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REVIEW

NLRP3 Inflammasome-Mediated Pyroptosis in Diabetic Nephropathy: Pathogenic Mechanisms and Therapeutic Targets

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Abstract: Diabetic nephropathy (DN) is a prevalent microangiopathic manifestation of diabetes mellitus (DM) and a pathological sequela of chronic glycemic disorders, characterized by several pathological features including glomerulosclerosis, podocyte loss, tubular epithelial atrophy and abnormal extracellular matrix accumulation. A growing body of research has underscored that chronic inflammatory microenvironments play a central role in the progression of DN. Pyroptosis, a newly defined form of programmed inflammatory necrosis, operates through the following molecular mechanism: inflammasome activation, gasdermin D (GSDMD)-mediated plasma membrane perforation and pro-inflammatory mediator release. Pyroptosis is triggered by the activation of the NOD-like receptor 3 (NLRP3) inflammasome. Classical (caspase-1) or non-classical (caspase-4/5/11) pathways activate pyroptosis by cleaving GSDMD, inducing enzymatic fragmentation of the GSDMD protein. GSDMD-N-terminal domain oligomerizes to form transmembrane pores, which further disrupt cellular osmotic homeostasis as well as membrane integrity. Inflammatory cascades are triggered when IL-1 and IL-18 are released as a result of subsequent cell lysis. This review systematically elucidates the pathobiological interplay between pyroptosis regulatory networks and the pathogenesis of DN and summarizes potential therapeutic compounds that mitigate pyroptosis by inhibiting NLRP3 inflammasome activation or blocking GSDMD pore formation. Preclinical studies suggest that targeting pyroptosis-related signaling molecules including NLRP3, caspase-1 and GSDMD may alleviate renal injury by suppressing inflammation-driven fibrosis and ameliorating glomerular dysfunction. Current studies emphasize that regulating pyroptosis mechanisms could slow DN progression, providing novel insights into the development of nephroprotective strategies.

Keywords: diabetic nephropathy, inflammation, pyroptosis, NLRP3, Caspase-1/4/5/11, GSDMD, IL-1β and IL-18

Introduction

Diabetic nephropathy (DN), also known as diabetic kidney disease (DKD), is one of the leading causes of mortality in people with diabetes mellitus (DM).[1] In addition, DN is a significant microvascular sequela of chronic DM and a predominant contributor to end-stage renal disease (ESRD), which is closely linked to increased mortality in diabetic populations.[2–4] Epidemiological analyses reveal a rapid escalation in global diabetes prevalence over recent decades.[5] There are 463 million people living with diabetes worldwide in 2019 per International Diabetes Federation (IDF) statistics and epidemiological models predict that the number will surge by 51% to 700 million by 2045.[6] DM is a global health crisis due to the expanding diabetic epidemic and DN.[7] According to the 2023 IDF report, the global incidence of type 2 diabetes (T2DM)-induced nephropathy surged by 74% from 1.4 million (1990s) to 2.4 million (2017s). Growing evidence suggests that DN is the primary single cause of ESRD.[8–10] Studies have also reported that diabetes-related ESRD cases increased globally from 22.1% (2000) to 31.3% (2015).[11] The above information underscores the critical need for early intervention and comprehensive management of DN in global public health. It is estimated that more than one-fifth of healthcare spending in the United States is primarily for T2DM with most of this

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focused on complication management for people with T2DM.[12] The burden of DN varies across regions of the globe and affects countries with varying income levels. Patients from low- and middle-income countries are often the least able to cope with the burden of DN and the healthcare costs of the disease.[13] Patients in low- and middle-income countries are unable to cope with the burden of DN and most healthcare facilities in these countries are unable to adequately meet the specific needs of precision renal care.[14]

The pathophysiology of DN progression is induced by impaired glucose homeostasis and ROS-mediated oxidative stress (OS) and prolonged inflammation and maladaptive fibrotic remodeling.[15] Accumulating evidence has shown that a variety of biological processes including inflammation, fibrosis of the renal interstitial spaces and OS further induce the progression of DN.[16–18] Additionally, current studies have demonstrated that cell death is believed to contribute to the progressive renal injury and depletion in DN.[19,20] Emerging mechanistic insights suggest that dysregulated programmed cell death pathways, specifically caspase-dependent apoptosis and gasdermin-mediated pyroptotic pathways, exacerbate diabetic microvascular complications, impair renal function during DN.[21]

Programmed cell death (PCD) is a genetically encoded mechanism that promotes the elimination of cells.[22] PCD regulates the shaping of organisms and maintains tissue stability and function.[23–25] The disruption of these pathways may result in developmental anomalies or pathologies.[26] Unlike cell necrosis, PCD is an efficient mechanism that can clear aging, damaged and malfunctioning cells, thereby maintaining the health of the tissues and organs. However, PCD can be disrupted or imbalanced, resulting in uncontrolled cell death, affecting cell communication and interactions and promoting disease progression.[27,28] DN leads to structural and functional damage to glomeruli through excessive apoptosis or impaired autophagy, ultimately resulting in podocyte PCD.[29] A variety of PCD forms such as apoptosis, autophagy, ferroptosis, pyroptosis and necroptosis are associated with podocyte damage in DN.[30] However, the underlying molecular mechanisms warrant further investigation. Emerging research delineates the specific roles of distinct PCD modalities such as apoptosis, autophagy and pyroptosis, in mediating inflammatory cascades, metabolic disorders and systemic pathologies.[31,32] Apoptosis is the most extensively characterized PCD mechanism and contributes to eliminating superfluous or compromised cells.[33–35] Both exogenous and endogenous pathways facilitate apoptosis and activate latent cysteine proteases, known as caspases, to systematically break down cellular components through lysis, ultimately leading to apoptosis.[36–38] Normal physiological features of cells depend on apoptosis, but dysfunction leads to pathological cell persistence (eg, tumorigenesis) while overactivation leads to tissue atrophy (eg, neurodegenerative diseases, ischemic injury).[34,39,40] Autophagy is a lysosome-dependent degradation system and maintains cellular homeostasis through the recycling of organelles and the degradation of proteins.[41] Impaired autophagy inversely affects postmitotic cell populations such as neurons and cardiomyocytes),[42] leading to neurodegeneration and cardiac dysfunction.[43–45] A similar contradiction exists in tumorigenesis. The catabolic process of autophagy regulates bioenergetic needs by recycling cellular components.[46] Tumor cells maintain viability under metabolic stress, which can have adverse effects on the body.[47] DN is characterized by abnormal autophagy, which leads to fibrotic remodeling of the kidneys.[48] Furthermore, exploring PCD in the context of DN may offer novel strategies to treat DKD.

Pyroptosis is an inflammatory form of caspase-dependent PCD in eukaryotic cells, which is characterized by cell swelling and plasma membrane large bubbles blowing, pore-induced intracellular traps (PITs) forming plasma membrane rupturing and pro-inflammatory intracellular contents releasing such as mature IL-1β and IL-18.[49–51] The released intracellular contents attract more immune cells and trigger local inflammation, thereby strengthening the immune defense function of cells.[52] This process is initiated by inflammasome activation, which further triggers proteolytic cleavage of gasdermin family proteins (eg, GSDMD) and subsequent plasma membrane pore formation. The features include osmotic disequilibrium, cytosolic content efflux and robust secretion of pro-inflammatory cytokines such as IL-1β and IL-18. Excessive pyroptosis drives uncontrolled and persistent inflammatory responses, thereby serving as a pathogenic driver of inflammatory disorders.[53] A growing body of evidence suggests that inflammation plays a contributory role in the pathogenesis of DN.[15,54,55] The persistence of pyroptosis can accelerate the progression of renal inflammation by mediating dysregulation of the chronic inflammatory microenvironment. Mechanistically, the activation of pyroptotic signaling pathways exacerbates insulin resistance and metabolic dysfunction in DN.[56–59] Consequently, inflammasome activation and pyroptotic cascades critically contribute to the pathogenesis of diabetic complications, particularly DN.[60] However, recent papers have reported that pyroptosis is accompanied by a massive

expression of pro-inflammatory mediators, leading to the progression of diabetes.[52,60,61] Qiu et al suggested that hyperglycemia-induced pyroptosis aggravated myocardial ischemia/reperfusion injury in diabetic rats.[62] Che et al have also confirmed that high glucose induces pyroptosis in neuronal cells.[63] Few studies have focused on the participation of pyroptosis-dependent signaling pathways in the pathogenesis of DN.

This narrative review systematically examines the molecular mechanisms underlying pyroptotic cell death and elucidates how the interplay between the inflammasome and pyroptosis exacerbates renal pathology in DN. We also summarize current evidence on emerging therapeutic strategies targeting inflammasome activation and pyroptotic signaling pathways, providing new clinical insights into the treatment and management of DN.

Molecular Mechanisms of Pyroptosis

Pyroptosis was initially characterized as an apoptotic-like process in macrophages infected with *Salmonella typhimurium*[64] and *Shigella flexneri*[65] during the 1990s. In 2001, Cookson and Brennan formally differentiated this lytic cell death from apoptosis by coining the term "pyroptosis"[66] The pyroptotic cascade comprises four key steps: (1) inflammasome activation, where multiprotein complexes (eg, NLRP3, AIM2) sense pathogen or damage-associated molecular patterns (PAMPs/DAMPs); (2) caspase-mediated signaling, triggering downstream effector pathways; (3) Gasdermin (GSDM) protein cleavage, which liberates the pore-forming N-terminal domain; and (4) plasma membrane permeabilization, driven by GSDM oligomerization. These transmembrane pores disrupt cellular water balance, causing cell enlargement and destruction, release of intracellular components and secretion of inflammation-triggering mediators including IL-1β and IL-18, thereby amplifying systemic inflammation.[67,68] Pyroptosis is primarily mediated through canonical (caspase-1-dependent) and non-canonical (caspase-4/5/11-dependent) pathways.

Canonical Pyroptosis

Inflammasome activation is initiated by PAMPs or DAMPs, which further induce the assembly of multiprotein signaling platforms essential for innate immune defense (Figure 1). The inflammasomes consist of intracellular pattern recognition receptors (PRRs), apoptosis-associated speck-like protein containing a caspase-recruitment domain (ASC), and inflammatory caspases.[69] Several PRRs have been identified including the NLR family (NLRP1/3/NLRC4), absent in melanoma 2 (AIM2) and pyrin with the NLRP3 inflammasome serving as the central mediator of canonical pyroptosis.[70–72] The NLRP3 protein consists of three distinct functional domains: a nucleotide-binding oligomerization domain (NOD), a leucine-rich repeat (LRR) at the C terminus, which recognizes PAMPs and DAMPs and a pyrin domain (PYD) at the N terminus that recruits ASCs through homotypic interactions.[73] Recent studies have found that NIMA-related kinase 7 (NEK7) controls NLRP3 oligomerization, ASC speck formation and caspase-1 activation downstream of potassium efflux, a key upstream signal for inflammasome activation.[74] NEK7 mediates the conformational rearrangement of NLRP3 into its active oligomeric state by binding the LRR domain.[75] ASC bridges NLRP3 and pro-caspase-1 through its bipartite architecture: its N-terminal PYD binds NLRP3, while the C-terminal caspase activation and recruitment domain (CARD) interacts with pro-caspase-1. Ligand binding triggers NLRP3 oligomerization and ASC speck formation, a process further stabilized by NEK7-mediated scaffolding, thereby facilitating proximity-induced autocleavage of pro-caspase-1 into its active form. Active caspase-1 has a dual function. It processes immature IL-1β/IL-18 into bioactive cytokines while cleaving GSDMD to liberate its N-terminal pore-forming fragment (GSDMD-NT).[76] GSDMD-NT subunits released from the cell cause cell swelling and rupture by self-assembling into nanoscale (10–15 nm) transmembrane pores. This process results in pyroptosis, which leads to the proliferation of IL-18 and the initiation of a self-amplifying inflammatory cascade.

Non-Canonical Pyroptosis

Cytosolic LPS, a structural hallmark of Gram-negative bacteria, directly activates the precursors of caspase-4, −5 and −11.[77–81] The activated caspases cleave GSDMD and release GSDMD-NT to disrupt the integrity of plasma membranes. Research has shown that nerve injury-induced protein 1 (NINJ1) is also necessary for inducing plasma membrane rupture during pyroptosis.[82] In addition, NINJ1 forms oligomeric clusters at the plasma membrane, which may result in catastrophic disintegration and the release of pro-inflammatory cytokines.[83] The caspases-4/5/11 indirectly trigger

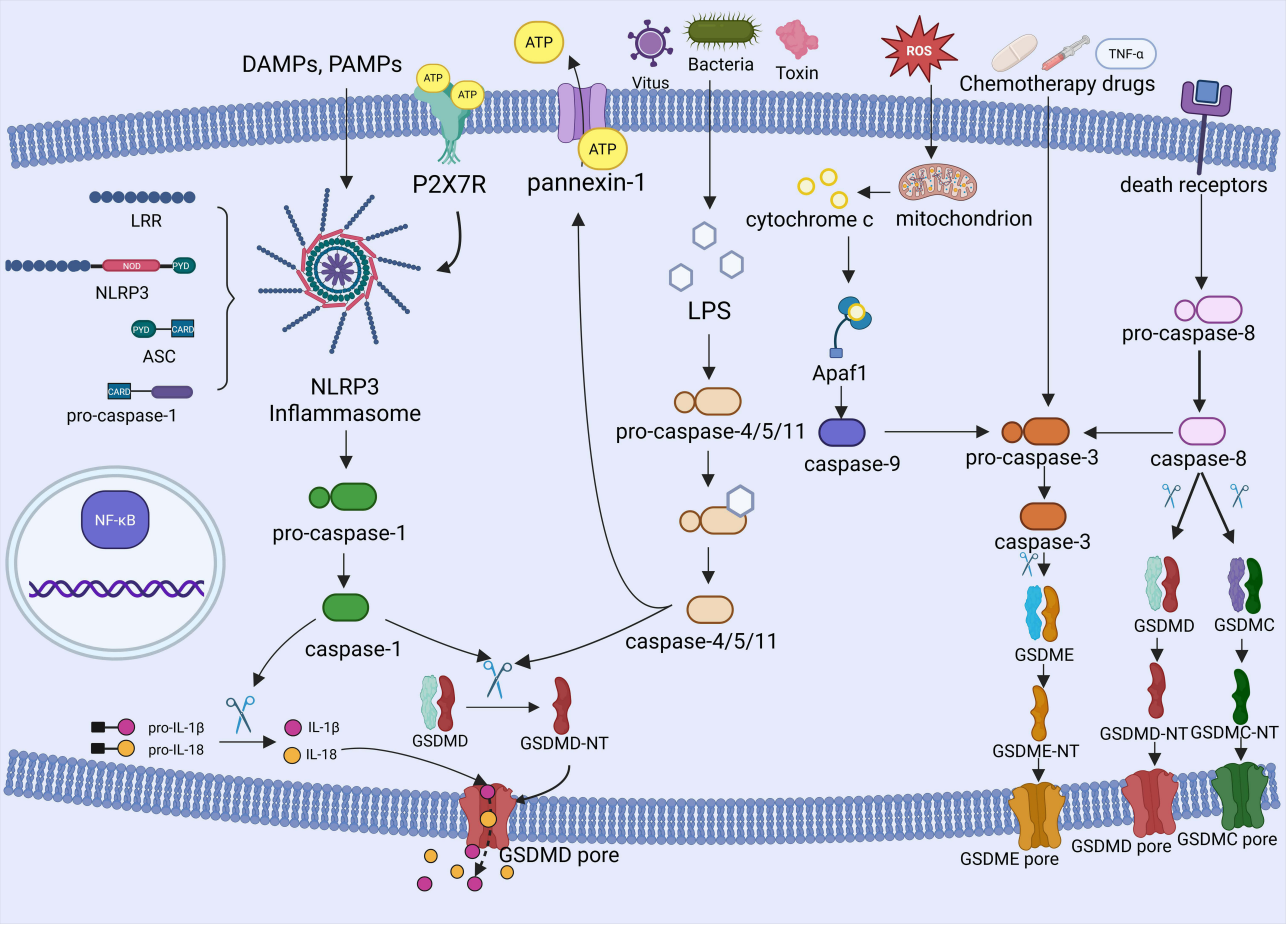

Figure 1 Cellular and molecular mechanisms of pyroptosis-related signaling pathways. Pyroptosis-related signaling pathways are typically activated by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), which trigger inflammasomes that promote the cleavage of pro-caspase-1 to produce a mature form of caspase-1. Active caspase-1 processes IL-1β and IL-18 into their biologically active forms, and cleaves GSDMD to release the N-terminal domain of GSDMD (GSDMD-NT). Oligomerized GSDMD-NTs insert into the plasma membrane, forming non-selective pores, disrupting ionic gradients and inducing osmotic cleavage, ultimately enabling extracellular release of pro-inflammatory cytokines. In addition, the non-canonical pyroptosis pathway is triggered by viral, bacterial, and toxin-stimulated lipopolysaccharide (LPS), which binds to pro-caspase-4/5/11 and cleaves it to form GSDMD-dependent pores, further activating pyroptosis-regulated cell death. In addition to infectious triggers, chemotherapeutic agents activate the caspase-3/GSDME pathway to induce pyroptosis, while mitochondrial stress and death receptor signaling indirectly engage this pathway through the upstream activation of caspase-8/9. Proteolytic cleavage of GSDME by activated caspase-3 generates N-terminal fragments (GSDME-N) that oligomerize into transmembrane pores. These lesions provoke membrane depolarization, cytoplasmic shrinkage, and eventual cell lysis. Notably, caspase-8 exhibits pyroptotic regulation through cleavage of GSDMC and GSDMD.

intracellular IL-18 production by activating the NLRP3 inflammasome, which recruits caspase-1 to mature and produce IL-18.[84] Caspase-11 further amplifies this cascade by proteolyzing the pannexin-1 membrane channel, triggering the massive release of ATP.[85] Extracellular ATP then binds P2X7 receptors (P2X7R), opening additional K□ efflux channels and reinforcing NLRP3 inflammasome assembly.[85] This self-sustaining cycle can synergistically amplify pyroptotic cell death and inflammatory cytokine release by linking membrane permeabilization, ion dysregulation and inflammasome activation.

Other Signaling Pathways

Emerging evidence reveals functional crosstalk between apoptotic caspases and pyroptotic pathways.[86–88] Caspases-3 can also mediate GSDME-dependent pyroptosis, which has traditionally been considered the primary regulator of apoptosis. Chemotherapeutic drugs and TNF-α trigger caspase-3 to cleave GSDME, releasing its N-terminal pore-forming fragment (GSDME-NT). This fragment translocates to the plasma membrane inducing lytic cell death.[89] Caspase-3 activation can occur through apoptotic initiators: caspase-8 (activated by death receptor oligomerization) or caspase-9 (triggered by mitochondrial cytochrome c release via APAF-1).[90] In addition to activating caspase-3, caspase-8

can also be activated by *Yersinia* outer protein-J (Yop-J) and directly induces cleavage of GSDMD to drive pyroptosis.[91] Death receptor signaling facilitates caspase-8-mediated proteolysis of GSDMC, resulting in the release of its pore-forming domain (GSDMC-NT).[92] Disruption of mitochondrial homeostasis, endoplasmic reticulum stress signaling and redox imbalance (ROS overproduction) further amplifies pyroptosis by activating the caspase-9/3/GSDME axis, thereby linking organelle damage to inflammatory cell death.[93] These findings highlight the mechanistic plasticity of caspase in coordinating the apoptosis-pyroptosis transition in different pathological contexts.

Pyroptosis in the Pathogenesis and Progression of DN

DN is a multifactorial inflammation-driven pathology characterized by heterogeneous mechanisms encompassing hemodynamic dysregulation, impaired glucose homeostasis, OS and genetic predisposition.[94–96] Evidence indicates that pyroptosis contributes the progression of DN by inducing sustained inflammatory cascades and damaging renal parenchyma.[97–99]

Pyroptosis in Podocytes

The glomerular filtration barrier, composed of podocytes, endothelial cells and the glomerular basement membrane, is indispensable for renal filtration homeostasis.[100,101] DN is caused by the loss of podocytes, terminally differentiated cells at the outermost layer of this barrier.[102] Both clinical and experimental studies have consistently demonstrated that podocyte injury is a key player in the progression of DN.[103,104] Under hyperglycemic conditions, ROS overgeneration and mitochondrial dysfunction induce oxidative stress, inflammatory activation and cytoskeletal disruption in podocytes, which further promotes apoptosis, detachment and proteinuria.[105,106] Ample evidence suggests that diabetic glomerular hyperfiltration imposes mechanical stress on podocytes, exacerbating foot process effacement and accelerating cell loss even in early-stage DN.[107–109]

Emerging evidence suggests that pyroptosis plays a key role in mediating podocyte demise in DN.[110] High glucose upregulates caspase-4/11 and promotes the cleavage of GSDMD in podocytes, whereas inhibition of pyroptosis ameliorates the progression of DN by preserving podocyte integrity and suppressing local inflammation.[111] Wu et al further demonstrated that NLRP3 inflammasome blockade mitigates podocyte damage through reducing lipid accumulation in diabetic kidneys.[112] The stimulator of interferon genes (STING) pathway has been implicated in regulating NLRP3-dependent pyroptosis.[113] STING deficiency attenuates podocyte inflammation, highlighting its therapeutic relevance.[114] Mechanistically, the overactivation of the mammalian target of rapamycin (mTOR) in diabetic podocytes enhances NF-κB p65 activity, thereby triggering NLRP3-dependent pyroptosis.[115]

Multifaceted regulatory mechanisms have been discovered in studies of molecular pathways. LPAR1 regulates lysophosphatidic acid (LPA) signaling at the Egr1 promoter, resulting in increased H3K27 trimethylation.[116] This epigenetic alteration elevates Egr1 levels, which in turn activate NLRP3 inflammasomes and pyroptosis in podocytes of streptozotocin (STZ)-induced diabetic mice.[116–118] Pharmacological interventions such as dapagliflozin and puerarin exhibit protective effects by targeting the miR-155-5p/HO-1/NLRP3 axis and modulating SIRT1/NLRP3/caspase-1 signaling, respectively.[119,120] Additionally, activation of the SIRT6/HIF-1α pathway ameliorates pyroptosis,[121] while deficiency of ATP-binding cassette transporter A1 (ABCA1) exacerbates non-canonical pyroptosis-related genes such as caspase-4/11, GSDMD, caspase-1 and IL1β via reduction–oxidation factor 1 (Ref-1)/Apurinic/apyrimidinic endonuclease 1 (APE1) axis.[122] Collectively, the findings suggest that pyroptosis is a key driver of podocyte loss, thereby providing an array of molecular targets for therapeutic intervention for DN.

Pyroptosis in Glomerular Endothelial Cells (GECs)

Hyperglycemia-induced damage to GECs occurs in the DN because they are exposed directly to circulating metabolites and inflammatory mediators.[123] GEC injury is correlated with podocyte foot process effacement in diabetic mouse models, occurring as early as three weeks after the onset of diabetes.[124] Endothelial dysfunction disrupts glomerular permeability and accelerates kidney disease progression, underscoring the importance of GECs in the pathogenesis of DN.[125] Hyperglycemia exacerbates metabolic disturbances in GECs, promoting ROS overproduction, mitochondrial dysfunction and subsequent pyroptotic cell death.[126] Shen et al demonstrated that notoginsenoside Fc reduces ROS

accumulation and alleviates mitochondrial damage by suppressing the expression of HMGCS2, thereby mitigating GEC pyroptosis.[127] Tanshinone IIA (Tan-IIA) attenuates NLRP3 inflammasome activation by decreasing the expression of TXNIP, thereby preserving the integrity of GEC in diabetic kidneys.[128] The ELABELA (ELA) peptide reversed elevated NLRP3 levels in glomerular endothelial in db/db mice through the inhibition of AMP-activated protein kinase (AMPK), demonstrating the possibility of a novel therapeutic strategy.[129]

Mechanistic studies further elucidate the involvement of canonical and non-canonical pyroptotic pathways in GEC injury.[61,130] Sodium butyrate alleviates hyperglycemia-induced pyroptosis by blocking caspase-1/GSDMD signaling.[131] Hirudin targets Irf2 to inhibit GSDMD cleavage and renal damage in STZ-induced DN mice.[132] Intriguingly, caspase-11/GSDMD activation drives non-canonical pyroptosis in GECs, as evidenced by reduced renal injury following GSDMD knockout.[133] Neutrophil extracellular traps (NETs) also exacerbate GEC pyroptosis in diabetic conditions. Both DNase I treatment and PAD4 gene deletion ameliorate glomerulopathy by degrading NETs and suppressing pyroptosis.[21] These findings collectively establish GEC pyroptosis as a critical mediator of diabetic glomerular injury, offering multiple targets for intervention including inflammasome modulation, redox balance restoration and NETs neutralization.

Pyroptosis in Glomerular Mesangial Cells (GMCs)

Glomerular mesangial cells (GMCs) regulate blood flow dynamics, maintain mesangial matrix homeostasis and maintain glomerular capillary architecture.[134] Hyperglycemia promotes macrophage-GMC crosstalk and excessive production of inflammatory cytokines and extracellular matrix proteins in diabetic patients. Notably, macrophage-derived exosomes exacerbate diabetic kidney injury by activating NLRP3 inflammasomes in GMCs,[135] positioning these cells as central mediators of diabetic nephropathy (DN) progression.

Recent studies have revealed molecular mechanisms governing the pyroptosis of GMCs. Du et al identified circLARP1B as a pro-pyroptotic regulator in high glucose (HG)-treated GMCs. Overexpression of circLARP1B upregulates NLRP3, caspase-1 and IL-1β/IL-18, whereas its silencing suppresses pyroptosis and inflammation via the miR-578/TLR4 axis.[136] Similarly, Zhan et al demonstrated that long non-coding RNA -Neat1 (NEAT1) is upregulated in HG-treated rat mesangial cells, influencing pyroptosis and inflammation of DN by modulating the miR-34c/NLRP3 signaling axis.[137] These findings highlight that non-coding RNAs are key epigenetic regulators of GMC pyroptotic pathways.

The erythroid 2-related factor 2 (Nrf2)/HO-1 axis represents another therapeutic target for DN. Lu et al discovered that activating Nrf2 signaling attenuated glucose-induced oxidative stress and inflammation in diabetic kidneys.[138,139] Specifically, the synthetic Nrf2 activator AB-38b inhibits NLRP3 and IL-1β expression in diabetic GMCs via the Nrf2/HO-1/NLRP3 cascade, demonstrating its potential to counteract pyroptosis-driven ECM accumulation.[140] Collectively, these studies indicate that GMC pyroptosis plays a critical role in the progression of glomerulosclerosis and DN.

Pyroptosis in Tubular Epithelial Cells (TECs)

Diabetic tubular injury is driven by hyperglycemia-induced oxidative stress, proteinuria and extracellular matrix (ECM) deposition, which further promote tubular necrosis, apoptosis and epithelial-mesenchymal transition.[141,142] TECs death exacerbates renal dysfunction and accelerates DN progression. Several clinical and experimental studies have shown that TEC pyroptosis plays an important role in the pathogenesis of DN.[143,144] GSDMD expression is higher in renal biopsies from DN patients and TECs and GSDMD levels are positively correlated with tubular injury severity in DN patients.[145] Discoid domain receptor 1 (DDR1) knockdown mitigates HG-induced pyroptosis by suppressing the NF-κB/NLRP3 axis, suggesting a regulatory role for this pathway.[146] TLR4/NF-κB signaling is activated in diabetic TECs, resulting in the assembly of NLRP3 inflammasomes and the induction of caspase-1-dependent pyroptosis. The inhibition of TLR4 could reduce the activation of NF-kB, thereby reducing GSDMD cleavage and IL-1β secretion in HG-exposed renal tubular epithelial cells (HK-2), further validating this mechanism.[147,148]

Non-coding RNAs (lncRNAs) regulate pyroptosis in TECs.[149] LncRNA XIST exacerbates pyroptosis by upregulating miR-15b-5p to enhance TLR4/NLRP3 signaling, whereas its silencing alleviates tubular injury.[150] The lncRNA MALAT1 suppresses miR-30c to induce NLRP3 inflammasome activation and the inhibition of MALAT1 inhibits caspase-1 and IL-1β release.[151,152] The novel lncRNA, PWARSN, is upregulated in proximal TECs of DKD patients

and aggravates pyroptosis through activating the TXNIP/NLRP3 pathway.[153] HG-induced DNA damage activates AIM2 inflammasomes, leading to pyroptosis in proximal TECs.[154] Human umbilical cord mesenchymal stem cells (hUC-MSCs) inhibit NLRP3/caspase-1 signaling and alleviate pyroptosis of renal tubular epithelial cells.[155] These findings indicate that suppression of pyroptosis provides a promising therapeutic avenue in the treatment of DN.

Suppressing the Pyroptosis-Related Signaling Pathways for the Therapeutic Regulation of DN

Triptolide

Triptolide is a bioactive diterpenoid derived from *Tripterygium wilfordii* Hook F with multimodal therapeutic properties. This compound exerts several functions such as anti-inflammatory, antioxidant, hypoglycemic and antifibrotic effects.[156–158] Diabetic nephropathy (DN) is characterized by hyperglycemia-induced OS, which induces podocyte injury through the production of reactive oxygen species (ROS) and lipid peroxidation.[159] TP suppresses NLRP3 inflammasome activation by activating nuclear factor Nrf2, a master regulator of redox homeostasis.[140] Mechanistically, Lv et al demonstrated that TP alleviates podocyte pyroptosis and suppresses the secretion levels of IL-1β and IL-18 via the Nrf2/ROS/NLRP3 axis, thereby attenuating glomerular inflammation and injury.[160]

Studies have revealed that TP modulates both proliferative and fibrotic pathways in DN.[160] Han et al revealed that TP inhibits mesangial cell hyperplasia by suppressing the PDK1/Akt/mTOR cascade, while concurrently ameliorating glomerulosclerosis through miR-137/Notch1 signaling regulation.[161,162] The multi-targeted action of TP in combating oxidative stress, inhibiting inflammasomes and modulating epigenetics make it an attractive candidate for the treatment of DN.

Sanziguben Polysaccharides

Sanziguben polysaccharides (SZP) are a primary component of Sanzigube, which show promising renoprotective effects in DN by inhibiting gut-renal axis modulation and inflammasome.[163] Experimental studies demonstrate that SZP treatment reverses hyperglycemia-induced TLR4/NF-κB/NLRP3 pathway activation in DN mice, downregulating ASC, caspase-1, and pro-inflammatory cytokines.[164] Notably, diabetic renal injury is exacerbated by gut dysbiosis characterized by reduced microbial diversity and overgrowth of LPS-producing Gram-negative bacteria.[165,166] SZP ameliorates this pathological crosstalk by restoring intestinal microbiota homeostasis, thereby reducing LPS translocation through compromised intestinal barriers and subsequent TLR4-mediated renal inflammation.[167] Furthermore, Zhou et al revealed that SZP inhibits NF-κB nuclear translocation in glomerular cells, attenuating cytokine-driven mesangial expansion and tubular injury.[163] Therefore, SZP can be positioned as a natural medicine for the multifaceted treatment of DN as a dual therapeutic modality that simultaneously targets gut-derived endotoxemia and intrarenal inflammation.

Hirudin

Hirudin is a natural component derived from leech salivary glands, which exerts thrombolytic and blood anticoagulant activities. Studies have suggested that hirudin can accelerate blood circulation and exert renoprotective effects in DN through multimodal mechanisms.[168] Previous studies have also demonstrated that hirudin inhibits the migration and pathological angiogenesis of endothelial cells beyond its well-characterized anticoagulant activity.[169] The interferon regulatory factor 2 (Irf2) is essential for triggering caspase-4 activation and subsequent cleavage of the GSDMD, which is another hallmark of non-canonical pyroptosis.[170] Han et al demonstrated that hirudin ameliorates glomerular injury in streptozotocin-induced DN mice by targeting Irf2-dependent GSDMD transcriptional activation and proteolytic processing.[171] The genetic ablation of GSDMD conferred resistance to diabetic renal damage, validating that this pathway plays an important role in the development of DN. Therefore, hirudin concurrently addressed inflammasome-driven pyroptosis in diabetic kidneys, as well as coagulation abnormalities.

Syringaresinol

Syringaresinol (SYR), a naturally occurring polyphenolic lignan, exerts dual renoprotective mechanisms in DN through redox balance restoration and inflammasome suppression.[172] Zhang et al revealed that SYR suppresses macrophage pyroptosis by directly targeting the caspase-1/NLRP3 signaling axis, thereby attenuating inflammatory cytokine production.[173] Concurrently, Li et al revealed that SYR enhances nuclear translocation and transcriptional activity of Nrf2 by inhibiting KEAP1/Nrf2 degradation.[174] Inflammasome assembly is countered by this mechanism, which eliminates hyperglycemia-induced ROS accumulation. Therefore, SYR mitigates the progression of OS-driven renal injury during DNP by scavenging ROS and inhibiting pyroptosis.

AB-38b

AB-38b, a synthetic α, β-unsaturated carbonyl compound derived from biphenyl diester precursors, possesses significant renoprotection in DN through dual modulation of antioxidant and inflammasome pathways.[175–177] Several preclinical studies have demonstrated the efficacy of this agent in reducing serum uremic toxins (BUN, Cr) and LDL-C levels while ameliorating glomerular structural abnormalities such as effacement of the foot process and accumulation of extracellular matrix.[140,178] Mechanistically, AB-38b activates the Nrf2/ARE signaling axis by suppressing Keap1-mediated degradation, thereby restoring NQO-1 and HO-1 antioxidant enzyme expression in diabetic renal cortices.[178] A pioneering study has revealed that A B-38b inhibits ROS overproduction to disrupt TXNIP/NLRP3 formation and lower caspase-1 activation and IL-1β secretion.[140] The coordinated actions on OS and pyroptotic signaling highlight the therapeutic potential of AB-38b, although clinical validation should be evaluated in the future.

Punicalagin

Punicalagin (PU) is the primary active component of pomegranate polyphenols in pomegranate peel and mitigates the progression of DN through antioxidative and pyroptosis-suppressive mechanisms.[179,180] Growing evidence suggests that PU can enhance superoxide dismutase (SOD) activity, which may attenuate the production of superoxide and nitric oxide (NO) during hyperglycemia.[181–186] The redox-balancing effect of this compound is synergistic with its direct inhibition of TXNIP and NLRP3. The kidneys of diabetic mice showed elevated levels of NLRP3, IL-1β, GSDMD and caspase-1. PU treatment inhibited the reversible increase of the TXNIP/NLRP3 axis expression.[179] Previous studies have revealed that PU attenuates both LPS-induced macrophage inflammation and hyperglycemia-induced podocyte pyroptosis.[181] The compound may be effective in treating DN and other OS-related nephropathy due to its multimodal effects that include free radical scavenging, suppression of inflammatory mediators, and disassembly of inflammasome complexes.

Carnosine

Carnosine, a water-soluble dipeptide comprising β-alanine and L-histidine, exhibits multifaceted biological properties including anti-inflammatory, antioxidant, anti-glycation and carbonyl scavenging activities.[187] Research has demonstrated that carnosine exerts potential therapeutic effects in the treatment of DN by modulating pyroptotic pathways.[188] Moreover, carnosine attenuated LPS-induced NLRP3 inflammasome activation and pyroptosis in aged rats with cognitive dysfunction.[189] The authors demonstrated that carnosine mitigates HG-induced podocyte injury by inhibiting NLRP3 inflammasome assembly and its downstream effectors. Zhu et al reported that carnosine treatment in STZ-induced diabetic mice reduced renal levels of NLRP3, ASC, pro-IL-1β, mature IL-1β and IL-18.[190] The immunofluorescence analysis indicated that caspase-1 and GSDMD colocalized with synaptopodin and carnosine effectively inhibited pyroptotic activity.[188] Studies have revealed that carnosine attenuates OS and mitigates inflammation in renal cells under high glucose conditions.[191,192] Therefore, carnosine can be considered a potential therapeutic agent for DN via targeting inflammasome-driven pyroptosis and maintaining glomerular integrity.

Biochanin A

Biochanin A (BCA), a naturally occurring methoxylated isoflavonoid, exhibits broad-spectrum pharmacological activities with therapeutic potential across multiple disease models.[193–199] BCA exhibits a wide range of beneficial effects in

addition to its well-described neuroprotective, chemopreventive and hepatoprotective properties, positioning it as a versatile therapeutic option for the treatment of metabolic disorders.[193,196] In addition, BCA has been shown to be effective in reducing inflammation in both in vitro and in vivo studies.[200–202] Treatment with BCA alleviated renal inflammation in mice with unilateral ureteral obstruction by suppressing NLRP3 inflammasome activation and lowering levels of active caspase-1, IL-1β and IL-18.[201] Further studies revealed that BCA mitigates mitochondrial dysfunction and attenuates GSDMD-mediated pyroptosis in diabetic kidneys through enhancing antioxidant activity and modulation of the NF-κB/NLRP3 axis in renal tubular epithelial cells.[203] Based upon these findings, BCA can inhibit the activation of apoptotic and pyroptotic cell death pathways, providing a multi-target approach for the treatment of DN.

Notoginsenoside Fc

Panax notoginseng is a widely recognized medicinal herb in traditional Chinese medicine, which exhibits a wide range of pharmacological properties including hemostatic, antithrombotic, anti-atherosclerotic and antitumor effects.[204–206] More than 150 saponins have been isolated from the roots and leaves of this medicinal herb.[207] Notoginsenoside Fc (Fc), a bioactive component, has shown significant therapeutic potential in the treatment of DN.[208] Previous studies have shown that Fc enhances the proliferation and migration of endothelial cells in diabetic vascular tissues under HG conditions, thereby promoting vascular repair.[209] A pioneering research has revealed that Fc further attenuates HG-induced endothelial dysfunction by suppressing pro-inflammatory cytokine secretion (eg, TNF-α, IL-1β, IL-6, ICAM-1) and regulating apoptotic-proliferative pathways.[210] Wei et al reported that Fc alleviates mitochondrial dysfunction and tubular injury in acute kidney injury models through activation of the SIRT3/SOD2 antioxidant axis.[211] Mechanistic studies have shown that Fc mitigates pyroptosis in glomerular endothelial cells (GECs) by downregulating key mediators such as TXNIP, NLRP3, cleaved caspase-1 and GSDMD-NT.[211] It has been demonstrated that HMGCS2 modulation promotes antipyroptotic effects in HG-induced GECs, as evidenced by reduced mitochondrial damage and pore formation following knockdown of HMGCS2 in HG-stimulated cells.[127] Multifaceted mechanisms including anti-inflammatory, autophagy-enhancing and pyroptosis-inhibitory functions, make Fc a promising multi-target agent for the treatment of DN.

Pyrroloquinoline Quinone

Pyrroloquinoline quinone (PQQ), a naturally occurring redox-active quinone compound, exhibits multifaceted biological effects including antioxidant, anti-aging and immunomodulatory activities.[212–216] In addition, PQQ possesses promising therapeutic efficacy against ischemia, inflammatory disorders and metabolic dysregulation and produces remarkable neuroprotective effects.[212] A study by Wang et al demonstrated that PQQ protects HK-2 against OS-induced apoptosis through activation of the PI3K/AKT/FOXO3a pathway and SIRT3-mediated mitochondrial homeostasis.[217] Furthermore, previous studies have shown that PQQ suppresses HG-induced inflammation and cellular senescence in HK-2 cells by inhibiting ROS overproduction and activating the KEAP1/NRF2 antioxidant axis.[218] Qu et al further established that PQQ attenuates renal fibrosis and improves glomerular function in diabetic murine models via targeting the ROS/NF-κB/NLRP3 inflammasome signaling cascade.[219] These preclinical studies suggest that PQQ may be renoprotective in the treatment of DN by modulating OS, inflammation and pyroptotic responses.

Astragaloside IV

The herb *Astragalus membranaceus* is an effective renoprotective herb and has been extensively used in traditional Chinese medicine to treat kidney disease.[220] Astragaloside IV (AS-IV), a bioactive saponin derived from Astragalus, exhibits multi-target therapeutic efficacy in the treatment of DN.[216,221] AS-IV combats OS, suppresses inflammatory responses and inhibits epithelial-mesenchymal transition (EMT) via selective inhibition of Wnt/β-catenin signaling pathway, thereby attenuating HG-induced renal injury.[222] Recently, Gao et al reported that AS-IV promotes the phosphorylation of p62, which competitively disrupts KEAP1-NRF2 binding, promoting NRF2 nuclear translocation to alleviate ROS accumulation and renal fibrosis.[223] Previous studies have revealed that AS-IV alleviates podocyte pyroptosis and mitochondrial ultrastructural damage by upregulating SIRT6 expression and downregulating HIF-1α, NLRP3, GSDMD and caspase-1.[121] Shen et al revealed that AS-IV restores mitochondrial function and counteracts OS-

induced podocyte apoptosis in diabetic kidneys by activating the NRF2-ARE/TFAM pathway.[224] He et al also reported that AS-IV elevates endogenous Klotho levels, a nephroprotective protein that suppresses NLRP3 inflammasome-mediated pyroptosis, offering a mechanism to preserve glomerular integrity.[225] Therefore, AS-IV presents a promising multi-target agent for the treatment of DN by targeting inflammatory and metabolic dysregulations in diabetic renal pathology.

Ginsenosides

Ginseng, a cornerstone of traditional medicine in East Asian cultures for thousands of years, has been extensively used to treat a wide range of pathologies.[226] Preclinical and clinical evidence have reported that ginseng exerts remarkable anti-inflammatory properties and provides potential therapeutic effects in the treatment of DN.[226] Ginsenosides are the primary bioactive constituents of ginseng, which exhibit a wide range of therapeutic properties including anti-fibrotic, antioxidant and anti-inflammatory actions.[227,228] In addition, ginsenosides alleviate apoptosis and pyroptosis-dependent cell death in diabetic kidneys.[115,229] Previous studies have found that ginsenosides mitigate renal dysfunction and downregulate pro-inflammatory cytokine levels (eg, IL-1, IL-6, TNF-α) in diabetic models, confirming their anti-inflammatory efficacy.[230] A stereoisomer of 20(S)-ginsenoside Rg3 improves insulin sensitivity, lipid metabolism and OS in STZ-induced DN murine models by modulating MAPK and NF-kB signaling.[231,232] Ginsenoside Rg5, a key component of black ginseng, inhibits NLRP3 inflammasome activation (ASC, caspase-1) and suppresses IL-1β/IL-18 secretion, leading to the alleviation of DN.[233,234] Studies have shown that Rg5 inhibits the nuclear translocation of NF-B and the phosphorylation of p38 MAPK, which further mitigates the inflammatory response.[235] In conclusion, these findings suggest that ginsenosides and their derivatives could potentially be used as multi-target drugs for DN intervention, confirming their clinical translation for the treatment of diabetes-associated renal failure.

Tanshinone IIA

Tanshinone IIA (Tan-IIA) is the main lipophilic bioactive constituent of *Salvia miltiorrhiza*, a traditional Chinese herb renowned for promoting blood circulation and resolving blood stasis.[236] Tan-IIA has traditionally been used to treat cardiovascular diseases.[237] Several lines of studies have demonstrated that Tan-IIA has therapeutic potential in DN due to its immune modulatory, anti-inflammatory and antioxidant properties.[128,237,238] Studies have revealed that Tan-IIA suppresses pro-inflammatory cytokine production and ameliorates metabolic dysfunction in rodent models with T2DM by inhibiting NF-B-mediated inflammatory cascades and enhancing AMPK activity.[239] Chen et al demonstrated that Tan-IIA attenuates proteinuria, podocyte foot process effacement and renal fibrosis in diabetic rats by inhibiting extracellular matrix (ECM) deposition and fibroblast activation.[240] Wu et al demonstrated that Tan-IIA inhibits hyperglycemia-induced pyroptosis by targeting the TXNIP/TRX1/NLRP3 inflammasome axis in glomerular endothelial cells.[128] Therefore, Tan-IIA could be a potential therapeutic drug candidate for the treatment of DN.

GLP-1 Receptor Agonists

The GLP-1 receptor agonist (GLP-1 RA) was initially developed for its glucose-lowering properties through the mimicry of incretin hormones.[241] GLP-1 RA suppresses systemic and renal inflammatory responses, thereby mitigating diabetic complications beyond glycemic control.[242] In addition, GLP-1 RA reduces urinary albumin excretion, glomerular filtration rate (eGFR) decline and the risk of macroalbuminuria, thus demonstrating their renoprotective properties.[243] Mechanistic studies demonstrate that liraglutide, a GLP-1 receptor agonist, inhibits the activation of the NLRP3 inflammasome in diabetic kidneys, downregulates the levels of caspase-1, GSDMD-NT and IL-1, which alleviates podocyte pyroptosis and ameliorates the progression of DN to end-stage renal disease.[244] Li et al further demonstrated that hyperglycemia-induced podocyte pyroptosis is driven by NF-κB/NLRP3 pathway activation. GLP-1 RAs such as liraglutide and semaglutide suppress this pathway and downregulate the expression of genes involved in pyroptosis and inflammation.[245] GLP-1RAs have demonstrated therapeutic effects, which provide a greater insight into the diagnosis and treatment of DN.

Dapagliflozin

Dapagliflozin, a pioneering sodium-glucose cotransporter 2 (SGLT2) inhibitor approved for T2DM, exerts glycemic control by promoting urinary glucose excretion.[246] Oraby et al found that dapagliflozin also exhibits nephroprotective effects in DN by inhibiting renal inflammation, OS and fibrosis and alleviating glucotoxicity-induced apoptosis.[247] Recent research has demonstrated that dapagliflozin alleviates podocyte pyroptosis in DN.[248] Zhang et al revealed that dapagliflozin inhibits the miR-155-5p/HO-1/NLRP3 axis in diabetic models, whereas palmitic acid (PA)-induced NLRP3 upregulation in podocytes (MPC5 cells) activates caspase-1 and elevates IL-1β/IL-18 levels (Table 1).[249] Dapagliflozin reverses this cascade by restoring HO-1 expression and downregulating NLRP3 inflammasome components, thereby attenuating pyroptosis.[249] Further mechanistic studies have shown that dapagliflozin inhibits both the NLRP3/caspase-1 pyroptotic pathway and the NF-kB/AMPK/NLRP3 inflammatory-metabolic pathway, suggesting a link between its renoprotective and antipyroptotic properties.[250,251] Therefore, dapagliflozin could be considered an effective drug for suppressing renal pyroptosis, which can address both the metabolic dysfunction of DN and pyroptosis-driven renal dysfunction.

Conclusions, Current Challenges and Future Perspectives

Pyroptosis, a lytic inflammatory cell death mechanism mediated by canonical caspase-1-dependent and non-canonical caspase-4/5/11-dependent pathways, plays a key role in driving renal cellular damage and the progression of DN. Central to this process is the NLRP3-caspase-1-GSDMD signaling axis, which orchestrates inflammasome activation, membrane permeabilization and the release of pro-inflammatory cytokines, linking hyperglycemia-induced cellular stress to clinical manifestations such as proteinuria and glomerular filtration decline.

Pyroptosis is thought to drive the pathogenesis of DN. Hyperglycemia triggers ROS/mTOR/NF-κB signaling in podocytes, leading to the activation of NLRP3 inflammasomes and inducing irreversible damage to the glomerular barrier. Microvascular injury is exacerbated by the activation of caspase-11/GSDMD and NETs-NLRP3 pathways in GECs. TLR4/NF-B triggers AIM2 inflammasome responses in TECs, which lead to pyroptosis. This review establishes pyroptosis as a unifying pathogenic contributor in DN. Current evidence suggests that lncRNAs regulate transcriptional and post-transcriptional networks in DN, thereby promoting renal inflammation.

The findings of this review redefine the pathophysiology of DN. Pyroptosis is emerging as the predominant type of inflammatory cell death, whereas apoptosis and autophagy have traditionally been the focus of research. The relevance of these findings is further enhanced when contextualized within existing research. Pyroptosis is a result of chronic inflammation related to DN. Previous studies have demonstrated that inhibiting inflammasome components may alleviate

Table 1 Compounds/Agents Targeting Pyroptosis-Related Signaling Pathways for the Therapeutic Regulation of DN

Compounds/Agents	Targeting of Inhibiting Pyroptosis-Related Signaling Pathways	Clinical Trial	References
Triptolide	Nrf2/ROS/NLRP3/caspase-1/GSDMD/IL-1β and IL-18	Preclinical	[160]
Sanziguben polysaccharides	TLR4/NF-κB/NLRP3/caspase-1	Preclinical	[163,167]
Hirudin	Irf2/caspase-4/GSDMD	Preclinical	[170,171]
Syringaresinol	NLRP3/caspase-1/GSDMD	Preclinical	[173]
AB-38b	TXNIP/NLRP3/caspase-1/GSDMD/IL-1β	Preclinical	[140]
Punicalagin	TXNIP/NLRP3/caspase-1/GSDMD/IL-1β	Preclinical	[179]
Carnosine	NLRP3/caspase-1/GSDMD/IL-1β and IL-18	Preclinical	[190]
Biochanin A	NF-κB/NLRP3/caspase-1/GSDMD/IL-1β and IL-18	Preclinical	[201,203]
Notoginsenoside Fc	TXNIP/NLRP3/caspase-1/GSDMD	Preclinical	[211]
Pyrroloquinoline quinone	ROS/NF-κB/NLRP3	Preclinical	[219]
Astragaloside IV	NLRP3/caspase-1/GSDMD	Preclinical	[121,225]
Ginsenosides	MAPK/NF-κB/NLRP3/caspase-1/GSDMD/IL-1β and IL-18	Preclinical	[231–235]
Tanshinone IIA	TXNIP/TRX/NLRP3	Preclinical	[128]
GLP-1 receptor agonists	NF-κB/NLRP3/caspase-1/GSDMD/IL-1β	Clinical Phase III	[244,245]
Dapagliflozin	miR-155-5p/HO-1/NLRP3/caspase-1/GSDMD/IL-1β and IL-18	Approved for T2DM	[249]

renal fibrosis and inflammation. This review provides an overview of specific molecular pathways involved in pyroptotic cell death including the NLRP3 inflammasome and GSDMD-mediated pores. This mechanistic explanation confirms existing studies and also provides a more detailed understanding of how pyroptosis contributes to the progression of DN, involving both metabolic dysregulation and chronic renal inflammation. This conversion provides an early intervention target for the treatment of DN.

The quality of life for patients with DN can be significantly improved through timely prevention and treatment. Targeting and regulating different pathways of pyroptosis can effectively mitigate the pathophysiology of metabolic imbalances, thereby restoring glomerular filtration and tubular reabsorption and alleviating DN. The current therapeutic protocols for DN primarily focus on controlling glycemic control, while neglecting the damage caused by inflammation. Natural compounds and traditional medicines have demonstrated efficacy in alleviating pyroptosis by targeting the NLRP3/GSDMD signaling axis, thereby preserving renal microstructure and slowing functional decline, which suggests a potential complement to metabolic-focused treatments. The validation of pyroptosis biomarkers in human diabetic kidney biopsies will establish the clinical relevance of these markers. Therefore, inhibiting pyroptosis may reduce the incidence of ESRD by alleviating the progression of DN at pre-fibrotic stages. Bioavailability challenges prevent natural compounds from offering advantages across a wide range of targets. Several synthetic agents such as AB-38b, have shown promise in preclinical models and require validation in clinical trials. The development of future drugs should be based on optimizing pharmacokinetics and validating the biomarkers for the early diagnosis of pyroptosis in humans.

The limitations of the existing studies must be acknowledged. Mechanistic insights obtained from animal models may not thoroughly explore the multifactorial pathology of DN in humans. The translation of preclinical findings into clinical practice faces significant challenges. The evaluation of further human cohorts, the optimization of drug delivery methods and addressing the bioavailability of certain natural compounds need to be addressed. The complex interaction between pyroptosis and other cell death pathways such as apoptosis and necroptosis also requires a more comprehensive understanding in order to avoid unintended therapeutic effects.

In summary, suppression of pyroptosis-regulated cell death offers a promising therapeutic avenue for the treatment of DN. However, rigorous clinical trials should be conducted to evaluate the safety and effectiveness of these therapeutic interventions, establish benchmarks against established first-line therapies and address translational challenges. Therefore, this effort will facilitate the development of precision medicine approaches for alleviating the global burden of DN-associated kidney failure.

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