in vivo* experiments demonstrated that TRAIL induced the expression of PANoptosis-related markers, including caspase-1, caspase-3, phosphorylated (p)-MLKL and p-RIPK1, via DR5 in DKD podocytes. In addition, the simultaneous activation of apoptosis, pyroptosis and necroptosis exacerbated proteinuria and renal injury in mouse models of DKD. These effects were mitigated by TRAIL inhibition or gene knockout, indicating that the TRAIL/DR5 axis mediates podocyte PANoptosis injury in DKD (156) (Table I).

Collectively, these findings suggest that PANoptosis may serve as a promising therapeutic target in CKD and DKD. However, given the complex and heterogeneous nature of CKD pathogenesis, current research on PANoptosis in this context remains limited. Further investigation is needed to elucidate the mechanistic roles and therapeutic implications of PANoptosis across diverse CKD etiologies.

Renal injury caused by drugs and other factors. Recent studies have increasingly focused on the role of PANoptosis in drug-induced renal injury (6,10,11,157,158). One investigation revealed that the herbicide atrazine, known for its nephrotoxic effects, can downregulate Sam50 expression in the kidney, resulting in mitochondrial DNA (mtDNA) instability and the release of mtDNA into the cytoplasm. This mtDNA release activates the stimulator of IFN genes (STING) pathway, which subsequently upregulates inflammatory cytokines and key PANoptosis-associated molecules, including AIM2, ZBP1 and pyrin. These molecular events drive STING-dependent PANoptosis in renal tissue, ultimately leading to renal failure (10).

Triptolide-induced multi-organ damage has also been linked to a systemic inflammatory response and the activation of various lytic cell death pathways. Notably, the cell death triggered by triptolide cannot be mitigated by the inhibition of a single pathway. It has been shown that triptolide simultaneously activates markers of pyroptosis, apoptosis and necroptosis in macrophages. Immunofluorescence and immunoprecipitation

assays have confirmed the colocalization and aggregation of ASC, RIPK3 and caspase-8, promoting the formation of the PANoptosome and inducing PANoptosis, which contributes to both nephrotoxicity and hepatotoxicity. Given that renal tubular epithelial cells and podocytes possess the molecular machinery required for all three forms of cell death, the authors of this previous study hypothesized that PANoptosis likely occurs in these renal cell types as well (157). In aristolochic acid nephropathy (AAN), administration of aristolochic acid I (AAI) has been shown to induce elevations in serum urea nitrogen and creatinine levels, and to induce PANoptosis in renal tubular epithelial cells. Both *in vitro* and *in vivo* experiments have demonstrated that inhibition of PANoptosis may alleviate AAI-induced renal injury, supporting its role in AAN pathogenesis (158). The anticancer agent CBL0137, either alone or in combination with LPS, has been shown to activate systemic inflammation and PANoptosis signaling. In mice, this treatment induced PANoptosis in macrophages and resulted in multi-organ injury, including kidney damage; mechanistically, CBL0137 promoted the formation of Z-DNA in macrophage nuclei, thereby activating ZBP1. By contrast, knockout of ZBP1 significantly reduced cell death induced by CBL0137 combined with LPS, highlighting the essential role of ZBP1 as a core component of the PANoptosome in mediating PANoptosis (11). In a mouse model sensitized to trichloroethylene, PANoptosis was observed in renal endothelial cells, and the pro-inflammatory cytokines TNF α and IFN γ appeared to act synergistically in driving this process. Inhibition of peripheral TNF α and IFN γ attenuated PANoptosis, preserved endothelial function and improved renal outcomes (6).

Beyond drug-induced renal injury, PANoptosis has also been implicated in renal damage resulting from non-chemical stressors. A recent study reported multi-organ injury, including damage to the kidneys and liver, following heatstroke. It was shown that ZBP1 mediates a PANoptosis-like cell death pathway during heatstroke, characterized by concurrent activation of apoptosis, pyroptosis and necroptosis. By contrast, deletion of ZBP1 abrogated this cell death process, and reversed the renal and hepatic damage induced by heatstroke (159) (Table I).

Treatment strategies and clinical significance of PANoptosis. Loss of parenchymal cells, together with proliferation or recruitment of maladaptive cells, disrupts cellular homeostasis and drives kidney injury and fibrosis (160,161). Modulating cell death programs may therefore represent an important approach to limiting renal damage across kidney diseases. Since PANoptosis encompasses multiple PCD patterns simultaneously, targeting and inhibiting these pathways in parallel may enhance renal protection. Although drugs directly targeting PANoptosis have not yet entered clinical trials, a number of compounds that act on its key node molecules are already in the clinical development stage for other indications (162-166), which provides a unique opportunity for the rapid initiation of clinical research on kidney diseases.

Molecules that act as central hubs in PANoptosis, such as ZBP1 and AIM2, can concurrently trigger pyroptosis, apoptosis and necroptosis in response to microbial or endogenous cues. Their inhibition or loss impairs activation of these effector modules and reduces cell death (82,167,168). Notably, these

hubs have been implicated in AKI, RCC, drug-induced nephrotoxicity and other renal pathologies, highlighting their broad relevance. At present, specific inhibitors for ZBP1 and AIM2 are scarce, and traditional treatment strategies mainly focus on the inhibition of their downstream factors. However, some new technologies are attempting to precisely degrade ZBP1. For example, a recent study on the covalent recognition-based PROTAC molecule has confirmed that it can cause upregulation of ZBP1 expression in H1N1 infection models, inhibit the downstream necroptosis pathway, reduce the phosphorylation levels of RIPK3 and MLKL, and simultaneously lower the expression levels of IL-18, IL-6, IL-1 β , TNF- α and IFN- β , effectively alleviating inflammation (169). In tumor research, it has been shown that the ZBP1 agonist CBL0137 can induce potent PANoptosis and antitumor immunity in mouse models of ZBP1-deficient melanoma (170). Conversely, necrosulfonamide, a small molecule inhibitor targeting the ZBP1 RHIM domain, can be used to alleviate therapeutic side effects (such as intestinal damage) (171). Recently, 4-sulfonic calixarenes have been described as being able to block the binding of dsDNA to the HIN200 domain of AIM2 and to inhibit AIM2 *in vivo*, further blocking the release of the downstream factors caspase-1, IL-1 β and GSDMD (172). Further work revealed that these compounds are structurally similar to the clinically approved drug suramin, which can also inhibit AIM2 (172).

Therapeutic targeting of PANoptosome components is also considered promising. For example, the NLRP3 inhibitor MCC950 has been shown to attenuate kidney injury in models of AKI (173-175), CDK (176,177), DKD (178,179) and RCC (180). It has shown good safety and efficacy both *in vivo* and *in vitro*. Another NLRP3 inhibitor, OLT1177 (dapsutrine), has been proven to effectively reduce inflammatory indicators and has been shown to possess a good safety profile in a phase II trial of acute gout attacks (181). This also indicates prospects for the treatment of kidney diseases driven by metabolic stress, such as DKD. Z-VAD-FMK, a broad-spectrum caspase inhibitor widely used to suppress apoptosis (182), and Nec-1, a necroptosis inhibitor targeting RIPK1, have both demonstrated protective effects in various kidney diseases (182,183), but have not yet entered clinical trials. GSK2982772 is another RIPK1 inhibitor that has been tested for safety and efficacy in phase II clinical trials for psoriasis (165,166), rheumatoid arthritis (162) and ulcerative colitis (163). Given that RIPK1 is a key hub of PANoptosis in multiple nephropathy models, reusing it for the treatment of inflammatory nephropathy (such as lupus nephritis) is an attractive clinically available strategy. Caspase-8 functions as a key regulator across pathways, simultaneously influencing apoptosis, necroptosis and pyroptosis, thereby determining the cell death mode following activation signals (62). A recent study reported that inhibition of the caspase-8/caspase-3/NLRP3/GSDME-mediated pathway alleviated pyroptosis and rescued renal tubular cell injury induced by uric acid (184). Another investigation revealed that TP53INP2, an autophagy-related protein, can inhibit RCC progression by regulating the caspase-8 apoptotic pathway (185). Another caspase inhibitor (emricasan) has been shown in a clinical study on non-alcoholic steatohepatitis to significantly reduce ALT levels and the activation of caspase-3/7 in patients with non-alcoholic fatty liver disease.

Although the results of this study have not been clinically translated, it provides a foundation for subsequent research on specific caspase inhibitors (such as those targeting caspase-8) (164). RIPK3 is also another important component of PANoptosomes. A novel inhibitor of RIPK3, Uhl5-38, has been proven to effectively block necroptosis of alveolar epithelial cells caused by IAV infection in mouse models by inhibiting MLKL, and the levels of IL-1 β and IL-18. In addition, it can reduce lung inflammation and mortality without affecting virus clearance or immune response (186). Its efficacy is consistent with other pre-clinical type I kinase inhibitors and comparable to that of currently Food and Drug Administration-approved drugs, such as sorafenib and dasatinib (186). In addition, sorafenib and edaravone have been shown to attenuate renal fibrosis induced by unilateral ureteral obstruction through inhibition of oxidative stress, inflammation and the RIPK3/MLKL pathway (187). Collectively, these findings suggest that targeting hub molecules and components of PANoptosis, including ZBP1, AIM2, RIPK1, NLRP3 and caspase family members, represents a promising therapeutic option for kidney diseases.

However, the interplay among apoptosis, pyroptosis and necroptosis complicates therapeutic development. These pathways often share molecular mediators and defense mechanisms, and they may coexist within the same kidney disease, acting either simultaneously or sequentially across different cell types. Furthermore, inhibition of one pathway may be compensated for by activation of others, resulting in limited therapeutic efficacy with single-target approaches. Therefore, identifying strategies that can simultaneously block multiple forms of cell death remains a key focus for future research.

5. Conclusion

Current evidence has indicated that PANoptosis may serve as a novel and promising therapeutic target in kidney diseases. Unlike interventions aimed at suppressing a single form of PCD, modulation of PANoptosis offers the potential to block multiple cell death pathways concurrently, thereby providing greater therapeutic benefit. This integrated approach represents a new direction for the prevention of kidney injury and the attenuation of disease progression; however, important challenges remain. Although key molecules involved in PANoptosis and their roles in distinct death pathways have been identified, the precise mechanisms by which these factors cooperate within the PANoptosome, and the hierarchy of control governing its assembly and signaling, are not yet fully understood. The dynamic and context-dependent composition of the PANoptosome, shaped by trigger signals, cell type and microenvironment, further complicates efforts to define universal assembly patterns. *In vivo*, notable technical barriers also exist in capturing transient, large multiprotein complexes and their intricate interaction networks. Additionally, the essential components, recruitment rules, sequential assembly mechanisms, and possible molecular switches or master regulators of PANoptosomes remain to be established. Finally, reports of PANoptosis in kidney diseases beyond AKI (8,110-112), CKD (150,155), DKD (156) and RCC (7,9,132-135) are limited (188). Its roles in hypertensive nephropathy, nephrotic syndrome, IgA nephropathy, lupus nephritis and polycystic

kidney disease remain largely unexplored. These knowledge gaps highlight urgent priorities for future investigation.

Summary and outlook. Current research has revealed the mechanistic complexity of PANoptosis, and its involvement in the onset, progression and potential treatment of AKI, RCC, CKD, DKD and drug-induced renal injury. The activation and composition of the PANoptosome are highly variable, reflecting the context-dependent nature of PANoptosis and offering deeper insight into its regulatory role in cell death. As a result, PANoptosis has emerged as a key process closely associated with the development of various kidney diseases and presents a promising avenue for identifying novel therapeutic targets. Nevertheless, the role of PANoptosis in disease is not unidirectional; its effects on disease progression and treatment can be dual in nature, which is particularly evident in renal malignancies, where PANoptosis may exert both pro-tumor and antitumor effects. Furthermore, the dominant cell death pathways and the composition of PANoptotic complexes may vary depending on disease etiology or pathological stage. In AKI and CKD, greater attention should be directed toward cell death occurring within the renal parenchyma, whereas in RCC, further investigation is required to elucidate how the tumor immune microenvironment shapes PANoptosis. These observations underscore the need for continued in-depth research to elucidate its regulatory mechanisms and disease-specific outcomes. Although recent advances have expanded the understanding, the clinical application of PANoptosis in kidney disease remains in its early stages, and numerous questions remain unanswered. For example, while it is known that the composition of the PANoptosome varies with different stimuli or disease states, the mechanisms underlying this variability remain unclear. Additionally, although specific sensors are required to initiate PANoptosis in response to pathogens or damage-associated signals, the precise identity and disease-specific roles of these sensors remain to be fully defined. Therefore, several future research directions merit attention. First, it is essential to discover and validate reliable biomarkers that can facilitate the precise selection of therapeutic strategies targeting PANoptosis. Second, kidney cell-specific mechanisms should be elucidated, as tubular epithelial cells, podocytes and endothelial cells may assemble PANoptosomes with distinct components and functional outputs, which is crucial for therapeutic specificity. Third, a detailed characterization of the assembly and regulatory mechanisms of renal PANoptosomes is needed to support the identification of small-molecule targets. Fourth, across diverse renal diseases, the validation of hub molecules and the identification of regulators of PANoptosomes will provide a foundation for the development of selective inhibitors.

Since its initial conceptualization in 2019, the concept of PANoptosis has rapidly advanced as a field, offering a transformative framework to understand the intricate interplay between cell death and inflammation in kidney diseases. Unlike strategies that focus on blocking a single cell death pathway, targeting the integrated process of PANoptosis holds promise for achieving more effective protection of kidney tissue, attenuation of inflammation and improved clinical outcomes. Despite ongoing challenges, continued investigation into kidney-specific mechanisms of PANoptosis, together with the verification of therapeutic targets, the development of efficient and safe pharmacological agents, and the incorporation of

precise biomarkers, is expected to drive major advances. Thus, targeted modulation of PANoptosis may emerge as a breakthrough approach in nephrology, providing novel therapeutic opportunities for currently refractory kidney diseases.

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LJ wrote the original manuscript. YL and LZ revised the manuscript. ZF and MW searched the literature, and made substantial contributions to conception and design. ZM edited the manuscript. ML revised and supervised the manuscript. Data authentication is not applicable. All authors contributed to the article, and read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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