Advances in understanding the NLRP3 inflammasome-mediated mechanisms and therapeutic targets in diabetic nephropathy (Review)

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Received December 23, 2025; Accepted April 23, 2026

DOI: 10.3892/ijmm.2026.5847

Abstract. Diabetic nephropathy (DN), a severe microvascular complication of diabetes, has exhibited a steadily increasing global incidence and is a major contributor to diabetes-related morbidity and mortality. DN is characterized by glomerular sclerosis, podocyte loss, tubular atrophy and excessive extracellular matrix deposition, among other features. The pathogenesis of DN is complex, involving multiple pathological processes, with the inflammatory cascade recognized as the core driver of its progression. Abnormal activation of the NLR Family Pyrin Domain Containing 3 (NLRP3) inflammasome, a key component of the innate immune system, can trigger pyroptosis and thereby aggravate renal injury. Whilst current literature primarily describes isolated mechanisms of DN, the present review summarizes the pathogenesis of DN and the NLRP3 inflammasome-related signaling pathways, proposing a novel three-tier hierarchical regulatory framework (upstream priming, midstream activation and downstream execution) for the five core NLRP3-related signaling pathways in DN, and systematically dissects the mitochondrial metabolic-cGAS-STING synergistic mechanism that drives NLRP3 activation, thus addressing the research gap in metabolic-immune crosstalk in DN. Furthermore, potential therapeutic agents targeting the NLRP3 inflammasome are discussed, and targeted therapeutic strategies stratified according to *in vivo* and *in vitro* validation evidence (such as small-molecule inhibitors, traditional Chinese medicine monomers/compounds and gene therapy) to provide a clear roadmap to clinical translation. Although current research on DN is limited, the findings and analyses assessed in the present review provide valuable insights into its pathogenesis, treatment, prognosis and directions for future experimental studies.

Contents

1. Introduction

Diabetes mellitus (DM) is the most common chronic metabolic disease worldwide, with its global incidence and prevalence rising continuously over the past 30 years: The number of adults living with diabetes has quadrupled from 198 million in 1990 to 828 million in 2022, and the age-standardized prevalence has doubled from 7.0 to 14.0%, with sustained growth observed in the vast majority of countries worldwide (1,2). Clinically, complications of DM mainly include coronary heart disease, peripheral artery disease, retinopathy, neuropathy and nephropathy (3). In recent years, the incidence of diabetic nephropathy (DN), a serious kidney disease, has continued to rise, 20 to 40% of patients with diabetes may develop kidney disease (4). Long-term hyperglycemia can alter the physiological microenvironment, triggering reactions such as oxidative stress (OS), pyroptosis, immune responses, mitochondrial dysfunction and lysosomal damage. These reactions can cause a series of abnormal adaptations, including glomerular hypertrophy, podocyte loss and mesangial matrix dilation. In the development of DN, activation of the NOD-like

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Key words: diabetic nephropathy, NLRP3 inflammasome, pathogenesis, pyroptosis, treatment strategy

Receptor family Pyrin domain containing 3 (NLRP3) inflammasomes is a key contributory factor in a variety of renal injury mechanisms (5,6).

The NLRP3 inflammasome is an essential intracellular multiprotein complex in innate immunity, predominantly expressed in the cytoplasm of innate immune cells such as macrophages, dendritic cells and mast cells, and is currently the most well-established inflammasome complex (7). The NLRP3 inflammasome recognizes multiple pathogen molecular patterns and endogenous danger signals, recruits and activates caspase-1 via the apoptosis-associated speck-like protein (ASC) aptamer, induces cleavage of downstream Gasdermin D (GSDMD) and regulates the release of IL-1β and IL-18, ultimately leading to pyroptosis (8). The NLRP3 inflammasome can be activated not only by various pathogenic and environmental stimuli, such as microbial cell wall components, nucleic acids and alum and silica, but also by endogenous hazard signals, such as lipopolysaccharides, adenosine triphosphate, hyaluronic acid, islet amyloid polypeptide, heme, oxidized mitochondrial DNA and the membrane attack complex (MAC) (9,10). In autoimmune diseases, arteriosclerosis and diabetic complications, abnormal activation of the NLRP3 inflammasome can trigger excessive inflammatory responses, acts as one of the key inflammatory mediators, rather than a sole dominant driver of tissue damage (11-13).

In the progression of DN, alterations in the renal microenvironment lead to excessive activation of NLRP3 inflammasomes, which trigger apoptosis and pyroptosis in glomerular mesangial cells, endothelial cells and tubular epithelial cells, ultimately resulting in chronic inflammation and renal fibrosis (14,15). Targeted inhibition of NLRP3-mediated pyroptosis is considered to be a potential therapeutic approach (16); NLRP3 knockout in diabetic mice was shown to alleviate streptozotocin-induced glomerular hypertrophy, glomerular sclerosis and mesangial matrix dilation (17). The present review introduces the structure and function of the NLRP3 inflammasome and examines the various pathways involved in its activation. The potential roles and mechanisms of the NLRP3 inflammasome in DN are discussed and finally, current therapeutic strategies targeting the NLRP3 inflammasome for the treatment of DN are summarized.

2. DN

DN is a specific form of kidney injury and the leading cause of end-stage kidney disease (18). The chronic renal failure resulting from DN is also a major cause of mortality among patients with DM (19,20). DN involves both structural changes in the kidneys and changes in kidney function (21). Structurally, DN includes glomerular mesangial dilation, thickening of the basement membrane, podocyte reduction, nodular glomerulosclerosis and endothelial cell destruction (22,23). Functionally, DN is characterized by increased albumin excretion and impaired glomerular filtration (24). In addition, a key pathogenic factor for the development of DN is persistent hyperglycemia and it has been shown to induce marked renal structural damage through advanced glycation end-product (AGE) accumulation, activation of the polyol and hexosamine pathways, stimulation of the renin-angiotensin-aldosterone and sympathetic nervous systems, and the onset of insulin resistance and endothelial dysfunction (25,26). Studies have shown that factors such as OS, immune response, mitochondrial damage, pyroptosis and podocyte autophagy can all cause damage to these cells (27,28), which disrupts the filtration barrier and leads to elevated proteinuria, abnormal glomerular filtration rate and elevated creatinine levels (29,30), thereby promoting the occurrence and development of DN (Fig. 1). During the development the DN, all of these factors trigger an inflammatory response, the core of which is the inflammasome. This cytoplasmic multiprotein complex activates the inflammatory protein caspase-1 and serves a key role in the innate immune system (31). The NLRP3 inflammasome, as a key participant, is widely involved in the inflammatory response by forming and releasing inflammatory cytokines, thereby exacerbating the development of DN (32,33).

3. NLRP3 inflammasome

Inflammasomes are large multiprotein complexes belonging to the pattern recognition receptor (PRR) family and serve a key role in the innate immune system (34). They are composed of inflammatory caspases and various sensors, including the nucleotide-binding domain and leucine-rich repeat-containing receptors (NLRs) family, pyrin and absent in melanoma 2 (AIM2) (35,36). Members of the NLR family typically contain three conserved structural domains: A C-terminal leucine-rich repeat (LRR) region, a central nucleotide-binding site and an NACHT domain responsible for oligomerization and an N-terminal effector domain (37,38). The NLR comprises several members, including NLRP1, NLRP3, NLRP6 and NLRC4, among which the NLRP3 inflammasome is the most well-characterized (39,40).

The NLRP3 inflammasome is composed of NLRP3, a multiprotein complex consisting of ASC and caspase-1 (41). This complex serves a key role in the immune system, recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) to initiate immune responses (42). Upon activation, the NLRP3 inflammasome recruits ASC to form speck-like aggregates, which facilitate the conversion of pro-caspase-1 into its active p10/p20 subunits (43). Activated caspase-1 subsequently processes the inactive precursors pro-IL-1 and pro-IL-18 into their mature, bioactive forms, thereby promoting the secretion of these key pro-inflammatory cytokines. Furthermore, caspase-1 cleaves the pyroptosis executioner protein GSDMD into its N- and C-terminal fragments, leading to membrane pore formation, cellular lysis and pyroptotic cell death (44,45).

The activation process of the NLRP3 inflammasome involves two stages (Fig. 2). In the initiation phase, nuclear factor-B (NF-κB) activation induces the toll-like receptor 4 (TLR4) signaling, increasing the production of NLRP3 and pro-inflammatory mediators (46). Upon recognition of danger signals and completion of inflammasome assembly, pro-caspase-1 is cleaved into its active form, initiating downstream immune responses (47). During the activation phase, multiple distinct stimulatory signals are required (48); a variety of stimuli capable of activating the NLRP3 inflammasome have been identified, including pathogenic factors, endogenous danger signals and environmental substances (49-51). To date, three main theories have been proposed to explain

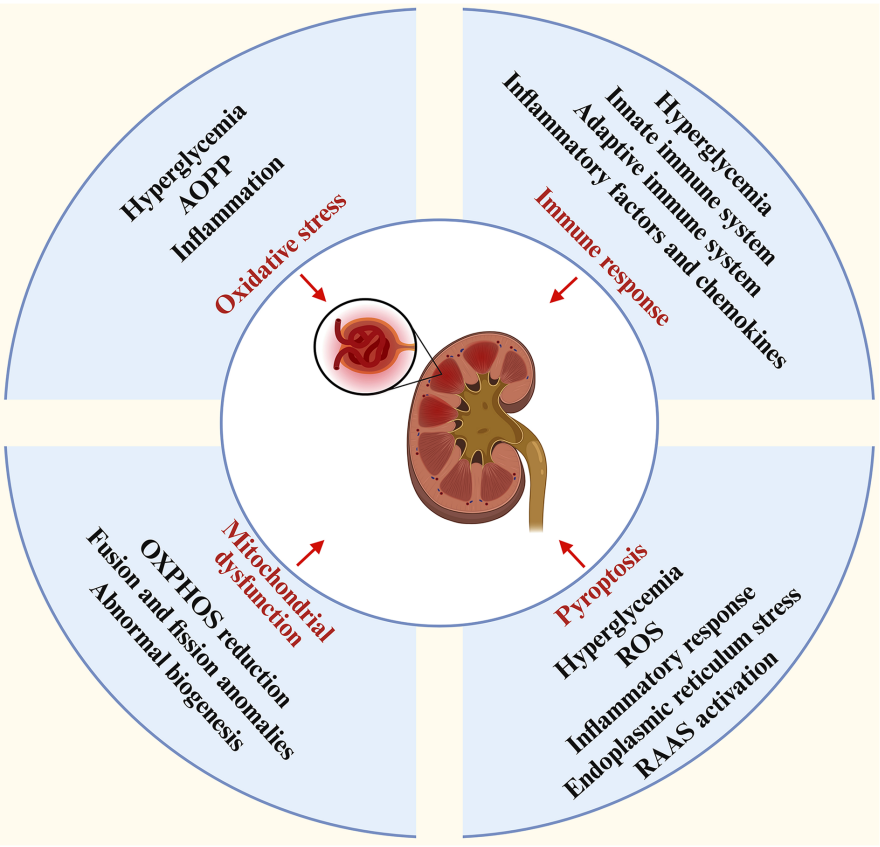

Figure 1. Schematic diagram illustrating the pathological mechanisms of hyperglycemia-induced renal injury. This is a mechanistic schematic centered on the kidney (with a magnified inset of renal tubules), which delineates the multi-pathway pathological processes of hyperglycemia-mediated renal injury across four quadrants. Hyperglycemia induces renal injury via the production of AOPP, inflammatory responses and oxidative stress; hyperglycemia activates the innate/adaptive immune systems, while regulating the release of inflammatory factors and chemokines to trigger immune responses; hyperglycemia induces pyroptosis through the generation of ROS, inflammatory responses and activation of the RAAS; hyperglycemia causes mitochondrial dysfunction, dysregulation of autophagy/fusion and impairment of OXPHOS. AOPP, advanced oxidation protein products; ROS, reactive oxygen species; RAAS, renin-angiotensin-aldosterone system; OXPHOS, oxidative phosphorylation.

the mechanism of NLRP3 inflammasome activation. The first theory posits that extracellular ATP stimulates the ATP-gated cation channel P2X7 on the cell membrane, leading to potassium efflux. Experimental evidence indicates that low intracellular K^+ levels can directly trigger NLRP3 inflammasome activation (52,53). The second theory is the lysosomal rupture model; studies have demonstrated that crystalline substances, such as cholesterol crystals, silica and aluminum salts, can cause lysosomal damage upon uptake, leading to the release of cathepsin B, which in turn activates the NLRP3 inflammasome (54,55). The third theory involves mitochondrial damage and increased reactive oxygen species (ROS) as triggers for NLRP3 inflammasome activation. Evidence indicates that IL-1 production diminishes in response to a loss of mitochondrial membrane potential ($\Delta\Psi m$) following RNA virus infection, which suggests that NLRP3 activation may be $\Delta\Psi m$-dependent. However, the exact mechanisms associating mitochondrial dysfunction to NLRP3 inflammasome activation have yet to be fully elucidated (56-58).

NLRP3 functions as a pivotal sensor in sterile inflammatory signaling and acts as a central regulator of chronic inflammatory disorders. Under homeostatic conditions, the NLRP3 inflammasome exerts beneficial effects by facilitating pathogen clearance, promoting tissue repair and preserving physiological balance. By contrast, its aberrant or sustained activation drives chronic inflammation and tissue damage (Table I) (59-87).

4. Roles of NLRP3 in DN progression

Pyroptosis. Pyroptosis of inflammatory and renal intrinsic cells mediated by the NLRP3 inflammasome is a key contributory cell death mode in renal inflammation and injury during DN. The canonical NLRP3 inflammasome-mediated pyroptosis pathway is the predominant pathway in DN, with considerable *in vivo* evidence, while the non-canonical (caspases-4/5/11-mediated) and caspase-3/GSDME-mediated pathways have presently been only validated *in vitro* and lack direct *in vivo* verification in DN models. The pyroptosis pathway is characterized by the formation of pores in the cell membrane, leading to cell rupture and the release of pro-inflammatory factors, exacerbating renal inflammation and fibrosis (88). This process is initiated by stimuli including hyperglycemia, OS, AGEs and lipotoxicity, in which activation of the NLRP3 inflammasome represents a pivotal event (89). Following NLRP3 inflammasome activation, Caspase-1 cleaves GSDMD and pro-IL-1β/IL-18, leading to the release of inflammatory mediators and the induction of pyroptosis (90).

There are three main molecular mechanisms of pyroptosis (Fig. 3). First, in the canonical inflammasome pathway, which

Table I. NLRP3 inflammasome-related diseases.

Disease	Related mechanism	(Refs.)
Respiratory system diseases		
Chronic obstructive pulmonary disease	Harmful particles or gases activate the NLRP3 inflammasome through the NF-κB signaling pathway or the P2X7 receptor pathway in lung epithelial cells, macrophages and dendritic cells.	(59,60)
Bronchial asthma	Allergens activate the TLR4/MyD88/NF-κB pathway and the NLRP3 inflammasome in airway macrophages, epithelial cells and dendritic cells.	(61)
Silicosis	SiO_2 can stimulate the assembly of NLRP3 and ASC, activating the NLRP3/Caspase-1/ IL-1β/IL-18 signaling pathway in macrophages.	(62)
Bacterial infectious pneumonia	Staphylococcus aureus pneumonia, NLRP3 inflammasome mediates lung injury induced by α-hemolysin and α-hemolysin activates IL-1β; streptococcus pneumoniae pneumonia, streptococcus pneumoniae hemolysin can activate the TLR4/NF-κB/NLRP3/Caspase-1/IL-1β/IL-18 signaling pathway.	(63,64)
Digestive system diseases		
HP-related stomach diseases	HP infection may activate the TNF/TNFR1/NLRP3/Caspase-1/IL-1β signaling pathway in gastric epithelial cells, mononuclear macrophages and lymphocytes.	(65)
Liver diseases	Activate the NLRP3/Caspase-1/IL-1β/IL-18 signaling pathway in liver tissue.	(66)
Inflammatory intestinal diseases	Activate the NLRP3/Caspase-1/IL-1β/IL-18 signaling pathway in intestinal mucosa or epithelial cells.	(67)
Acute pancreatitis/acute severe pancreatitis	Activating NLRP3 inflammasome in acinar cells.	(68)
Bone and joint system diseases		
Rheumatoid arthritis	Activate the TLR4/NF-κB/NLRP3/Caspase-1/IL-1β signaling pathway in synovial tissue.	(69)
Osteoarthritis	Activate the PI3K/Akt/NF-κB/NLRP3 in articular chondrocytes or macrophages and monocytes.	(70)
Osteoporosis	Activating NLRP3 inflammasome in osteoclasts.	(71)
Gouty arthritis	Uric acid crystals activate the NLRP3 inflammasome.	(72)
Intervertebral disc degeneration	Mitochondrial dysfunction, endoplasmic reticulum stress and ROS damage can activate the NLRP3 inflammasome.	(73)
Cardiovascular diseases		
Atherosclerosis	Activating NLRP3 inflammasome in arterial tissue.	(74)
Heart failure	Activating NLRP3 inflammasome in myocardial cells.	(75)
Myocardial ischemia-reperfusion injury	The outflow of ROS and K^+ activates the NLRP3 inflammasome in myocardial fibroblasts or microvascular endothelial cells.	(76)
Central nervous system diseases		
Traumatic brain injury	Activate NLRP3 inflammasome in neurons, astrocytes and microglia.	(77)
Parkinson's disease	Activating NLRP3 inflammasome in microglia.	(78)
Alzheimer's disease	Enhancing Aβ aggregation by activating NLRP3 inflammasome in the brain promotes the development of neuroinflammation and Tau lesions.	(79)
Multiple sclerosis	Activating NLRP3 inflammasome in MS plaque.	(80)
Cerebral ischemia	Activate the NLRP3/Caspase-1/IL-1β pathway.	(81)

Table I. NLRP3 inflammasome-related diseases.

Disease	Related mechanism	(Refs.)
Autoinflammatory diseases		
Muckle-Wells syndrome	NLRP3 gene mutations lead to its persistent activation.	(82)
Neonatal-onset multisystem inflammatory disease	NLRP3 gene mutations lead to its persistent activation.	(83)
Familial cold autoinflammatory syndrome	NLRP3 gene mutations lead to its persistent activation.	(84,85)
Metabolic diseases		
Non-alcoholic steatohepatitis	Activate the NLRP3/Caspase-1/IL-1β pathway.	(86)
DM	Activate the NLRP3/Caspase-1/IL-1β pathway.	(87)

This table summarizes NLRP3 inflammasome-related diseases across multiple physiological systems and their corresponding core pathogenic mechanisms. Aβ, β-amyloid; ASC, Apoptosis-associated speck-like protein containing a CARD; Caspase-1, Cysteinyl aspartate specific proteinase 1; DM, Diabetes Mellitus; HP, Helicobacter pylori; IL-1β, Interleukin-1β; IL-18, Interleukin-18; MyD88, Myeloid differentiation primary response 88; MS, Multiple sclerosis; NF-κB, Nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain containing 3; PI3K, Phosphatidylinositol 3-kinase; K+, Potassium ion; Akt, Protein kinase B; P2X7, Purinergic 2X7 receptor; ROS, Reactive oxygen species; SiO2, Silicon dioxide; TLR4, Toll-like receptor 4; TNF, Tumor necrosis factor; TNFR1, Tumor necrosis factor receptor 1.

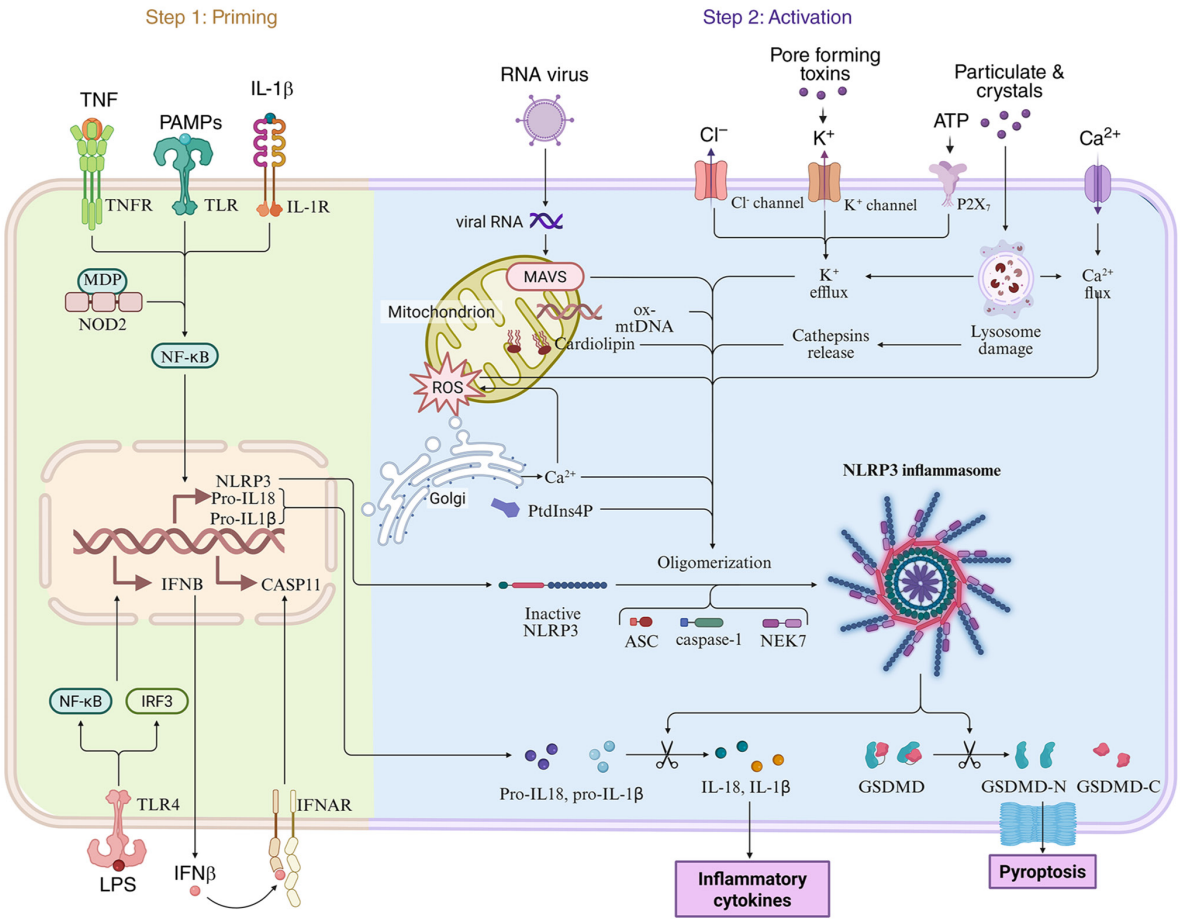

Figure 2. Schematic diagram illustrating the two-step activation process of the NLRP3 inflammasome. This mechanistic figure depicts the dual-phase regulatory cascade in immune cells, priming and activation, in which black arrows indicate promotion. ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CASP11, cysteinyl aspartate specific proteinase 11; GSDMD, Gasdermin D; GSDMD-C, Gasdermin D C-terminal domain; GSDMD-D, Gasdermin D N-terminal domain; IRF3, interferon regulatory factor 3; LPS, lipopolysaccharide; MAVS, mitochondrial antiviral signaling protein; MDP, muramyl dipeptide; NEK7, NIMA-related kinase 7; NLRP3, NOD-like receptor family pyrin domain containing 3; NOD2, nucleotide-binding oligomerization domain-containing 2; ox-mtDNA, oxidized mitochondrial DNA; PAMPS, pathogen-associated molecular patterns; P2X7, purinergic receptor P2X7; ROS, reactive oxygen species; TLR, toll-like receptor.

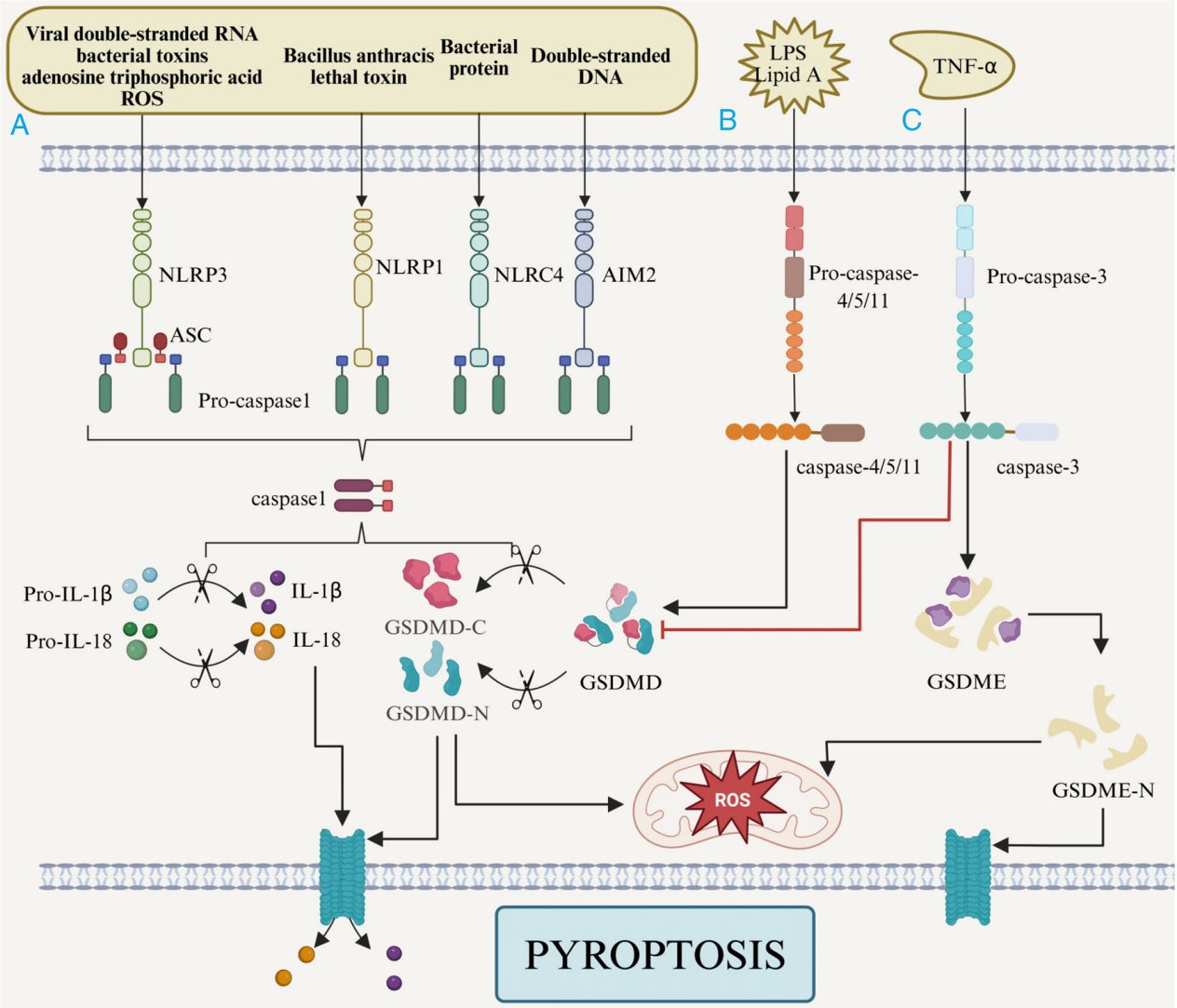

Figure 3. Schematic representation of pyroptosis signaling pathways mediated by distinct inflammasomes. This figure illustrates the molecular pathways through which diverse stimuli activate specific inflammasomes, leading to pyroptosis mediated by the caspase family and GSDM proteins. (A) The left panel depicts the canonical inflammasome pathway; (B) the central panel illustrates the non-canonical inflammasome pathway; (C) the right panel represents the caspase-3-mediated inflammasome pathway. In this diagram, red lines indicate inhibitory interactions, while black lines denote activating interactions. GSDM, gasdermin. AIM2, absent in melanoma 2; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; GSDM, Gasdermin; LPS, Lipopolysaccharide; NLRP1, NOD-like receptor family pyrin domain containing 1; ROS, reactive oxygen species.

is predominant in DN, the two most important processes are the activation of inflammasomes and the cleavage of the Gasdermin family. PAMPs and DAMPs are recognized by PRRs, and activation of PRRs by bacteria, viruses and various pathological factors leads to the assembly of different inflammasomes, with the participation of connexin and effector proteins (91,92). Subsequently, pro-caspase-1 is recruited by the inflammasome and activated as cleaved caspase-1. Cleaved caspase-1 can activate IL-1 and IL-18 (93). Activated IL-1 and IL-18 can be released outside the cell independently of the Gasdermin family to mediate the inflammatory cascade. GSDMD can be cleaved into the GSDMD-N terminal, which possesses pore-forming properties, and the GSDMD-C terminal, a key process in pyroptosis (94).

In the atypical inflammasome pathway, caspases-4, -5 and -11 directly detect pathogen molecules via their caspase recruitment domains (CARDs), leading to caspase-1 activation, IL-1 and IL-18 maturation, GSDMD cleavage and IL-1 release (95,96). GSDMB does not induce pyroptosis via its N-terminal domain, as other Gasdermin family members do, but instead promotes caspase-4 activity by directly binding to the caspase-4 CARD domain (97). Subsequently, activated caspase-4 can form membrane pores via GSDMD activity and potassium influx can activate NLRP3. Another study demonstrated that the downregulation of caspase-4 inhibits TNF-α-induced pyroptosis in human pulmonary artery endothelial cells, as well as the activation of GSDMD and GSDME (98). Furthermore, caspase-11 recognizes its substrates, predominantly GSDMD, via the P1'-P4' region of the target protein (99,100).

Finally, the caspase-3-mediated inflammasome pathway is also associated with pyroptosis as caspase-3 is activated during LPS-induced pyroptosis (101). GSDME can also be cleaved by caspase-3, leading to a transition from apoptosis to pyroptosis (102). When NLRP3-specific inhibitors were used to suppress NLRP3-mediated pyroptosis, ATP induced

pyroptosis in macrophages via the caspase-3/GSDME axis (103). Meanwhile, activated caspase-3 also inactivates the pore-forming domain of GSDMD, which inhibits GSDMD-mediated pyroptosis (104). Notably, both GSDMD-NT (N-terminal) and GSDME-NT can act on mitochondria, leading to increased ROS production, inducing apoptosis, further stimulating the release of inflammatory substances and exacerbating tissue damage (105,106). Notably, the non-canonical inflammasome pathway and caspase-3/GSDME-mediated pyroptosis pathway have not been validated using *in vivo* DN models, whereas the canonical NLRP3/caspase-1/GSDMD pathway is fully supported by multiple genetic and pharmacological *in vivo* studies (88,90,107).

The progression of DN is associated with pyroptosis, which is regulated by five interacting hierarchical core signaling pathways (NF-κB/NLRP3, TXNIP/NLRP3, Nrf2/HO-1/NLRP3, HIF-1α/NLRP3 and PTEN/PI3K/Akt) (TXNIP, thioredoxin-interacting protein; Nrf2, nuclear factor erythroid 2-related Factor 2; HO-1, heme oxygenase-1; HIF-1α, hypoxia-inducible factor-1α) rather than independent mechanisms (Fig. 4). These pathways form an upstream-downstream regulatory hierarchy with extensive crosstalk and are divided into three modules: NF-κB acts as the top upstream module, priming NLRP3 inflammasome by transcriptionally upregulating NLRP3, pro-IL-1, pro-IL-18, and activating TXNIP/HIF-1α; the midstream module (TXNIP/NLRP3, Nrf2/HO-1/NLRP3, HIF-1/NLRP3) mediates NLRP3 activation (TXNIP binds NLRP3 via ROS, Nrf2/HO-1 negatively regulates ROS/TXNIP/NF-κB but is impaired in DN and HIF-1α forms a positive feedback loop); the PTEN/PI3K/Akt pathway serves as the final facilitator, as hyperglycemia inactivates PTEN to hyperactivate Akt, amplifying the cascade and promoting NLRP3-ASC-caspase-1 assembly (108-110). Collectively, these pathways converge to three core nodes (NF-κB-mediated priming, ROS-TXNIP-induced NLRP3 oligomerization and Akt-mediated execution) to drive aberrant NLRP3 activation and pyroptosis in DN, indicating multi-pathway synergistic targeting as a rational therapeutic strategy.

OS. OS refers to a pathological state in which the generation rate of ROS and reactive nitrogen species (RNS) in the body exceeds the clearance capacity of the endogenous antioxidant system, resulting in an imbalance in oxidative and antioxidant homeostasis (111). OS in DN is predominantly caused by the overproduction of ROS and RNS, induced by factors such as hyperglycemia and AGEs (112). A previous study has shown that hyperglycemia can induce OS and podocyte damage by mediating the Von Hippel-Lindau E3 ubiquitin ligase, which promotes the ubiquitin-mediated degradation of glucose-6-phosphate dehydrogenase (113). Advanced oxidation protein products (AOPPs) are oxidation-modified products formed after plasma proteins are attacked by ROS (114); AOPPs can synergize with AGEs to activate NADPH oxidase (NOX), leading to excessive ROS production and NF-κB activation, thereby triggering the Wnt/β-catenin signaling pathway and ultimately mediating podocyte dedifferentiation and epithelial-mesenchymal transition (EMT) (115). This oxidative imbalance mediates kidney injury through multiple pathways, including glomerular endothelial cell damage, mesangial cell proliferation, increased extracellular matrix (ECM) deposition, induction of podocyte apoptosis, suppression of podocyte protein expression, EMT-related pathological changes, inflammatory factor-driven injury, renal vascular endothelial cell impairment and mitochondrial dysfunction (116).

In the pathological progression of DN, the NLRP3 inflammasome serves a pivotal role by driving the OS-inflammation-cell injury cascade. Under hyperglycemic conditions, aberrant NOX activation and dysfunction of the mitochondrial electron transport chain in renal tissues lead to excessive ROS production, which acts as a key initiating signal for NLRP3 inflammasome activation (117-119).

ROS can induce NLRP3 oligomerization through multiple mechanisms. First, ROS directly oxidize TXNIP, promoting its binding to NLRP3 and thereby relieving Trx-mediated inhibition of NLRP3 (120). Second, ROS disrupt lysosomal membrane stability, leading to the release of cathepsin B and subsequent proteolytic signaling (121). Third, ROS trigger the release of mitochondrial (mt) DNA and the accumulation of mtROS, which activate innate immune responses through DAMPs (122). After NLRP3 activation, ASC is recruited and caspase-1 is cleaved, promoting the conversion of IL-1β and IL-18 precursors into mature inflammatory factors (123). IL-1β activates the NF-κB pathway in renal interstitial fibroblasts, induces expression of monocyte chemoattractant protein-1 (MCP-1) and intercellular adhesion molecule-1 (ICAM-1), which exacerbates macrophage infiltration and renal interstitial fibrosis. IL-18, together with IFN-γ, promotes M1-type polarization in renal tubular epithelial cells and amplifies the local inflammatory response (124-126). Meanwhile, caspase-1-mediated cleavage of GSDMD forms pore-forming proteins, causing pyroptosis in podocytes and renal tubular epithelial cells, disrupting the glomerular filtration barrier and inducing tubulointerstitial injury (127,128). Notably, inflammatory factors form a positive feedback loop with OS signaling. IL-1β and TNF-α enhance ROS production by upregulating NOX subunits, while ROS further amplify the inflammatory cascade by activating NLRP3. This cycle ultimately contributes to mesangial matrix expansion, basement membrane thickening and tubular atrophy, thereby accelerating the progression of DN (129,130). OS-driven NLRP3 inflammasome abnormal activation not only serves as the core hub of DN inflammatory damage, but also acts as a key molecular node connecting glycolipid metabolism disorder and renal tissue fibrosis (Fig. 5).

Mitochondrial damage. Mitochondria, as the prominent energy-metabolism organelles within cells, play an indispensable role in aerobic respiration (131). Podocytes are rich in mitochondria, which are decisive for the normal physiological function and energy supply of podocytes (132). In the pathological process of DN, mitochondrial dysfunction is considered a key mechanism of podocyte damage, involving abnormalities in oxidative phosphorylation (OXPHOS), dysregulation of mitochondrial dynamics, defects in biosynthesis, dysregulation of autophagy and interactions among multiple signaling pathways (133-135). Hyperglycemia promotes the formation of AGEs from glucose, which then bind to RAGE on the surface of renal cells, generating a large amount of ROS via NOX. ROS can directly attack mitochondria, disrupt mitochondrial

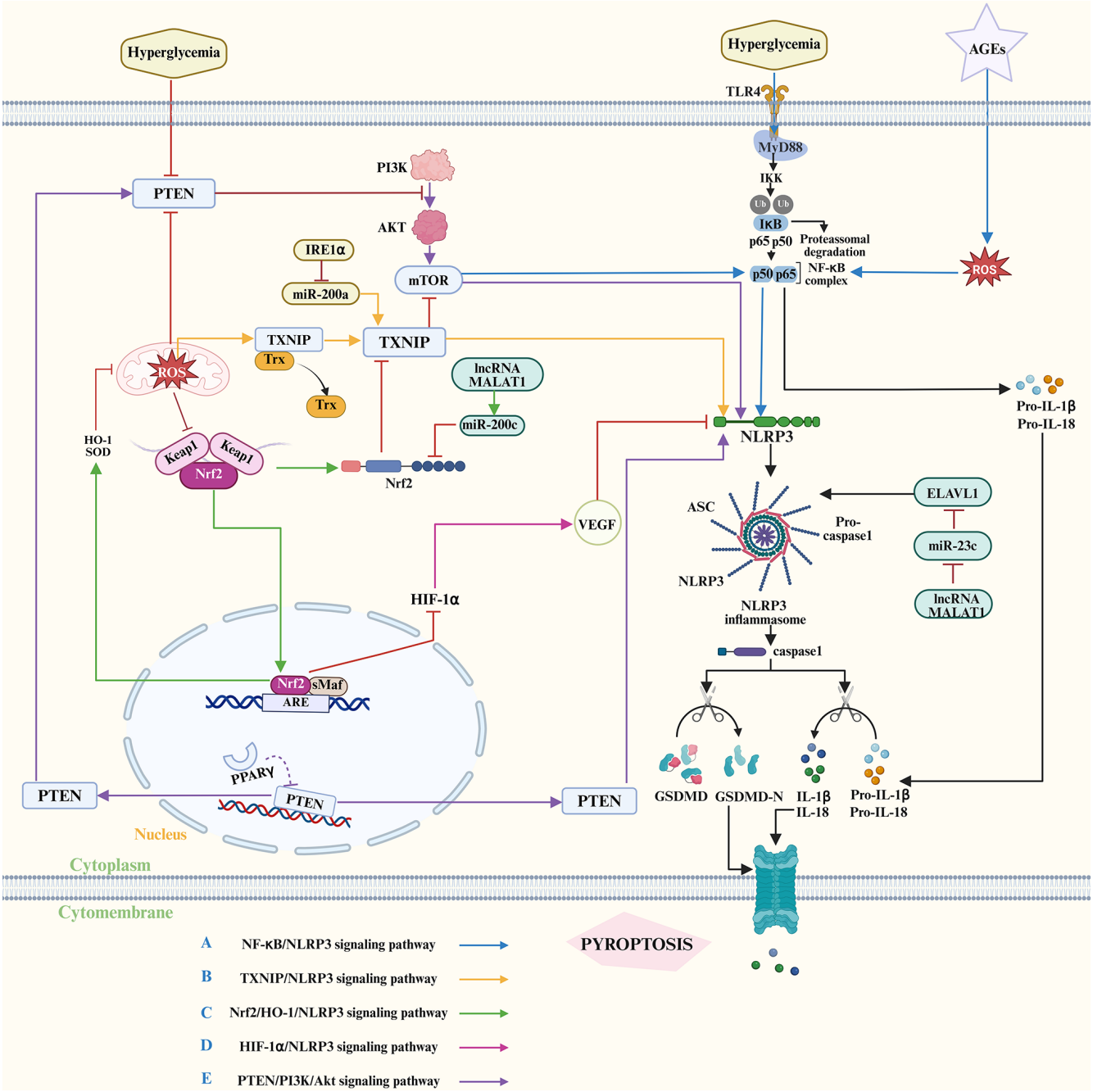

Figure 4. Schematic diagram illustrating the mechanism by which hyperglycemia regulates NLRP3 inflammasome activation and mediates pyroptosis via multiple signaling pathways. This figure elucidates the upstream-downstream regulatory hierarchy and crosstalk of five core signaling pathways in hyperglycemic DN, as well as their convergent nodes that ultimately drive NLRP3 inflammasome activation and pyroptosis. (A) NF-κB/NLRP3 signaling pathway (blue): The upstream priming hub that transcriptionally activates NLRP3, TXNIP and HIF-1α; (B) TXNIP/NLRP3 signaling pathway (yellow): Midstream oxidative activation signal, directly inducing NLRP3 oligomerization; (C) Nrf2/HO-1/NLRP3 signaling pathway (green): Negative feedback regulator that suppresses NF-κB and TXNIP to inhibit NLRP3 activation; (D) HIF-1α/NLRP3 signaling pathway (pink): Midstream metabolic activation signal, amplifying NLRP3 transcription and ROS production; (E) PTEN/PI3K/Akt signaling pathway (purple): The downstream convergent executor that integrates all upstream signals to promote NLRP3 inflammasome assembly. Red lines represent inhibitory effects and black lines denote promotional effects. AGEs, advanced glycation end products, ARE, antioxidant response element; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; ELVAV1, ELAV like RNA binding protein 1 (alias HuR); GSDMD, Gasdermin; HIF-1α hypoxia inducible factor 1α; HO-1, heme oxygenase 1; Keap1, Kelch Like ECH Associated Protein 1; lncRNA, long non-coding RNA metastasis associated lung adenocarcinoma transcript 1; MyD88, myeloid differentiation primary response 88; miR, microRNA; NLRP3, NOD-like receptor family pyrin domain containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; SDO, superoxide dismutase; sMaf, small musculoaponeurotic fibrosarcoma oncogene homolog; TLR, toll-like receptor 4; Trz, thioredoxin; TXNIP, thioredoxin interacting protein.

membrane structure, activate MAPK pathway, phosphorylate the subunit of the mitochondrial respiratory chain complex and inhibit OXPHOS efficiency. Furthermore, this downregulates the expression of mitochondrial antioxidant enzymes, weakens the clearance ability of mtROS and intensifies OS (136,137). The novel molecular mechanism by which mitochondrial damage activates the NLRP3 inflammasome mainly involves the regulatory role of mitochondrial metabolites and the participation

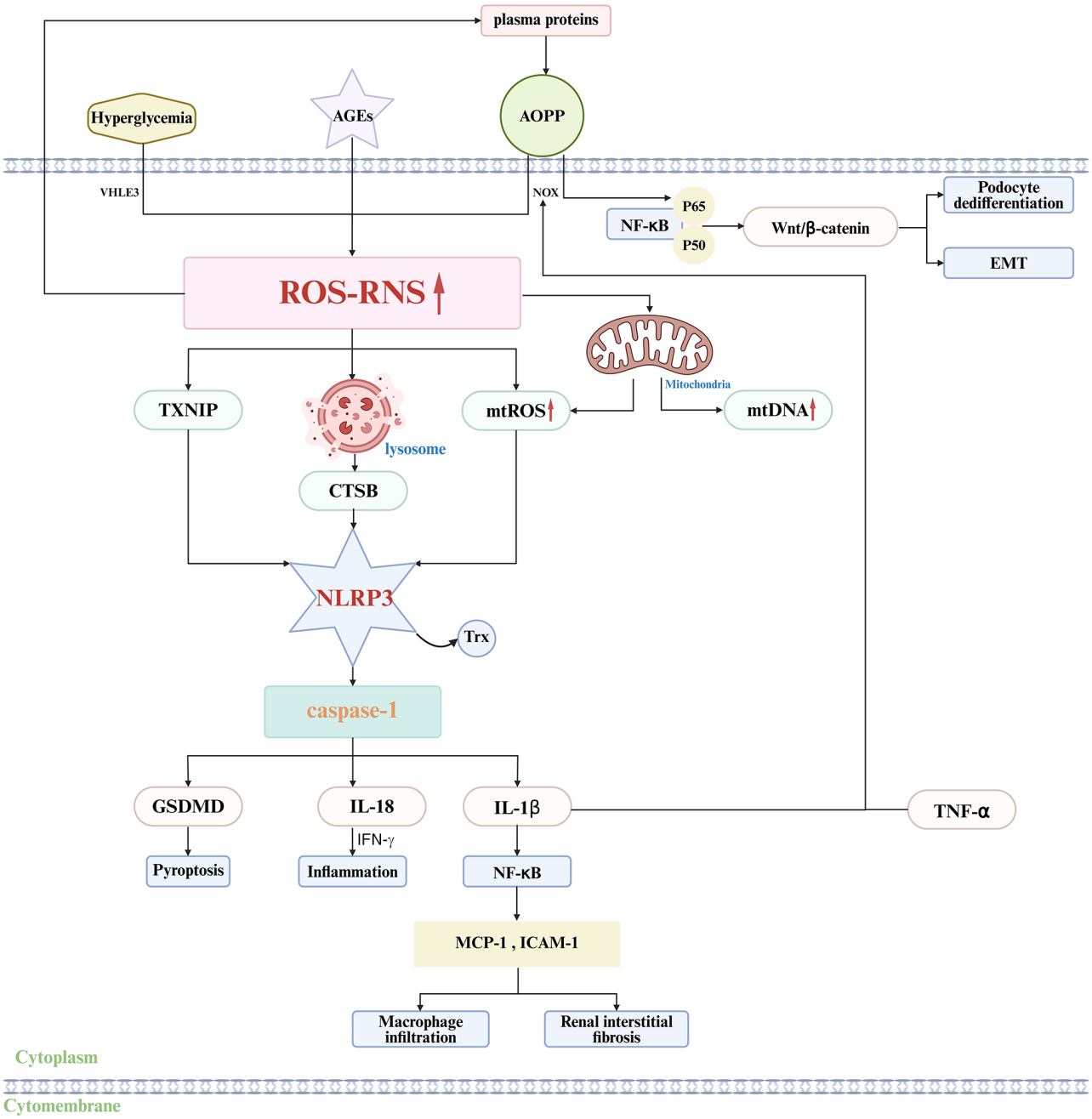

Figure 5. Schematic representation of the molecular mechanisms underlying hyperglycemia, AGEs and AOPP induced renal injury. This figure delineates the molecular pathways through which hyperglycemia, AGEs, AOPP and plasma proteins synergistically trigger elevated reactive oxygen species-reactive nitrogen species levels, subsequently mediating renal cell pyroptosis, inflammation and fibrosis via the NLRP3 inflammasome axis. Within this schematic, red arrows denote an increase, while black arrows indicate activation or promotion. AGEs, advanced glycation end products; AOPP, advanced oxidation protein products; CTSB, Cathepsin B; EMT, epithelial-mesenchymal transition; GSDMD, Gasdermin D; ICAM-1, intercellular adhesion molecule 1; MCP-1, monocyte chemoattractant protein 1; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; NLRP3, NOD-like receptor family pyrin domain containing 3; RNS, reactive nitrogen species; TOS, reactive oxygen species; Trx, thioredoxin; TXNIP, thioredoxin interacting protein.

and synergy of the cGAS-STING pathway (138). It first manifests as the dual effects of succinic acid; under hyperglycemic conditions, the mitochondrial tricarboxylic acid cycle becomes impaired, leading to succinic acid accumulation. Whilst excess succinic acid upregulates NLRP3 transcription by stabilizing HIF-1α, it also inhibits mitochondrial succinate dehydrogenase, which promotes electron leakage from the electron transport chain and enhances mtROS production. Together, this creates a positive feedback loop (139). A further mechanism of action is the mitochondrial targeting effect of ceramides, with ceramide synthase 6 catalyzing mitochondrial ceramides, which leads to mtDNA release and NLRP3 activation (140). In addition, hyperglycemia-induced enhanced glycolysis leads to intracellular lactic acid accumulation. Lactic acid directly binds to the NLRP3 promoter region by modifying histone H3 lysine 18 to promote its transcriptional activation (141). Regarding the cGAS-STING pathway, hyperglycemia-induced mitochondrial damage leads to mtDNA leakage into the cytoplasm; cGAS recognizes mtDNA to generate cGAMP, which activates STING and recruits TBK1, which phosphorylates IRF3 and NF-κB to

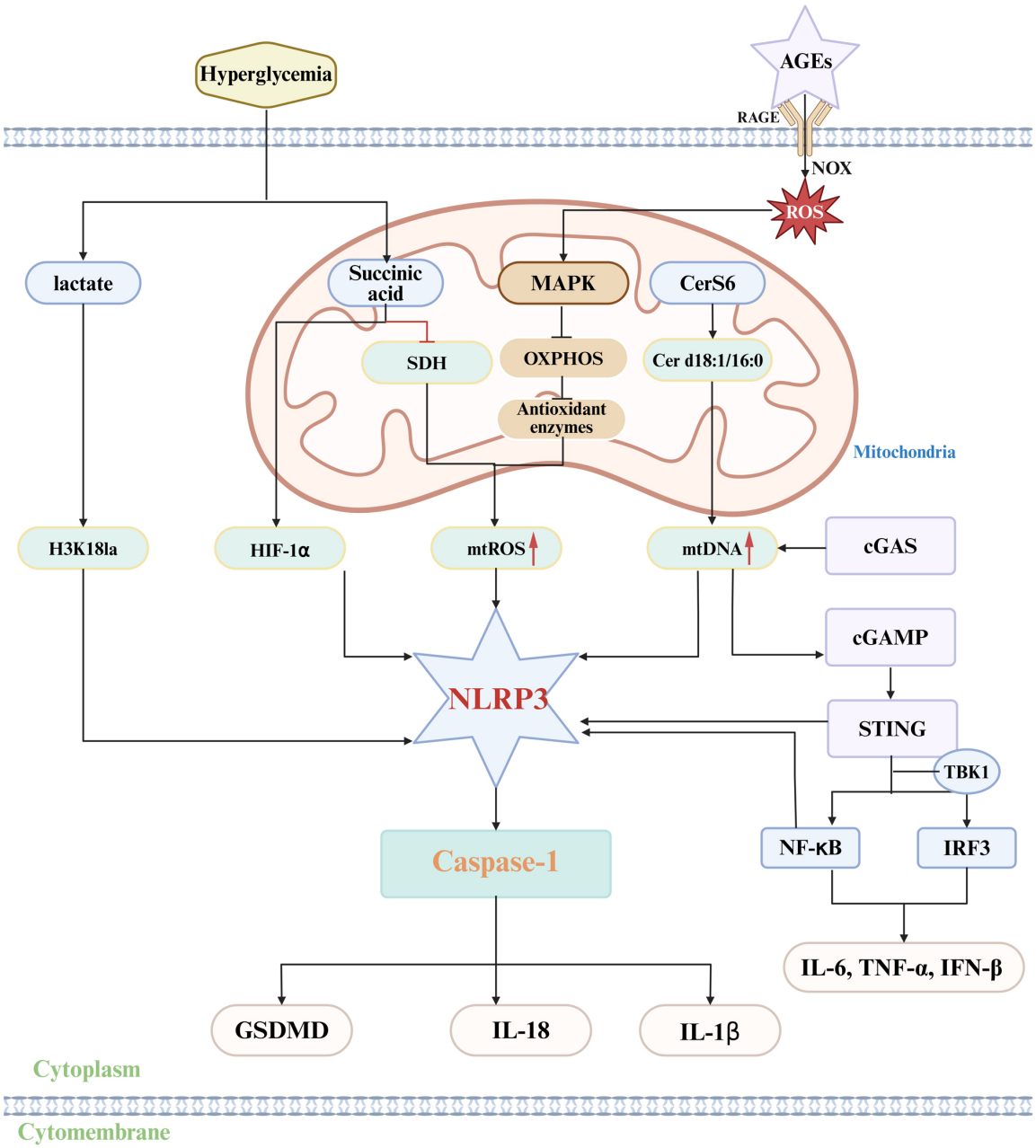

Figure 6. Schematic diagram illustrating the molecular mechanism through which hyperglycemia and AGEs regulate NLRP3 inflammasome activation via mitochondrial pathways. This figure delineates the molecular cascades whereby hyperglycemia and AGEs (acting via receptor for AGEs [RAGE] binding) modulate mitochondrial function, subsequently activating the NLRP3 inflammasome and triggering downstream inflammatory responses and cell death pathways. Within this schematic, red arrows denote increased activity or levels, whereas black arrows signify molecular promotion or activation events. AGEs, advanced glycation end products; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; CerS6, Ceramide Synthase 6; SDH, succinate dehydrogenase; OXPHOS, oxidative phosphorylation; mtROS, mitochondrial reactive oxygen species; mtDNA, mitochondrial DNA; cGAS, cyclic GMP-AMP synthase; cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; SITNG, stimulator of interferon genes; TBK1, TANK-binding kinase 1; NLRP3, NOD-like receptor family pyrin domain containing 3; IRF3, interferon regulatory factor 3; GSDM, Gasdermin; H3K18la, Histone H3 Lysine 18 Lactylation; HIF-1α, hypoxia inducible factor 1 subunit α.

promote the expression of pro-inflammatory factors such as Interferon-beta (IFN-β), IL-6 and TNF-α. At the same time, the cGAS-STING pathway can act synergistically with NLRP3 by upregulating NLRP3 transcription and enhancing mtROS production, thereby facilitating inflammasome assembly and further exacerbating the progression of DN (Fig. 6) (142,143).

Immune response. The immune-mediated damage of DN centers on the overactivation of innate immune pathways, which work in synergy to drive the inflammatory cascade and fibrosis in the kidneys (144). The initial triggers of injury include hyperglycemia, glycotoxicity, AGEs and OS, all of which cause cellular damage and lead to the release of DAMPs and mtDNA. These danger signals subsequently activate TLRs (such as TLR2 or TLR4) and the NLRP3 inflammasome (145,146). TLR signaling induces the expression of pro-inflammatory cytokines (such as IL-6 and TNF-α) and ICAM-1 through the NF-κB pathway, which promotes the infiltration of macrophages and T cells. Meanwhile, the NLRP3 inflammasome mediates the maturation and release

of IL-1β and IL-18 via caspase-1, amplifying the inflammatory response and triggering podocyte apoptosis (147,148). In terms of immune cell effects, macrophages recruit and release fibrotic factors through CCL2-CCR2 signaling, and T cells enhance the inflammatory response through IFN-γ, both of which form a pro-inflammatory and pro-fibrotic positive feedback loop with innate cells (149,150). Ultimately, these immune mechanisms lead to the thickening of the glomerular basement membrane, mesangial dilation, interstitial fibrosis and loss of podocytes, resulting in pathological features such as proteinuria and a gradual decline in renal function, which in turn cause glomerular sclerosis and tubulointerstitial fibrosis driven by chronic inflammation, eventually developing into end-stage renal disease (151,152).

In DN, the activation of NLRP3 inflammasomes drives renal immunopathological damage through multiple mechanisms. The core effect is the amplification of the inflammatory cascade. Upon activation of the NLRP3/caspase-1 pathway, mature IL-1β and IL-18 are released through cleavage of their precursors, triggering infiltration of immune cells such as macrophages and T cells into the renal interstitium and inducing the secretion of chemokines such as MCP-1 and IL-6, thereby forming a positive feedback inflammatory loop. Additionally, IL-1β activates the MAC via the classical complement pathway, directly damaging the glomerular basement membrane (153-155). At the level of intrinsic kidney cell damage, NLRP3 activation results in the loss of podocyte slit diaphragm proteins and fusion of podocyte foot processes, leading to proteinuria. NLRP3 activation also induces pyroptosis of renal tubular epithelial cells through the CD36-mtROS-NLRP3 axis, releasing pro-inflammatory contents. Simultaneously, NLRP3 activation promotes mesangial cell proliferation and ECM secretion, accelerating glomerular sclerosis (156-158). During fibrosis, IL-1β and IL-18 promote fibroblast activation and collagen deposition by upregulating TGF-β, inducing EMT and causing mitochondrial dysfunction through sustained mtROS production, which leads to renal interstitial fibrosis and an irreversible decline in renal function (159-161). The multifaceted effects of this pathological network indicate that the NLRP3 inflammasome serves as a central regulatory node for both immune-mediated injury and fibrotic progression in DN (Fig. 7).

Autophagy. Autophagy is a highly conserved process in eukaryotic cells, in which autophagosomes enclose damaged organelles, misfolded proteins or pathogens and fuse with lysosomes to degrade their contents (162). It is mainly classified into three types based on substrate handling and function: Macroautophagy, microautophagy and chaperone-mediated autophagy. Podocyte autophagy is the process by which glomerular podocytes selectively or non-selectively degrade damaged intracellular components through pathways primarily mediated by macroautophagy, and is supplemented by chaperone-mediated autophagy. This process regulates cellular metabolism and stress responses, ultimately preserving podocyte survival, structural integrity and filtration function (163).

In DN, hyperglycemia directly inhibits podocyte autophagy through three main mechanisms. First, DN activates negative regulatory pathways of autophagy via the PI3K-AKT-mTOR and PKC-mTOR pathways, where mTORC1 suppresses the assembly and activation of the autophagy initiation complex, which blocks autophagy initiation. Second, hyperglycemia-induced NF-κB translocation into the nucleus allows NF-κB to bind the negative regulatory element in the Beclin1 promoter, downregulating Beclin1 expression and activity and inhibiting autophagy nucleation. Finally, excessive ROS and mtROS production damages lysosomal membranes, resulting in lysosomal membrane permeabilization (LMP) (164,165). LMP causes lysosomal hydrolases to leak into the cytoplasm, degrading autophagy-related proteins, blocking autophagosome degradation, disrupting autophagic flux and leading to autophagosome accumulation (166). Blocked autophagy initiation, defective nucleation and disrupted flux lead to a marked reduction in podocyte autophagic activity, preventing effective clearance of damaged intracellular components, particularly mitochondria. This causes mitochondrial dysfunction, activates the NLRP3 inflammasome and aggravates cellular injury (132,167).

The activation of the NLRP3 inflammasome involves two stages, initiation and activation, followed by the subsequent release of effector molecules. During the activation phase, hyperglycemia and autophagy deficiency synergistically activate the NF-κB pathway. Hyperglycemia triggers NF-κB through PKC-b2 and the AGEs-RAGE pathway, with AGEs binding to RAGE to activate MAPK and NF-κB, leading to phosphorylation and nuclear translocation of the NF-κB subunit. At the same time, impaired autophagy causes accumulation of mtROS from damaged mitochondria, which promotes oxidative modification and ubiquitin-mediated degradation of IκBα and further enhances NF-κB activity (168,169). Activated NF-κB binds to the κB binding site in the promoter region of NLRP3, pro-IL-1β and pro-IL-18 genes after entering the nucleus, which markedly upregulates their mRNA transcription and protein expression levels, thus providing the necessary components for inflammasome assembly (170). Mitochondrial dysfunction caused by autophagy defects leads to the release of multiple DAMPs in the activation phase. mtROS oxidize cysteine residues in NLRP3, which alters the conformation of NLRP3 and converts it into an active state. The loss of the mitochondrial outer membrane potential triggers the opening of the mitochondrial permeability transition pore, causing mtDNA to leak into the cytoplasm, where it either directly binds to the LRR domain of NLRP3 or indirectly promotes NLRP3 oligomerization via the cGAS-STING pathway. Once activated, NLRP3 oligomerizes through the NACHT domain, recruits the adaptor protein ASC via the CARD domain, and induces ASC self-polymerization through the PYD domain to form the ASC speck, which subsequently recruits pro-caspase-1 and drives its autocatalytic activation (171,172). In the effector molecule release phase, activated caspase-1 generates mature cytokines by specifically cleaving pro-IL-1β and pro-IL-18. At the same time, caspase-1 cleaves the pyroptosis effector protein GSDMD to produce the GSDMD-N terminal fragment, which inserts into the podocyte membrane to form pores, leading to cytoplasmic content leakage and triggering podocyte pyroptosis, thereby exacerbating DN progression (Fig. 8) (173).

Crosstalk between NLRP3 inflammasome and other major inflammatory/fibrotic pathways in DN. DN is driven by a complex, interconnected network of inflammatory and

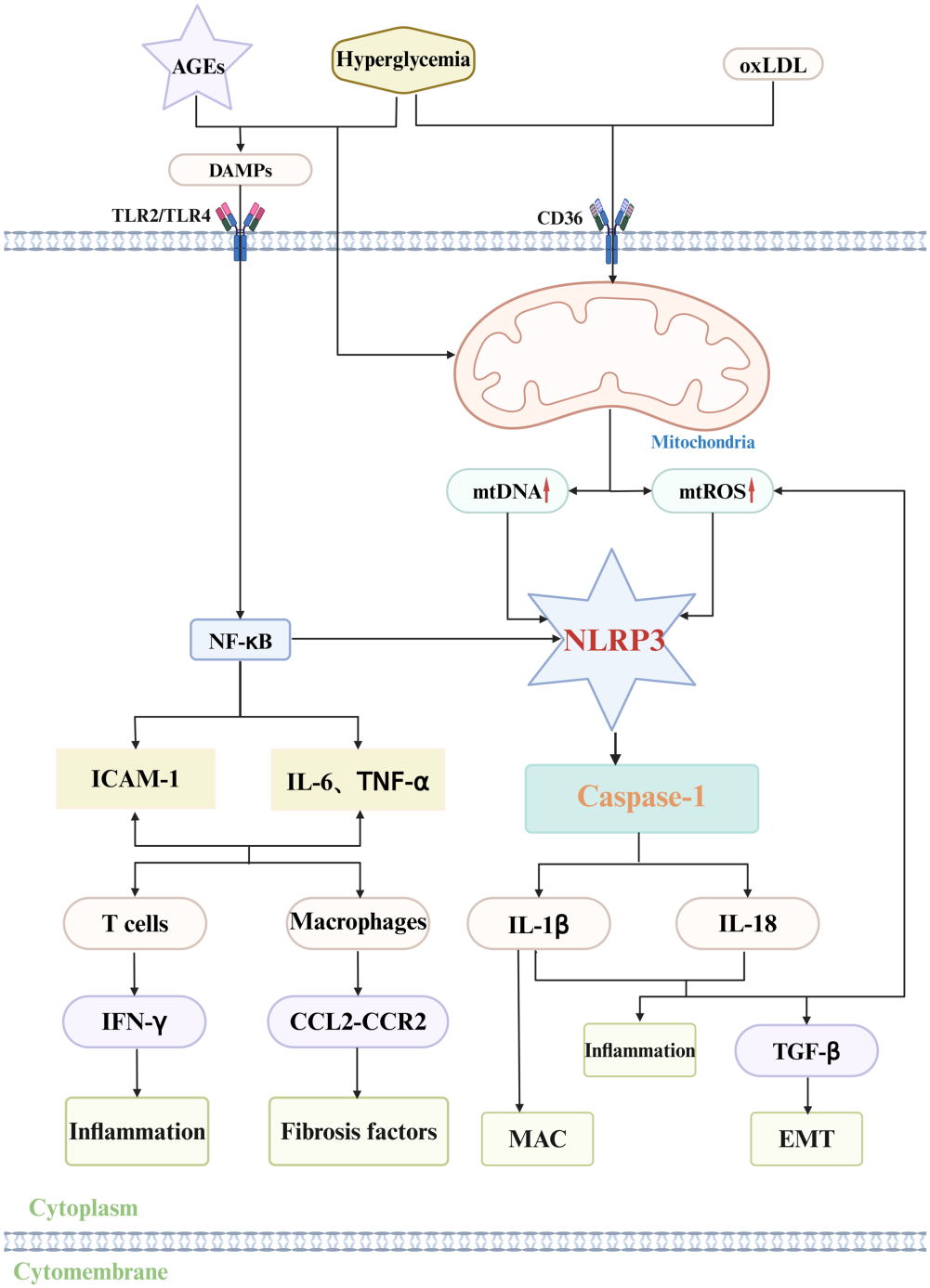

Figure 7. Schematic diagram illustrating the molecular mechanism through which AGEs, hyperglycemia and oxidized low-density lipoprotein mediate pathological responses via the receptor-mitochondria-NLRP3 inflammasome axis. This figure delineates the multi-step cascade by which these factors synergistically drive inflammation, fibrosis and epithelial-mesenchymal transition through activation of this pathway; red arrows denote upregulation, whereas black arrows indicate activation. AGEs, advanced glycation end products; oxLDL, oxidized low-density lipoprotein; DAMPs, damage-associated molecular patterns; TLR, toll-like receptor; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; NLRP3, NOD-like receptor family pyrin domain containing 3; ICAM-1, intercellular adhesion molecule 1; CCL2-CCR2, CC Chemokine Ligand 2 - CC Chemokine Receptor 2; MAC, membrane attack complex; EMT, epithelial-mesenchymal transition.

fibrotic signaling cascades, in which the NLRP3 inflammasome acts as a key synergistic hub rather than an exclusive dominant pathogenic mechanism. The canonical TGF-/Smad pathway, as the core fibrotic driver that mediates excessive ECM deposition and tubular EMT in DN, engages in bidirectional crosstalk with the NLRP3 inflammasome: TGF-upregulates TXNIP expression to potentiate NLRP3 activation, while IL-1 generated by NLRP3 inflammasome signaling in turn amplifies TGF-mediated renal fibrosis, forming a pro-fibrotic positive feedback loop (174,175). The TLR4/MAPK/NF-κB pathway serves as a pivotal upstream priming signal for the global inflammatory cascade in DN and operates in parallel with the NLRP3 axis, transcriptionally inducing the expression of NLRP3, pro-IL-1β and pro-IL-18 and cooperating with the NLRP3 inflammasome to promote renal macrophage infiltration and sustained

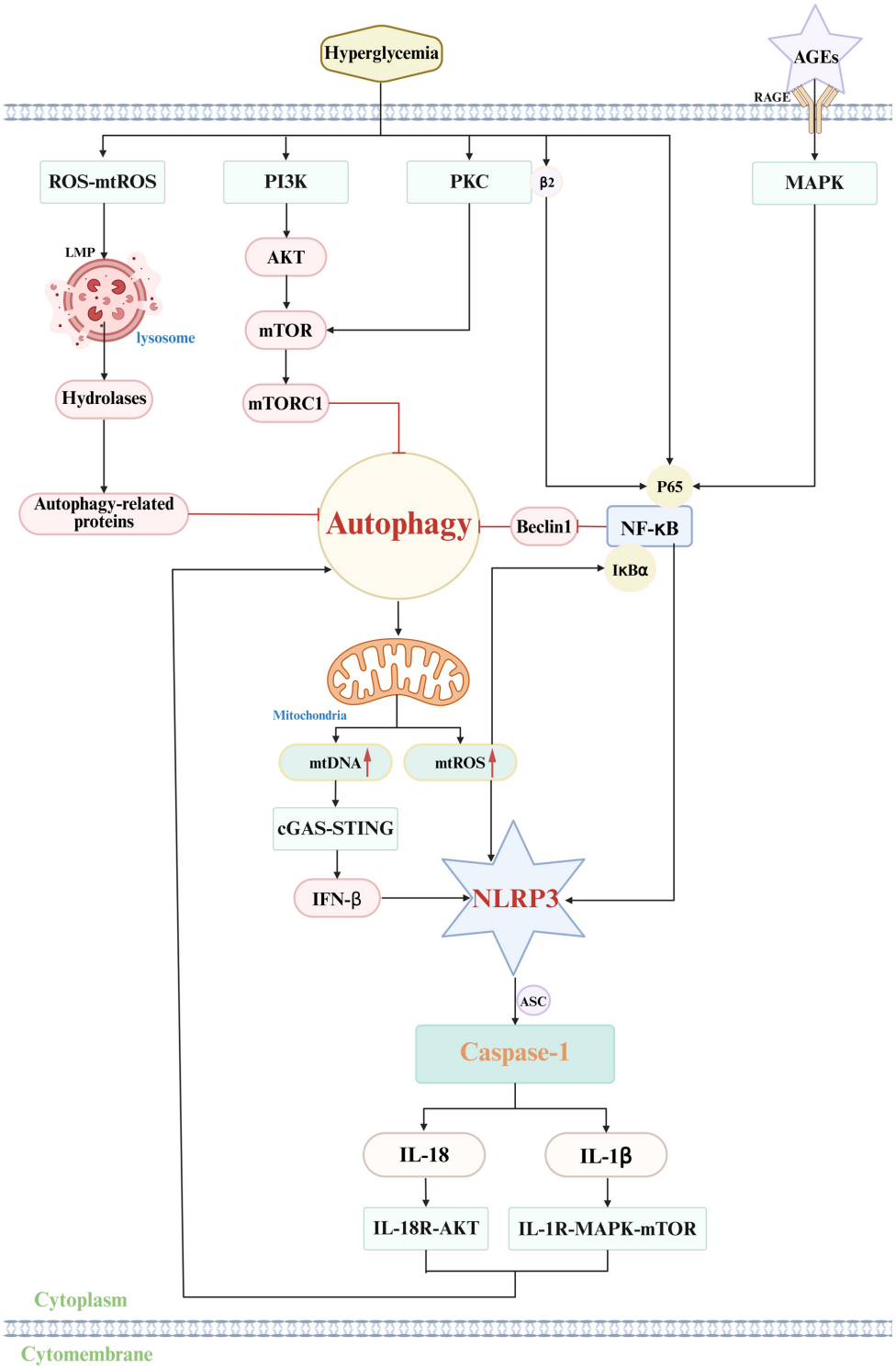

Figure 8. Schematic representation of the molecular mechanism whereby hyperglycemia and AGEs mediate NLRP3 inflammasome activation through modulation of the autophagy-mitochondria axis. This figure delineates the molecular pathways through which hyperglycemia and AGEs regulate autophagic processes via multiple signaling routes, consequently impacting mitochondrial homeostasis and triggering NLRP3 inflammasome activation, while incorporating feedback regulatory loops mediated by downstream cytokines. Red arrows denote increased activity or abundance; black arrows indicate activation or promotion. AGEs, advanced glycation end products. AGEs, advanced glycation end products; RAGEs, receptor for advanced glycation end products; ROS, reactive oxygen species; mtROS, mitochondrial reactive oxygen species; LMP, lysosomal membrane permeabilization; mtDNA, mitochondrial DNA; cGAS-STING, cyclic GMP-AMP synthase - stimulator of interferon genes; NLRP3, NOD-like receptor family pyrin domain containing 3; ASC, apoptosis-associated speck-like protein containing a CARD.

inflammatory responses, thereby collectively exacerbating inflammatory renal injury (7,144). The AGEs/RAGE pathway constitutes a core metabolic-immune linkage in DN, whereby hyperglycemia-induced AGEs bind to their receptor RAGE simultaneously and activate the NLRP3 inflammasome and the MAPK/NF-κB signaling cascade, acting as a common upstream trigger that bridges metabolic disorders and inflammatory activation across multiple DN-related

Table II. Therapeutic drugs targeting NLRP3-mediated pyroptosis.

Preparation	Mechanism	(Refs.)
Saxagliptin/liraglutide	NLRP3/Caspase-1/IL-1β pathway	(190,191)
ManNAc	Inhibiting the ROS/NLRP3 signaling pathway	(192)
DPP-4i	Regulating the ROS/NF-κβ/NLRP3 signaling pathway	(193)
Linagliptin	CRP/CD32b/NF-κB/NLRP3 axis	(194)
Sanziguben polysaccharides	TLR4/NF-κB/NLRP3 signaling pathway	(195)
AB-38b	ROS/TXNIP/NLRP3/Caspase-1/IL-1β pathway	(196)
Carnosine	NLRP3/Caspase-1/GSDMD/IL-1β and IL-18 signaling pathway	(197)
Biochanin A	NF-κB/NLRP3/Caspase-1/GSDMD/IL-1β and IL-18 signaling pathway	(198)
BAY 11-7082	Inhibiting the NLRP3 inflammasome activation by inhibiting NLRP3-ATPase activity	(184)
Irbesartan	Inhibiting the NLRP3 inflammasome activation by activating the Nrf2/Keap1 pathway	(199)
Agmatine and Pioglitazone	Regulating the α-klotho/ERS/HMGB1/NF-κB/NLRP3 inflammasome signaling pathways	(200)
Montelukast	HMGB1/TLR4/NF-κB/NLRP3 inflammasome signaling pathway and autophagy pathways	(201)

This table summarizes therapeutic agents targeting the NLRP3 inflammasome and their corresponding core pharmacological regulatory mechanisms. ATPase, Adenosine triphosphatase; CRP, C-reactive protein; Caspase-1, Cysteinyl aspartate specific proteinase 1; DPP-4i, Dipeptidyl peptidase 4 inhibitor; ERS, Endoplasmic reticulum stress; CD32b, Fc gamma receptor IIb; GSDMD, Gasdermin D; HMGB1, High mobility group box 1; IL-1β, Interleukin-1β; IL-18, Interleukin-18; Keap1, Kelch-like ECH-associated protein 1; ManNAc, N-acetyl-D-mannosamine; Nrf2, Nuclear factor erythroid 2-related factor 2; NF-κB, Nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain containing 3; ROS, Reactive oxygen species; TXNIP, Thioredoxin interacting protein; TLR4, Toll-like receptor 4.

pathways (21,176). The JAK/STAT pathway primarily mediates the transduction of pro-inflammatory cytokines including IL-6 and IFN-γ in DN; its activation facilitates the assembly of the NLRP3 inflammasome, whereas inflammatory cytokines released upon NLRP3 activation further stimulate the JAK/STAT cascade, establishing a signal amplification loop that aggravates renal inflammatory damage (144,177,178). The Wnt/β-catenin pathway promotes podocyte dedifferentiation and renal fibrosis, with its activation closely associated with OS, a key initiator of NLRP3 inflammasome activation. The Wnt/β-catenin pathway acts in parallel with NLRP3-mediated pyroptosis to jointly induce renal structural lesions and functional deterioration (179-181). Collectively, these pathways interact and synergize to propel the pathological progression of DN, and the NLRP3 inflammasome functions as a key contributory component within this multi-pathway regulatory network.

5. Roles and prospects of targeting NLRP3 in DN

Therapeutic treatment. Targeting the NLRP3 inflammasome represents a promising contributory therapeutic strategy for DN, complementing interventions against other major inflammatory and fibrotic pathways. Notable progress has been made in developing NLRP3-specific inhibitors. MCC950, the first selective NLRP3 inhibitor to enter preclinical studies, has demonstrated marked efficacy in db/db mouse models of DN. By suppressing the NLRP3/caspase-1/IL-1β pathway, MCC950 reduced renal inflammation and fibrosis, improved renal function parameters and alleviated glomerular basement membrane thickening as well as podocyte injury (182,183). BAY11-7082, a compound initially identified as an NF-κB inhibitor, has been rigorously verified to suppress NLRP3 inflammasome activation specifically by inhibiting NLRP3 ATPase activity in DN models, and this renoprotective effect is independent of its canonical NF-κB inhibitory function. The specificity of this mechanism in DN is supported by multiple lines of evidence: i) BAY11-7082 directly binds to the NACHT (ATPase) domain of NLRP3 in renal intrinsic cells and diabetic mouse kidneys, without targeting the ATPase of other NLR family inflammasomes (such as NLRC4 and AIM2) (184); ii) the anti-inflammatory and renal protective effects of BAY11-7082 are completely lost in NLRP3-knockout diabetic mice and NLRP3-silenced renal cells, excluding off-target anti-inflammatory interference (183); and iii) the low concentration used in DN studies exerts no notable cytotoxicity on renal cells (normal cell viability and apoptosis rate), ruling out non-specific cytotoxic effects as a confounding factor (185). Other studies have shown that dapagliflozin inhibits the miR-155-5p/HO-1/NLRP3 axis in diabetic models, reduces pyroptosis and delays DN development (186). In addition, multiple pathways exist to reduce DN by inhibiting NLRP3 (187-189) (Table II) (190-201).

Traditional Chinese medicine treatment. With the development of traditional Chinese medicine, certain monomers of Chinese herbs have been identified for use in the treatment of DN. Astragaloside IV (AS-IV), the main active ingredient of *Astragalus membranaceus*, has pharmacological effects including anti-inflammatory, antioxidant, hypoglycemic,

lipid-lowering and anti-fibrotic effects (202). Studies have shown that AS-IV inhibits hyperglycemia-induced NLRP3 activation in mouse podocytes and reduces podocyte death by upregulating SIRT6 and downregulating HIF-1α, thereby suppressing the expression of NLRP3, caspase-1, GSDMD, IL-1β and IL-18. In addition, AS-IV increases endogenous Klotho expression levels by modulating the NF-κB/NLRP3 signaling pathway while improving OS, protecting glomerular podocytes, reducing inflammation and alleviating endoplasmic reticulum stress (203-205). Triptolide, an essential active ingredient extracted from the traditional Chinese medicine *Tripterygium wilfordii*, reduces hyperglycemia-induced EMT in podocytes, inhibits NLRP3 inflammasome activation and prevents pyroptosis of podocytes (206). The mechanism is associated with upregulation of Nrf2 and HO-1 protein expression and a reduction in ROS levels (207,208). Ginsenosides are active monomer components of ginseng and have a wide range of pharmacological properties, including antioxidant, anti-inflammatory, hypoglycemic and anti-aging effects (209). Different ginsenosides exert their effects through distinct mechanisms. Compound K inhibits TXNIP-mediated NLRP3 inflammasome activation, thereby reducing the expression of inflammatory cytokines such as IL-1β and IL-18, improving renal function and mitigating inflammatory injury (210). Ginsenoside Rg1 protects DN podocytes from hyperlipidemic-induced damage through the mTOR/NF-κB/NLRP3 signaling axis (211). Ginsenoside Rg3 inhibits NLRP3 inflammasome activation in human and mouse macrophages, blocks IL-1β secretion and caspase-1 activation and improves renal injury (212). Ginsenoside Rg5 inhibits NLRP3 inflammasome activation, reduces inflammatory response, lowers blood glucose, creatinine and urea nitrogen levels, and improves renal pathology (213). Other monomers of traditional Chinese medicine have been reported to delay the progression of DN by inhibiting NLRP3 (Table SI) (203-251).

The application of traditional Chinese medicine prescriptions has also demonstrated notable therapeutic benefits in DN. Buzhong yiqi decoction is reported to inhibit activation of the NLRP3 inflammasome pathway, restore the Th1/Th2 immune balance and alleviate DN progression (237). The Yi shen pai du formula, composed of *Astragalus membranaceus*, rhubarb, leeches and silkworm pupae, can reduce OS and the release of inflammatory factors, relieve renal fibrosis, prevent EMT in renal tubular epithelial cells and inhibit the formation of NLRP3 inflammasomes, mainly by activating the Nrf2 pathway (238,239). Zuogui-jiangtang-yishen is derived from the classic Chinese medicine formula Zuogui pills and targets the mROS-NLRP3 axis, inhibiting intestinal-origin Trimethylamine N-oxide-induced pyroptosis, improving glucose and lipid metabolism disorders, protecting renal function and delaying DN progression (240,241). The Yiqi-huoxue-jiangzhuo formula has been shown to improve chronic kidney disease (CKD) and its associated complications. Its cardioprotective effects in CKD mice are associated with modulation of the gut microbiota and inhibition of the NLRP3 inflammasome (242,251). Tongluo yishen decoction, composed of *Salvia miltiorrhiza* and *Stephania tetrandra*, can improve renal fibrosis by regulating NLRP3-mediated cell death and had a notable effect in rat models after 2 weeks of intervention (243,244). Numerous traditional Chinese medicine prescriptions have also been reported to reduce DN by inhibiting NLRP3 (Table SI) (203-251).

Gene therapy. Gene therapy refers to introducing functional exogenous genes into target cells to correct or compensate for diseases caused by defective or abnormal genes. It also encompasses genetic modification techniques in which exogenous genes are delivered into appropriate recipient cells so that their gene products exert therapeutic effects. In a broader sense, gene therapy includes various strategies and emerging technologies that intervene at the DNA level to treat human diseases. Specifically, in the context of the present topic, gene therapy can be applied as a novel strategy for NLRP3 inflammasome-mediated therapeutic targeting in DN, by regulating the expression of NLRP3 inflammasome-related genes or delivering functional genes to inhibit NLRP3-mediated neuronal pyroptosis and neuroinflammation, thereby achieving therapeutic effects on diabetic neuropathy (252,253).

Regulation of non-coding RNA. MicroRNAs (miRNAs/miRs) are key post-transcriptional regulators involved in metabolic and inflammatory processes, offering new insights into the molecular mechanisms underlying DN. Non-coding RNAs modulate gene expression through epigenetic pathways and thus present opportunities for the development of preventive therapeutics. Experimental studies have shown that specific miRNAs, such as miR-192, can alleviate kidney injury (254,255). Long non-coding RNAs (lncRNA), such as lncRNA MALAT1, can indirectly regulate the NLRP3 pathway by adsorbing miRNA. This non-coding RNA-targeted intervention offers a new direction for gene therapy (256,257) (Table III) (258-263). Silencing the NLRP3 or ASC gene using RNA interference may effectively reduce inflammasome expression in renal tissue, thereby attenuating the inflammatory response.

CRISPR-Cas9 gene editing. The CRISPR-Cas9 system has emerged as a powerful gene-editing tool capable of precisely cutting, inserting or deleting DNA sequences. Knocking out the NLRP3 gene with CRISPR can directly block inflammasome assembly and activation, reduce IL-1β and IL-18 secretion, and thereby alleviate renal inflammation (264,265). Although the application of the technology in kidney disease is still in its early stages, its precision offers a promising direction for targeted therapy (Table IV) (266-270).

6. Conclusion

The present review outlines the multifactorial pathogenesis of DN. It should be emphasized that the NLRP3 inflammasome does not operate as the sole dominant mechanism in DN; rather, it functions in concert with other pathways. In contrast to existing reviews, the present study proposes a novel hierarchical regulatory framework for NLRP3 inflammasome activation in DN, systematically dissects the mitochondrial metabolic-cGAS-STING synergy mechanism, and provides evidence-stratified therapeutic strategies for clinical translation as a complementary approach to other anti-inflammatory and anti-fibrotic therapies. Several pathways involved in NLRP3 inflammasome activation were discussed, including

Table III. The molecular mechanism of gene therapy regulating NLRP3 inflammasome in DN.

Authors, year	LncRNA	Overexpression/ inhibition	Mechanism	(Refs.)
Zhang *et al*, 2025	SNHG7	Inhibition	TLR4/NF-κB/NLRP3/Caspase-1/GSDMD signaling pathway	(258)
Liu *et al*, 2023	SNHG16	Inhibition	Inhibiting the TLR4/RAS/NF-κB/NLRP3/Caspase - 1 GSDMD signaling pathway	(259)
Zhuang *et al*, 2024	ZFAS1	Inhibition	Inhibiting the miR-525-5p/SGK1/NLRP3 signaling pathway	(260)
Xu *et al*, 2022	XIST	Inhibition	Inhibiting the TLR4/NLRP3 signaling pathway by upregulating miR-15b-5p	(261)
El-Lateef *et al*, 2022	NEAT2	Inhibition	Inhibiting the NLRP3/Caspase-1/GSDMD signaling pathway by targeting miR-206	(262)
Zhan *et al*, 2020	NEAT1	Inhibition	NLRP3/Caspase-1/IL-1β by upregulating miR-34c	(263)

This table summarizes the regulatory roles, intervention modes (overexpression or inhibition), and underlying molecular mechanisms of long non-coding RNAs targeting the NLRP3 inflammasome, along with the corresponding cited literature. Caspase-1, Cysteinyl aspartate specific proteinase 1; GSDMD, Gasdermin D; IL-1β, Interleukin-1β; LncRNA, Long non-coding RNA; miR, MicroRNA; NF-κB, Nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain containing 3; NEAT1, Nuclear enriched abundant transcript 1; NEAT2, Nuclear enriched abundant transcript 2; RAS, Renin-angiotensin system; SGK1, Serum/glucocorticoid regulated kinase 1; SNHG7, Small nucleolar RNA host gene 7; SNHG16, Small nucleolar RNA host gene 16; TLR4, Toll-like receptor 4; XIST, X-inactive specific transcript; ZFAS1, Zinc finger antisense 1.

Table IV. Gene editing and NLRP3 inflammasome.

Authors, year	Disease	Function	Mechanism	(Refs.)
Lv *et al*, 2022	Lupus nephritis	Knocking out CD36	CD36 activates NLRP3 inflammasomes.	(266)
Kadowaki *et al*, 2025	Multiple sclerosis	Knocking out the C-type lectin domain-containing 16A gene	CLEC16A activates NF-κB/NLRP3/ Caspase-1/GSDMD signaling pathway.	(267)
Tian *et al*, 2022	Non-alcoholic steatohepatitis	Knocking out mortality factor 4-like protein 1	MRG15 activates TUFM/NLRP3/ Caspase-1/GSDMD signaling pathway.	(268)
Zhuo *et al*, 2024	Acute lung inflammation	Knocking out protease-activated receptor 2)	PAR2 activates ERK/NLRP3/ Caspase-1/GSDMD signaling pathway.	(269)
Monjarret *et al*, 2023	Chronic granulomatous disease	Activating nicotinamide adenine dinucleotide phosphate oxidase complex 2	NOX2 activates NF-κB/NLRP3/ Caspase-1/GSDMD signaling pathway.	(270)

This table summarizes the application of gene editing interventions in NLRP3 inflammasome-associated diseases, including target diseases, regulatory functions of gene editing, core molecular mechanisms, and corresponding cited literature. CLEC16A, C-type lectin domain-containing 16A; CD36, Cluster of differentiation 36; Caspase-1, Cysteinyl aspartate specific proteinase 1; ERK, Extracellular regulated protein kinases; GSDMD, Gasdermin D; MRG15, Mortality factor 4-like protein 1; NOX2, Nicotinamide adenine dinucleotide phosphate oxidase complex 2; NF-κB, Nuclear factor kappa-B; NLRP3, NOD-like receptor family pyrin domain containing 3; PAR2, Protease-activated receptor 2; TUFM, Tu translation elongation factor, mitochondrial.

key signaling molecules such as NF-κB, TXNIP, Nrf2 and PI3K/Akt, which act via interconnecting mechanisms and contribute to the complexity of inflammasome activation. In addition, therapeutic strategies targeting NLRP3 inflammasomes to alleviate renal injury in DN were summarized. Overall, the multifactorial pathogenesis of DN remains incompletely understood. The NLRP3 inflammasome is a key contributory hub within the inflammatory network of DN, acting in synergy with TGF-β/Smad, TLR4/NF-κB and other core pathways. Further investigation into the crosstalk between NLRP3 and parallel pathways will facilitate the development of combination therapeutic strategies for DN, with the expectation that more effective and precise clinical interventions will be developed in the future.

Acknowledgements

Not applicable.

Funding

This research is supported by the Doctoral Research Start-up Fund Project of Mudanjiang Medical University (grant no. 2021-MYBSKY-027); Heilongjiang Province Natural Science Foundation Project (grant no. SS2023H003); Heilongjiang Province Traditional Chinese Medicine Research Project (grant no. ZHY2024-212); Basic Scientific Research Business Research Project of Heilongjiang (grant no. 2024-KYYWF-0502); Program for Young Talents of Basic Research in Universities of Heilongjiang Province (grant no. YQJH2024254).

Availability of data and materials

Not applicable.

Authors' contributions

HY and XW conceived and supervised the present study; HY, XW, ShLi, XG, TX, SaLi, RY and TL analyzed data; XW wrote the manuscript. All authors reviewed the results and approved the final version of the manuscript. Data authentication not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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