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# Pyroptosis: The Determinator of Cell Death and Fate in Acute Kidney Injury

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**Keywords**
Acute kidney injury · Pyroptosis · Mechanism · Treatment

**Abstract**
***Background:*** Acute kidney injury (AKI) is kidney damage that leads to a rapid decline in function. AKI primarily occurs when the tubular epithelium is damaged, causing swelling, loss of brush margin, and eventual apoptosis. Research has shown that tubular epithelial cell damage in AKI is linked to cell cycle arrest, autophagy, and regulation of cell death. ***Summary:*** Pyroptosis, a type of programmed cell death triggered by inflammation, is believed to play a role in the pathophysiology of AKI. Cumulative evidence has shown that pyroptosis is the main cause of tubular cell death in AKI. Thus, targeted intervention of pyroptosis may be a promising therapeutic approach for AKI. This review delves deep into the cutting-edge research surrounding pyroptosis in the context of AKI, shedding light on its intricate mechanisms and potential implications for clinical practice. Additionally, we explore the exciting realm of potential preclinical treatment options for AKI, aiming to pave the way for future therapeutic advancements. ***Key Messages:*** Pyroptosis, a highly regulated form of cell death, plays a crucial role in determining the fate of cells during the development of AKI. This intricate process involves the activation of inflammasomes, which are multi-protein complexes that initiate pyroptotic cell death. By understanding the mechanisms underlying pyroptosis, researchers aim to gain insights into the pathogenesis of AKI and potentially identify new therapeutic targets for this condition.

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## Introduction

Acute kidney injury (AKI) is a severe condition characterized by a rapid decline in kidney function, often caused by toxins, contrast agents, sepsis, and cardiovascular surgery [1, 2]. The prevalence of AKI is estimated to be between 1% and 66% [3], and the in-hospital mortality rate from AKI is 12.4% [4]. In addition to the high medical costs associated with AKI, there is an increased risk of developing chronic kidney disease and cardiovascular disease [5, 6]. AKI can lengthen hospital stays and increase medical expenses [7]. Currently, there are no effective treatments or interventions for AKI [8]. However, research on the mechanism of AKI could lead to better prognoses. Inflammation and tubular epithelial cell (TEC) death are typical features of AKI. TECs are the primary target of AKI, experiencing degeneration, apoptosis, necrosis, and shedding due to factors such as ischemia, contrast agents, and toxins [9]. The damaged TECs synthesize and release bioactive factors and chemokines, which contribute to the chemotaxis and

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activation of inflammatory cells, causing an exacerbated inflammatory response [10]. Ultimately, this leads to poor repair and proliferation of TECs, culminating in apoptosis, pyroptosis, and necrosis of TECs [5].

Cell death is a vital biological process that can occur through various mechanisms resulting from normal tissue metabolism or physical stress. Cell death can be classified as either programmed or non-programmed [11]. Apoptosis was previously thought to be the only form of programmed cell death until the discovery of necrotic apoptosis and inflammatory cell death. Currently, the Cell Death Nomenclature Commission recognizes 12 distinct types of cell death [12]. Pyroptosis, initially believed to be a form of apoptosis, was discovered by Zychlinsky et al. [13] in 1992 when murine macrophages were infected with Salmonella typhi. Pyroptosis is fundamentally different from apoptosis and depends on Caspase-1. In contrast to other forms of cell death, pyroptosis involves cell growth until the membrane bursts, leading to significant inflammatory reactions [14]. The process consists of the activation of both the classical and nonclassical inflammasome pathways [15], with caspases and Gasdermin D (GSDMD), a family of molecules, playing a vital role [16, 17]. According to Shao et al. GSDMD, a direct molecular inducer of pyroptosis, induces the formation of tiny pores in the cell membrane that allow the release of potassium ions and cytokines like interleukin 18 (IL-18) and IL-1 leading to pyroptosis [18] (Fig. 1). Pyroptosis has been observed in different medical situations, including lipopolysaccharide (LPS)-induced pyroptosis, alcoholic hepatitis-induced hepatocytes, and cardio-cerebral ischemia-reperfusion injury (IRI) [19, 20]. Recent studies have focused on pyroptosis in AKI and have discovered small molecule substances that effectively minimize the damage caused by AKI, laying the foundation for AKI therapies (Fig. 2). This work provides an overview of recent developments in understanding pyroptosis in AKI and its potential treatment.

## Ischemia-Reperfusion Injury AKI

### *Pyroptosis in TECs*

In 2014, pyroptosis was identified in the IRI model of AKI (IRI-AKI). The levels of pyroptosis-related proteins, including Caspase-1, Caspase-11, and IL-1β, substantially increased after 6 h of IRI and reached their highest levels after 12 h. Additionally, hypoxia can result in pyroptosis in the renal TEC line (NRK-52E), characterized by the creation of cell membrane pores and the significant release of lactate dehydrogenase (LDH). Low-dose thiomycin pretreatment can prevent IRI-induced pyroptosis and renal tissue damage [21]. Pyroptosis of RTECs is a crucial event following IRI, as demonstrated by the involvement of the Caspase-1 and Caspase-11 families. In contrast, using Caspase-11 knockout mice to create an IRI-AKI model showed less renal function deterioration, tubular damage, macrophage and neutrophil infiltration, and urinary IL-18 excretion [22]. Nuclear factor E2 correlated factor 1 (Nrf1) is an important transcription factor that plays a crucial role in regulating cellular oxidative stress levels. It has been suggested that microRNA (miRNA) miR-92a-3p could potentially target Nrf1. Oxidative stress can be reduced by inhibiting miR-92a-3p, thereby decreasing the expression levels of NOD-, leucine-rich repeat- and pyrin domain-containing protein 3 (NLRP3), Caspase-1, GSDMD-N, IL-1β, and IL-18 in vitro and in vivo. The heme oxygenase-1 (HO-1) inhibitor zn-prophyrin-IX can inhibit Nrf1 expression, decrease oxidative stress, and pyroptosis. Therefore, by targeting Nrf1, inhibition of miR-92a-3p can alleviate oxidative stress and pyroptosis in RTEC in IRI [23]. The spermatogenesis transcription factor (Tisp40) is also associated with renal IRI. Tisp40 and GSDMD-N expression significantly increased in the IRI-AKI model, accompanied by RTEC pyroptosis. Tisp40 overexpression can worsen RTEC pyroptosis, as evidenced by increased levels of GSDMD-N, NLRP3, and other proteins. Small interfering RNA targeted intervention in Tisp40 expression in cell experiments can reverse the above situation [24]. Furthermore, decreased Sirtuin 1 (SIRT1) protein levels and endoplasmic reticulum stress (ERS) have been observed in type 1 diabetes mellitus with IRI damage. Various studies have indicated the notable involvement of pyroptosis, a programmed cell death mechanism, in renal IRI, particularly in diabetic rodents, where SIRT1-induced ERS activation mediates it [25]. Tripartite motif containing 8 (TRIM8), a protein member of the TRIM family, has also been linked to IRI. Knocking down TRIM8 results in improved cell viability, reduced expression of reactive oxygen species (ROS) and pyroptosis-associated proteins such as NLRP3, apoptosis-associated speck-like protein containing a CARD (ASC), Caspase-1, Caspase-11, IL-1β, and GSDMD-N, indicating its role in regulating oxidative stress caused by hypoxia/reoxygenation (H/R) by activating the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway, and subsequently reducing pyroptosis and apoptosis in vitro [26]. Apart from GSDMD-mediated pyroptosis, a study has also identified the involvement of GSDME-mediated pyroptosis in cell damage caused by in vitro and in vivo models of cobalt chloride-induced H/R-AKI. Caspase-3, Caspase-8, and Caspase-9-specific inhibitors can significantly suppress GSDME-mediated pyroptosis. Autophagy, upstream of pyroptosis, can induce GSDME-mediated pyrosis through both endogenous and exogenous apoptosis pathways [27].

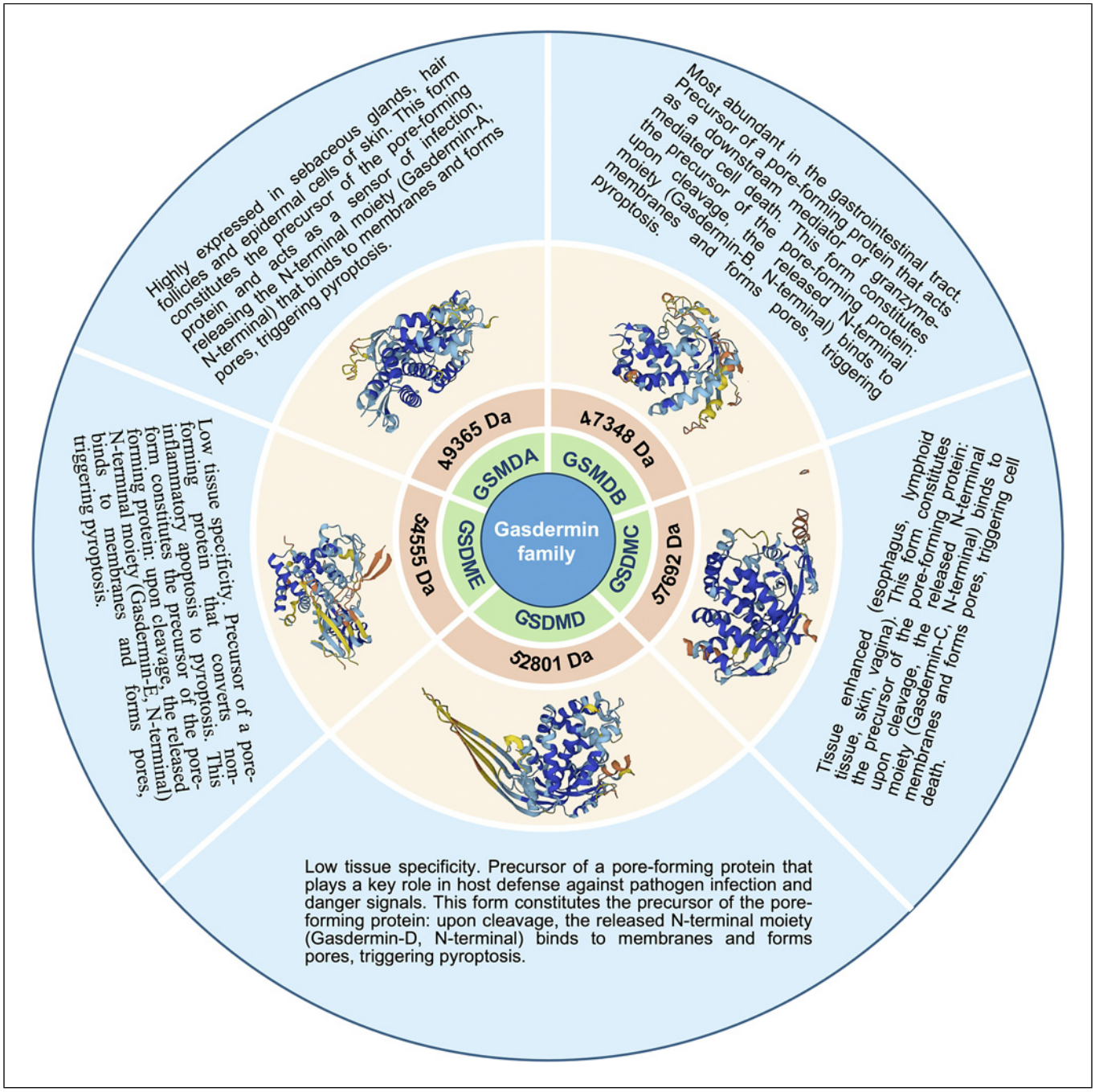



**Fig. 1.** Basic characteristics of executioners of pyroptosis. Information was collected from GeneCards, The Human Protein Atlas, and the 3D structure was predicted using the AlphaFold2.

*Targeted Intervention for Pyroptosis in IRI-AKI*

Next, we summarized the evidence that targeted intervention for pyroptosis is a potential therapy for IRI and holds significance in clinical settings (Table 1). Tajima et al. [28] discovered that treatment with β-hydroxybutyric acid (β-OHB) in mice can reduce renal tissue damage by decreasing the expression of Caspase-1 and pro-inflammatory cytokines. Further research confirmed that β-OHB inhibits pyroptosis via epigenetic control of Forkhead Box O3 (FOXO3) [28]. Disulfiram, a medication used

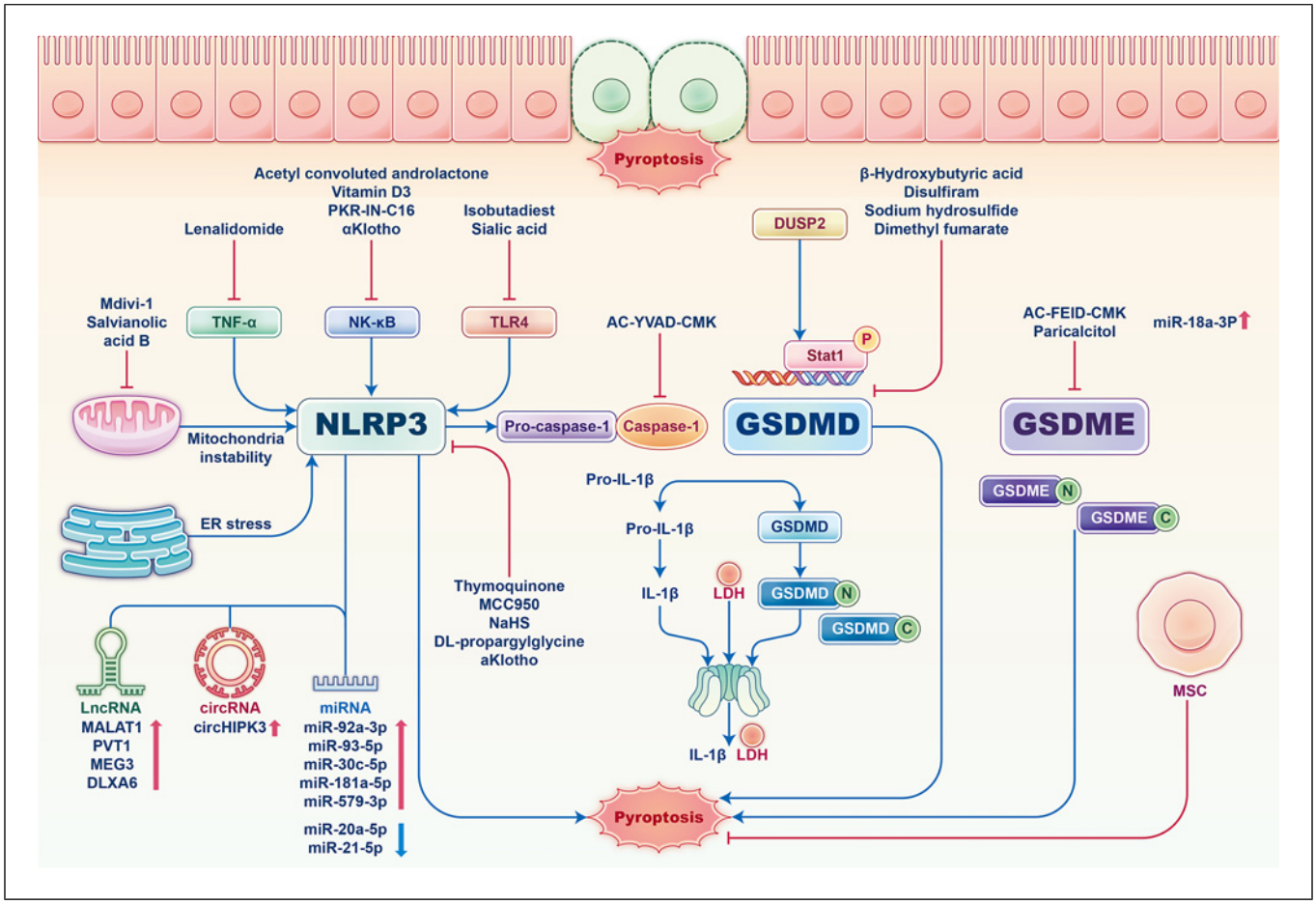



**Fig. 2.** Targets and regulatory mechanisms of pyroptosis in relation to AKI.

to treat alcohol addiction, has been found to reduce cellular pyroptosis in mouse macrophages and improve renal impairment following IRI in mice. However, the drug mainly blocks the classical pyroptosis-related proteins, Caspase-11, and GSDMD-mediated pyroptosis, as opposed to the nonclassical pyroptosis pathway represented by NLRP3 and ASC. A simulation of three-dimensional space configuration revealed a binding between disulfiram and the Toll/interleukin-1 receptor (TIR) domain of Toll-like receptor 4 (TLR4), leading to the assumption that disulfiram might inhibit cell pyroptosis by antagonizing TLR4 and inhibiting the Caspase-11/GSDMD pathway [29]. In our previous study, we discovered that it blocks GSDMD-induced pyroptosis in TECs by reducing the transcriptional control of GSDMD through phosphorylation of signal transduction and transcriptional activator 1 in the IRI-AKI model [30]. Other studies have shown that vitamin D3 can reduce the production of ROS and inhibit the nuclear factor kappa B (NF-κB) signaling pathway, thus hindering pyroptosis [31]. Salvianolic acid B, a water-soluble compound extracted from Salvia, has potent antioxidant properties, and Pang et al. [32] discovered that it significantly decreases the expression of NLRP3, Caspase-1, GSDMD, and IL-1β in kidney tissues of the IRI-AKI group. In vitro experiments have further confirmed that salvianolic acid B pretreatment helps increase Nrf2 levels by inhibiting oxidative stress, pro-inflammatory cytokines, and NLRP3 inflammasome activation, reducing pyroptosis. Ni et al. [33] reported decreased $H_2S$ levels and $H_2S$ synthetase activity in the IRI-AKI model. Furthermore, treating NaHS to increase $H_2S$ levels improves renal histopathological damage and mitigates pyroptosis. In vitro experiments have also shown that NaHS can reverse H/R-induced cell damage. MCC950 (NLRP3 inhibitor) or DL-Propargylglycine (PAG, CSE inhibitor) can also significantly reduce pyroptosis, indicating that inhibiting the NLRP3/Caspase-1 axis may be a feasible approach to mitigate pyroptosis and reduce renal damage [33].

**Table 1.** Potential treatment methods for treating pyroptosis in AKI

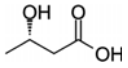
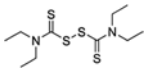
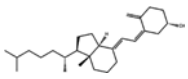
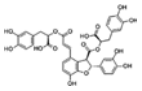
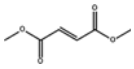
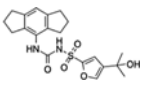
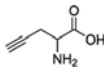
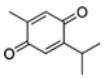
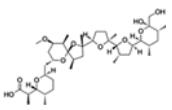
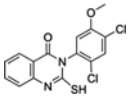
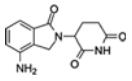
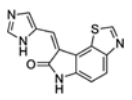
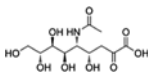
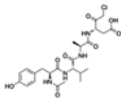
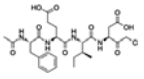
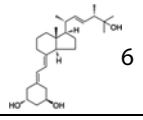
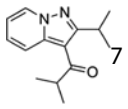
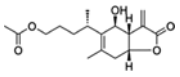
| | Small molecules or drugs | Molecular formula | Chemical structure | AKI type |
|---|---|---|---|---|
| GSDMD inhibitors | β-Hydroxybutyric acid [28] | $C_4H_8O_3$ |  | IRI-AKI |
| | Disulfiram [29] | $C_{10}H_{20}N_2S_4$ |  | IRI-AKI |
| | Vitamin D3 [31] | $C_{27}H_{44}O$ |  | IRI-AKI |
| | Salvianolic acid B [32] | $C_{36}H_{30}O_{16}$ |  | IRI-AKI |
| | Sodium hydrosulfide [33] | NaHS | NA | IRI-AKI |
| | Dimethyl fumarate [34] | $C_6H_8O_4$ |  | RI-AKI |
| NLRP3 inhibitors | MCC950 [33] | $C_{20}H_{24}N_2O_5S$ |  | IRI-AKI |
| | DL-propargylglycine [33] | $C_5H_7NO_2$ |  | IRI-AKI |
| | TQ [35] | $C_{10}H_{12}O_2$ |  | SA-AKI |
| | Nigericin [36] | $C_{40}H_{68}O_{11}$ |  | CIS-AKI |
| DRP1 inhibitors | Mdivi-1 [37] | $C_{15}H_{10}Cl_2N_2O_2S$ |  | SA-AKI |

**Table 1** (continued)

| | Small molecules or drugs | Molecular formula | Chemical structure | AKI type |
|---|---|---|---|---|
| TNF-α inhibitors | Lenalidomide (CC-5013) [38] | $C_{13}H_{13}N_3O_3$ |  | SA-AKI |
| | PKR-IN-C16 [39] | $C_{13}H_8N_4O_5$ |  | SA-AKI |
| | Sialic acid [40] | $C_{11}H_{19}NO_9$ |  | SA-AKI |
| | Bone marrow mesenchymal stem cells [41] | NA | NA | SA-AKI |
| Caspase-1 inhibitors | AC-YVAD-CMK [42] | $C_{24}H_{33}ClN_4O_8$ |  | SA-AKI |
| GSDME inhibitors | ACE-FEID-CMK [43] | $C2_7H_{37}ClN_4O_9$ |  | SA-AKI |
| | Paricalcitol [44] | $C_{27}H_{44}O_3$ |  | CIS-AKI |
| TLR4 antagonist | Ibudilast [45] | $C_{14}H_{18}N_2O$ |  | FA-AKI |
| NF-κB inhibitors | Acetylbritannilactone [46] | $C_{17}H_{24}O_5$ |  | CI-AKI |
| | αKlotho [47] | NA | NA | RI-AKI |

IRI-AKI, ischemia-reperfusion injury acute kidney injury; SA-AKI, sepsis-associated acute kidney injury; CIS-AKI, contrast-induced acute kidney injury; RI-AKI, rhabdomyolysis-induced acute kidney injury.

*Sepsis AKI*

Sepsis-associated AKI (SA-AKI) is prevalent in patients with severe sepsis. It is regarded as one of the most severe sepsis-related complications, with sepsis causing over 50% of the AKI in the intensive care unit, significantly increasing morbidity and mortality [48]. While previous studies suggested that the primary mechanism of SA-AKI was renal hypoperfusion resulting from vasodilation, hypotension, and shock caused by sepsis, it has been recently discovered that programmed cell death, including apoptosis, necrotizing apoptosis, pyroptosis, and autophagy, are involved in SA-AKI. Autophagosome formation in the early stages of SA-AKI helps inhibit various types of programmed cell death, but with disease progression, programmed cell death begins to play a critical role, such as Caspase-11 and Caspase-1-dependent GSDMD-mediated pyroptosis [49]. It was suggested that typical pyroptosis activation and inflammasome formation, delayed biological response by the kidneys to septic injury, dominated the

**Table 2.** Dysregulation patterns of non-coding RNA in pyroptosis in AKI

| | Type | Location | Regulation | AKI type |
|---|---|---|---|---|
| miR-92a-3p [23] | microRNA | Chromosome 13 | Upregulation | IRI-AKI |
| miR-93-5p [53] | microRNA | Chromosome 7 | Upregulation | SA-AKI |
| miR-579-3p [61] | microRNA | Chromosome 5 | Upregulation | SA-AKI |
| circHIPK3 [67] | circRNA | Chromosome 11p13 | Upregulation | SA-AKI |
| MALAT1 [68] | lncRNA | Chromosome 11q13.1 | Upregulation | SA-AKI |
| PVT1 [69] | circRNA | Chromosome 8q24 | Upregulation | SA-AKI |
| miR-181a-5p [71] | microRNA | Chromosome 1 | Upregulation | SA-AKI |
| MEG3 [72] | lncRNA | Chromosome 14q32.3 | Upregulation | SA-AKI |
| DLX6-AS1 [73] | lncRNA | Chromosome 7q21.3 | Upregulation | SA-AKI |
| miR-30c-5p [74] | microRNA | Chromosome 1 | Upregulation | SA-AKI |
| miR-20a-5p [69] | microRNA | Chromosome 13 | Downregulation | SA-AKI |
| miR-21-5p [70] | microRNA | Chromosome 17 | Downregulation | SA-AKI |

IRI-AKI, ischemia-reperfusion injury acute kidney injury; SA-AKI, sepsis-associated acute kidney injury.

transition from AKI to chronic kidney disease [50]. In addition, SA-AKI pathophysiology involves various cell types, including macrophages, vascular endothelial cells, and RTECs, which undergo different modes of cell death. Therefore, targeted interventions addressing each cell type's specific mode of cell death can mitigate AKI damage [51].

*Macrophage Pyroptosis in SA-AKI*

The classic model of SA-AKI is LPS-induced SA-AKI, characterized by pyroptosis of RTECs as evidenced by the increased expression of pyroptosis-related proteins Caspase-11 and GSDMD. The suppression of proteins linked to pyroptosis in mice exposed to LPS occurred significantly in cases where the mice were deficient in Caspase-11. Pyroptosis of RTECs resulting from Caspase-11 has been identified as a prominent factor in SA-AKI [52]. In addition to SA-AKI, there is a significant influx of inflammatory cells, including both M1 and M2 macrophages, in renal tubules, which play a vital role in controlling inflammation. Recent research has suggested that M1 and M2 macrophages contribute to the onset of AKI by producing inflammatory factors and causing cell death, including pyroptosis. MiR-93-5p, involved in the regulation of pyroptosis, was found in the exosomes of M1 and M2 macrophages by Juan et al. [53]. Moreover, tumor necrosis factor exosomes (TNF-Exo), released by TNF-stimulated neutrophils, stimulates M1 macrophage activation and controls NLRP3 inflammasome expression through the NF-κB signaling pathway, causing macrophage pyroptosis [54]. Regarding SA-AKI, RTEC is the paramount affected cell, and LPS-mediated RTEC pyroptosis plays an essential role in the pathophysiology of AKI. Macrophage migration inhibitory factor (MIF) and pyroptosis-associated protein were abundantly expressed in cecal ligation and aspiration (CLP)-induced SA-AKI mouse model mouse kidney tissue and LPS-treated human kidney-2 cells (HK-2 cells). Additionally, NLRP3 inflammasome was significantly reduced in CLP-induced SA-AKI after the inhibition of MIF topoisomerase activity by (S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid methyl ester (ISO-1). In vitro MIF knockdown reduced NLRP3 inflammasome-mediated pyroptosis in LPS-damaged HK-2 cells [55]. Pyroptosis also occurred in renal tubular cells with increased insulin-like growth factor 2 mRNA binding protein 1 [56].

*Regulation of Pyroptosis in SA-AKI*

Interferon regulatory factor 2 (IRF2) expression was significantly increased in serum and LPS-treated HK-2 cells in patients with SA-AKI. Downregulation of IRF2 promoted cell proliferation and inhibited cell death and apoptosis. IRF2 inhibition reduced the levels of inflammatory factors (IL-1β, IL-18, IL-6, and TNF-α), decreased the expression of Caspase-4 and GSDMD, and improved the survival rate of IRF2−/− mice after CLP. It was suggested that IRF2 deficiency inhibits inflammation and pyroptosis by inhibiting nonclassical inflammasomes [57]. The matrix glycoprotein thrombospondin-1 and upstream stimulatory factor 2 are also highly expressed in SA-AKI patients. Silencing hrombospondin-1 protects mice from SA-AKI, reducing the expression of NLRP3, Caspase-1, GSDMD-N, IL-1β, and IL-18 while increasing cell viability and reducing LDH activity, thus reversing cell

morphology [58]. Targeted interventions were directed at Krüppel-like factor 6 (KLF6) and Metadherin (Mtdh) to significantly inhibit the occurrence of pyroptosis in vivo and in vitro [59, 60]. Conversely, Growth arrest-specific 5 (GAS5) and SIRT1 expression decreased significantly, while miR-579-3p increased substantially in the SA-AKI model. GAS5 triggered the SIRT1/PGC-1a/Nrf2 pathway negatively, reducing pyroptosis and directly modulating miR-579-3p, providing a protective effect on SA-AKI [61]. Another study showed that the rate of pyroptosis increased following the pretreatment of cells with Znpp and decreased following pretreatment with hemin. HO-1 inhibited pyroptosis via tensin homologe (PTEN)-induced putative kinase 1 (PINK1) in PINK1 KO RTECs [62]. Transcription factors may also play an essential role in the signaling pathway in the regulation of pyroptosis. For instance, ETS Proto-Oncogene 1 (ETS1), a transcription factor, can bind to the upstream promoter transcription site of NLRP3 and trans-activate the NLRP3 of RTEC, knockdown of ETS1 significantly inhibits pyroptosis [63]. Similarly, in LPS/ATP-induced HK-2 cells, the enhancer binding protein β (C/EBPβ) or mitochondrial transcription factor A (TFAM) is upregulated, knocking down C/EBPβ inhibits LPS combined with ATP-induced cell damage and the secretion of IL-1β and IL-18. Additionally, C/EBPβ upregulates TFAM expression levels by binding directly to the TFAM promoter. TFAM overexpression reversed the effect of C/EBPβ deletion on pyroptosis. Knocking down C/EBPβ inhibits the NLRP3 inflammasome-mediated Caspase-1 signaling pathway by inactivating the TFAM/advanced glycation end-products pathway. The interaction of C/EBPβ and TFAM promotes pyroptosis by activating the NLRP3/Caspase-1 signaling axis, thereby promoting the occurrence of AKI [64]. TRAF-interacting protein with forkhead-associated domain is also involved in pyroptosis by activating mitochondrial damage and may be a therapeutic target to treat SA-AKI [43]. Researchers have also found that Caspy2-GSDMEb-mediated pyroptosis of fish RTEC is the key to triggering SA-AKI. ACE-FEID-CMK, a competitive peptide at the GSDMEb cleavage site in zebrafish, has been shown to effectively alleviate SA-AKI at the in vivo level by blocking the pyroptosis signaling pathway [65].

*Non-Coding RNA and Pyroptosis*

Non-coding RNA (ncRNA) is a functional RNA molecule that is transcribed from DNA but not translated into proteins, mainly including miRNAs and long ncRNAs (lncRNA), circular RNA (circRNA), small nucleolar RNA, and tRNA. There is growing evidence that ncRNAs play an essential role in kidney damage and repair [66]. CircRNA has been involved in several inflammatory diseases, including SA-AKI (Table 2). In the *Candida albicans*-induced SA-AKI model, the authors observed high expression of circRNA homeodomain-interacting protein kinase 3 (circHIPK3) in SAKI, while circHIPK3 silencing reduced kidney damage in SA-AKI mice and enhanced cell viability in SA-AKI by reducing inflammatory responses and cellular senescence. Mechanically, circHIPK3 upregulates KLF6 expression by competitively binding miR-124-3p, thereby promoting the binding of KLF6 and NLRP3, activating NLRP3/Caspase-1-mediated cell pyroptosis, and ultimately aggravating the SA-AKI inflammatory response [67]. In addition, in lncRNA, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) and miRNA-135b-5p bind to regulate NLRP3 positively. This paper suggests the role of lncRNA MALAT1/miRNA-135b-5p/NLRP3 signaling cascade in regulating LPS-induced pyroptosis in HK-2 cells [68]. Not only that, but also research teams found that plasmacytoma variant translocation 1 (PVT1) expression was significantly elevated in SA-AKI mouse models and LPS-induced HK-2 cells, while miR-20a-5p expression was significantly reduced. The knockdown of miR-20a-5p significantly promoted LPS-induced cell pyroptosis. In addition, PVT1 knockdown can target the miR-20a-5p/NLRP3 signaling pathway to inhibit LPS-induced pyroptosis [69]. miR-21-5p in extracellular vesicles obtained from adipose tissue-derived stromal cells facilitates TEC repair in AKI by reducing TEC pyroptosis and inflammatory response [70]. miR-181a-5p inhibits pyroptosis in sepsis-induced AKI by downregulating NIMA-related kinase 7 (NEK7) [71]. Maternal expression gene 3 (MEG3) is an imprinted gene involved in tumorigenesis and is associated with cell pyroptosis in multiple organs. Both LPS-induced animal and cellular models found significant upregulation of MEG3 expression. MEG3-knockdown RTEC treated with LPS showed decreased pyroptosis cells, downregulation of LDH, IL-1β, and IL-18 secretion, and decreased GSDMD expression. Bioinformatics analysis screened miR-18a-3P, and further experiments showed that MEG3 controls GSDMD expression by acting as a ceRNA for miR-18a-3P, thereby promoting pyroptosis in RTEC cells [72]. In addition, lncRNA distal-less homeobox 6 antisense 1 (DLX6-AS1) expression is upregulated in the serum of patients with septic AKI. DLX6-AS1 expression was

positively correlated with serum creatinine levels in patients with septic AKI. In vitro experiments showed that DLX6-AS1 was significantly upregulated after LPS treatment of HK-2 cells, accompanied by increased expression of NLRP3, IL-1β, and IL-18 and the production of pyroptosis, while DLX6-AS1 knockdown could inhibit the pyroptosis induced by LPS-2 cells [73]. In addition to lncRNAs, small RNAs are also involved in the regulation of pyroptosis. Studies have found that miR-30c-5p expression decreases in SA-AKI models and is associated with NLRP3/Caspase-1-mediated pyroptosis. Overexpression of miR-30c-5p can alleviate renal damage by inhibiting pyroptosis of HK-2 cells, and thioredoxin-interacting protein (TXNIP) is further found to be the direct target of miR-30c-5p. The upregulation of miR-30c-5p inhibited the expression of TXNIP, thereby inhibiting the expression of NLRP3, ASC, Caspase-1, and the secretion of inflammatory cytokines [74].

*Potential Treatment for Pyroptosis*

The investigation of pyroptosis in SA-AKI has also identified certain targets for intervention that hold clinical translational significance, such as natural products, biological agents, and small molecule compounds (Table 1). Thymoquinone (TQ) is one of the most potent ingredients in black seeds. It has a variety of beneficial properties, including anti-inflammatory and antioxidant activity. The possible protective effect of TQ on kidney injury in septic BALB/c mice has been reported in the literature. TQ inhibits cecal ligation and perforation (CLP)-induced elevated serum creatinine and urea nitrogen levels. At the same time, it can significantly inhibit CLP-induced high levels of NLRP3, Caspase-1, Caspase-3, Caspase-8, TNF-α, IL-1β, and IL-6, indicating that TQ may be a potential therapeutic agent for LPS-induced AKI [35]. Mitochondria play a vital role in energy metabolism. Dynamin-related protein 1 (DRP1) is an essential regulator of mitochondrial division. A significant increase in DRP1 expression was observed in animal and cellular SA-AKI models. The DRP1 inhibitor Mdivi-1 can reduce NLRP3 inflammasome-mediated pyroptosis and improve mitochondrial function. It has been suggested that the mechanism of action of Mdivi-1 may inhibit mitochondrial division, protect mitochondrial function, and thus reduce pyroptosis [37]. AKI is a common complication of acute liver failure (ALF). Wang et al. [38] established ALF and AKI mouse models using LPS/D-Gal and the TNF-α inhibitor CC-5013 (lenalidomide). The study found a significant increase in TNF-α/the high mobility group box 1 (HMGB1) pathway activation and cell pyroptosis in the LPS+WT group. Using TNF-α inhibitor CC-5013 can significantly improve the pathological damage and liver and kidney function of mice and reduce M1 macrophage infiltration. Its main mechanism is to inhibit the activation of the TNF-α/HMGB1 signaling pathway and mitigate pyroptosis. The TNF-α/HMGB1 inflammatory signaling pathway was shown to play an essential role in the apoptosis of ALF and AKI [38]. AKI often undergoes mitochondrial division. Previous studies have shown that HO-1 has cytoprotective effects on AKI during endotoxin shock. In the LPS-induced rat SA-AKI model, HO-1 and PINK1 were significantly elevated at both the mRNA and protein levels, and rats showed increased inflammation, oxidative stress, mitochondrial division, and pyroptosis levels. After the upregulation of HO-1 in normal rats, pyroptosis was inhibited, mitochondrial division and oxidative stress inflammatory response were reduced, and renal function was improved. This effect was reversed by adding Znpp, a HO-1 inhibitor [75]. Protein kinase R (PKR) is involved in the inflammatory response of bacterial infection, and the specific PKR inhibitor C16 (PKR-IN-C16) can effectively inhibit LPS-induced elevation of pro-inflammatory cytokines and chemokines. C16 blocks the activation of NF-κB and inhibits the PKR/eIF2α signaling pathway in AKI after LPS stimulation. In addition, C16 significantly inhibits pyroptosis, mainly by reducing the expression of NAIP, CIITA, HET-E, and TP1, leucine-rich repeat, NLRP3, Caspase-1, IL-1β, and IL-18 proteins [39]. Sialic acid, also known as N-acetylneuraminic acid, neutralizes LPS toxicity and reduces renal failure in early treatment of SA-AKI by reducing LPS toxicity and subsequently inhibiting LPS-activated TLR4/PKC/gp91/ER stress/apoptosis/autophagy/pyrosis signaling [40]. Bone marrow mesenchymal stem cells (BMSCs) are a class of adult stem cells present in bone marrow tissue, and studies have confirmed that exogenous administration of BMSCs can reduce pathological damage in SA-AKI rats. Its main mechanism is to inhibit inflammation and promote mitochondrial autophagy in RTEC and HK-2 cells of SA-AKI rats while upregulating the expression of Parkin and SIRT1 in HK-2 cells, thereby inhibiting apoptosis and cell pyroptosis of RTECs in kidney tissues [41]. Also, human BMSCs-derived extracellular vesicles reduce inflammation and pyroptosis in AKI via miR-223-3p/the epigenetic eraser histone deacetylase 2 (HDAC2)/sucrose nonfermenting 1-related kinase (SNRK) [76]. AC-YVAD-CMK is a Caspase-1 inhibitor,

and administration of AC-YVAD-CMK significantly reduces SA-AKI, which mainly inhibits the accumulation of neutrophils and macrophages in kidney tissue, inhibits the production of inflammatory cytokines and reduces the expression of Caspase-1, NLRP-1, IL-1β, IL-18, and GSDMD in renal tissue. The Caspase-1 inhibitor AC-YVAD-CMK exerts a renoprotective effect by inhibiting pyroptosis [42]. Saroglitazar (SAR), a dual PPAR-α/γ agonist, alleviates rats' LPS-induced hepatic and renal injury. SAR could be considered a prophylactic anti-inflammatory antioxidant drug against LPS-induced liver and kidney injury [77].

### Poison-Induced AKI

*Cisplatin-Induced AKI*

Cisplatin is one of the most effective antineoplastic drugs, but its use is limited due to its high degree of nephrotoxicity. Cisplatin-induced AKI is clinically common and a well-established model for laboratory research into AKI. Literature reports from the past 3 decades have shown that a variety of cell death methods, including apoptosis, necrosis, pyroptosis, ferroptosis, and mitochondrial permeability transition-mediated necrosis, are involved in cisplatin-induced AKI pathogenesis [78]. In recent years, it has been discovered that the active form of GSDMD, GSDMD-N, mediates inflammatory cell death in a variety of diseases. However, the role of GSDMD shear fragments (GSDMD-N) in CIS-AKI is unclear. Li et al. [79] found that a significant increase in GSDMD-N was observed in the CIS-AKI model, while in the GSDMD strip model, the shear fragment of GSDMD-N was significantly reduced, and renal function damage and inflammation were reduced considerably. Injection of GSDMD-N clipping fragments through the tail vein can aggravate kidney damage and inflammation. These findings suggest that activation of GSDMD may be involved in cisplatin-induced AKI by triggering pyroptosis [79]. Miao et al. [22] upregulated Caspase-11 in primary RTECs treated with cisplatin or H/R to promote shearing and conversion of GSDMD to GSDMD-N, thereby triggering cell scorching and promoting IL-18 release. Vitamin D/vitamin D receptor (VDR) has been shown to inhibit NF-κB-mediated inflammation. High-dose paricalcitol (a VDR agonist) pretreatment reduced renal function, tissue damage, and cell death in CIS-AKI model mice while upregulating VDR and reducing NLRP3, GSDMD-N, Cleaved-Caspase-1 and IL-1β, while in VDR knockout mice, cisplatin-induced kidney damage was more severe than in wild-type mice, pyroptosis-related proteins were further increased, and the effect of paricalcitol was eliminated. It is suggested that vitamin D/VDR can reduce CIS-AKI by inhibiting NF-κB-mediated NLRP3/Caspase-1/GSDMD necrosis [44]. In addition to GSDMD, GSDME is a newly discovered mediator of pyroptotic GSDME-N by lysis of Caspase-3. Xia et al. [80] constructed GSDME-specific knockout mice to study the role of GSDME in renal cell pyrosis and the pathogenesis of AKI. They found that after cisplatin treatment, human TECs underwent GSDME-mediated pyroptosis, and GSDME-N expression increased while promoting IL-1β and LDH release and reducing cell viability. In GSDME-specific knockout mice, kidney damage and inflammation were significantly milder. In vitro experiments have confirmed that inhibition of Caspase-3 can block the lysis of GSDME-N and reduce cisplatin-induced pyroptosis and kidney damage of renal TECs in AKI.

*Folic Acid-Induced AKI*

Tubular damage caused by folic acid (FA), characterized by extensive inflammation, is also a common model of AKI (FA-AKI). Apoptosis is a pro-inflammatory form of cell death due to inflammatory caspase activation, which is involved in developing AKI. Ibudilast is a TLR4 antagonist used clinically to exert anti-inflammatory effects on asthma. Interestingly, Researchers found that ibudilast treatment reversed FA-induced mouse AKI, that ibudilast reduced levels of NLRP3 and apoptosis-related proteins (Caspase-1, IL1-β, IL-18, and GSDMD cleavage), and that ibudilast administration inhibited FA-induced TLR4 upregulation, blocked NF-κB nuclear translocations and reduced phosphorylation of NF-κB and IκBα, p38, ERK, and JNK. Thus, this study confirms the protective effect of ibudilast on FA-induced AKI in mice [45].

*Gentamicin-Induced AKI*

Hemolysin co-regulatory protein 1 (HCP1) motivates the expression of active caspase-1 and the activation of the NLRP3 inflammasome, which leads to the cleavage of GSDMD-N, an increase in the release of active IL-1β, and ultimately pyroptosis [81]. There was an increase in the expression of pyroptosis-related markers and pyroptosis-induced cell death in gentamicin (GM)-induced AKI. Studies done in vitro consistently showed that GM significantly increased pyroptosis and the expression of the protein linked to it in NRK-52E cells. Bufalin treatment, however, prevented

these GM effects from occurring both in vivo and in vitro. Further, we found that Nigericin (NLRP3 agonist) could reverse the effects of bufalin on GM-induced pyroptosis [36]. Doxorubicin was administered to rats as a single intraperitoneal injection to elicit the renal injury model. The vasodilator peptide adrenomedullin (ADM) is widely distributed in many tissues and has powerful protective effects [82]. In NRK-52E cells, cadmium-inhibited TFEB function causes an increase in ROS to promote pyroptosis, which sheds new light on the therapeutic targets for cadmium-induced kidney diseases [83].

*Contrast-Induced AKI*

The most common reason for hospital-acquired kidney failure is contrast-induced AKI (CI-AKI). Treatment with iopromide (IOP) resulted in kidney damage, increased expression of Caspase-1, IL-1, IL-18, NLRP3, and GSDMD, and LDH releasing, suggesting that IOP induces AKI by activating pyroptosis. Acetylbritannilactone pretreatment partially inhibited the progression of CI-AKI, pyroptosis, and ensuing renal inflammation. It implies that acetyl consulted guards against IOP-induced AKI and offers a target for CI-AKI treatment [46]. By limiting the activation of NLRP3 inflammasomes, Klotho also lessens renal tubular cell pyroptosis in CI-AKI, according to Zhu et al. [47] In contrast agent-treated HK-2 cells, they revealed that Klotho was able to prevent NLRP3 inflammasome activation and cell pyroptosis. Additionally, they identified that Klotho prevented NLRP3 inflammasome activation and cell pyroptosis by inhibiting autophagy in the AKT/mTOR pathway and lowering mitochondrial ROS levels, which increased autophagy. Fu et al. [84] further confirmed that Klotho has a protective effect on CI-AKI via suppressing oxidative stress, inflammation, and NF-κB/NLRP3-mediated pyroptosis that contributes to the potential therapy of CI-AKI. Zhang et al. [85] reported that contrast agents can cause pyroptosis in RTECs, knockout Caspase-4/5 can reduce the occurrence of pyroptosis in human RTECs and reduce the release of mature IL-1β, in Caspase-11 knockout mice, the degree of CI-AKI damage is reduced, while the loss of Caspase-11 in RTEC inhibits the cleavage of GSDMD. It has been suggested that Caspase-11 plays an important role in AKI [85]. By blocking the TLR4/MyD88/NF-B signaling pathway, Yue et al. [86] discovered that the meglumine diatrizoate (MEG) in vitro model that causes CI-AKI could be reduced by pretreatment with atorvastatin. By activating the ROS/NLRP3/Caspase-1/GSDMD signaling pathway, exposure to iohexol can cause pyroptosis in HK-2 cells. By controlling the NLRP3 inflammasome pathway, baicalin lessened iohexol-induced pyroptosis in HK-2 cells [87].

*Rhabdomyolysis-Induced AKI*

Rhabdomyolysis is a severe ailment that frequently leads to AKI (RM-AKI). Although it is well known that double-stranded DNA (dsDNA) released from impaired muscles could have a role in the RM-AKI pathogenesis, the precise mechanism involving the contribution of dsDNA remains unclear [88]. Melanoma deficiency factor 2 (AIM2), acting as a receptor for dsDNA, forms inflammasomes and triggers GSDMD-mediated pyroptosis. A study conducted using a mouse model of RM-AKI demonstrated that AIM2 deletion resulted in a significant accumulation of macrophages, leading to the delayed recovery of kidney function and persistent fibrosis. Additionally, deleting AIM2 limits macrophage pyroptosis and promotes inflammation by recruiting macrophages of the CXCR3+/CD206+ phenotype. In vitro experiments have also demonstrated that treating AIM2-deficient macrophages with dsDNA promotes the activation of the STING-TBK1-IRF3/NF-κB pathway and subsequent inflammatory factor upregulation. Therefore, AIM2-mediated pyroptosis could eliminate macrophages before initiating pro-inflammatory signaling [89]. Li and his colleagues have discovered that myoglobin promotes macrophage M1 polarization while activating macrophage pyroptosis via the RIG-I/Caspase-1/GSDMD signaling pathway in the crush syndrome-induced AKI model. They found that dimethyl fumarate, a pyroptosis inhibitor, not only reduces damage caused by the crush syndrome-induced AKI but also suppresses M1 polarization and pyroptosis in macrophages [90]. Antioxidants, pentoxifylline, and thiamine could be a potential renoprotective approach for RM patients by targeting TLR4/NF-B and NLRP3/caspase-1/gasdermin mediated-pyroptosis pathways [34].

## Conclusion

In conclusion, current research indicates that multiple modes of cell death are involved in both the occurrence and progression of AKI and controlling regulated cell death is a novel approach to AKI treatment. However, several obstacles must be overcome before applying this treatment strategy in clinical settings. First, different stages and degrees of AKI damage can trigger varying modes of regulated cell death in renal TECs. Additionally, AKI caused by the same etiology may involve numerous controllable cell death modes in TECs, including

apoptosis, apoptosis-like necrosis, MPT-driven cell death, ferroptosis, and other cell death modes. Therefore, a combination of different regulated cell death inhibitors may further restrict TEC death, ultimately alleviating AKI. Overall, there is still a long way to go from basic research to clinical application for preventing and treating AKI by inhibiting the controlled death of RTECs.

## Conflict of Interest Statement

The authors have no conflicts of interest to disclose. J.Z. is now the Managing Editor/Associate Editor of the Journal.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## Author Contributions

J.X. drafted the review; J.Z. designed, approved, and revised the review.

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