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REVIEW

Regulation of pyroptosis in diabetic nephropathy by long non-coding and circular RNAs

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Abstract

Diabetic nephropathy (DN) is a major complication of diabetes mellitus, predominantly affecting the kidneys of diabetic patients and resulting in increased morbidity and mortality. Current standard treatments for diabetes have proven insufficient in halting the progression of DN, highlighting the urgent need for innovative and more effective therapeutic strategies. Pyroptosis, a pro-inflammatory regulated cell death process, has been previously associated with DN development. Recent evidence indicates that the NLRP3 inflammasome, a key inflammatory pathway complex, promotes DN through pyroptosis. Consequently, inhibiting inflammasome activity has emerged as a promising therapeutic target against DN, in conjunction with pyroptosis. This review introduces non-coding RNAs (ncRNAs), particularly circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs), as potential regulators of pyroptosis in DN, as recent studies have documented their dysregulation in DN pathogenesis. In this study, we aim to discuss the characteristics of lncRNAs, circRNAs, and pyroptosis and explore their potential interconnection in DN development. By elucidating the link between these RNA molecules and pyroptosis, our goal is to deepen our understanding of the underlying mechanisms of the disease. This knowledge could lead to the identification of new therapeutic targets and the development of innovative treatments for DN by modulating pyroptosis.

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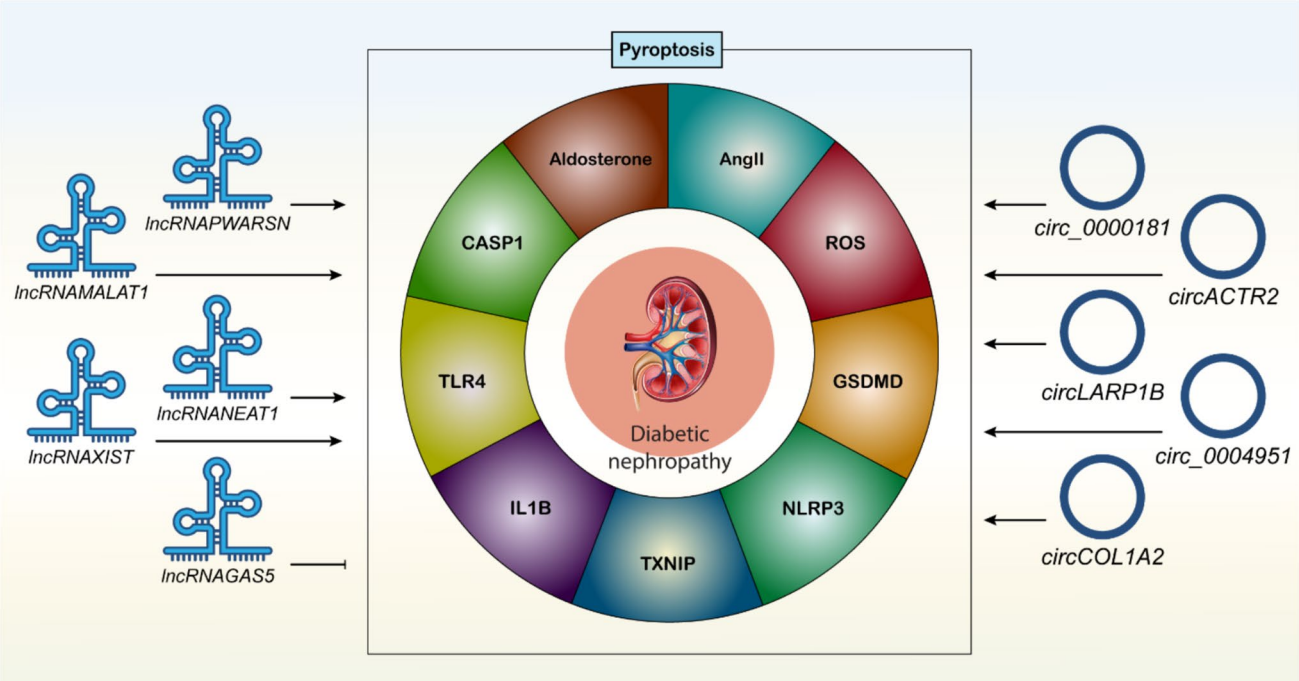
Graphical Abstract



Keywords Circular RNA · Diabetes mellitus · Diabetic nephropathy · Inflammation · Long non-coding RNA · Pyroptosis

Abbreviations

ACE	Angiotensin I-converting enzyme
ADAR	Adenosine deaminase RNA specific
AGER/RAGE	Advanced glycation end-product specific receptor
AGEs	Advanced glycation end products
AGTR1	Angiotensin II receptor type 1
AKT	AKT serine/threonine kinase
ALB	Albumin
AngII	Angiotensin II
ATF6	Activating transcription factor 6
BAX	BCL2-associated X, apoptosis regulator
CARMN	Cardiac mesoderm enhancer-associated non-coding RNA
CASP1/ICE	Caspase 1
CAT	Catalase
CCL2/MCP-1	C-C motif chemokine ligand 2
CD274/PD-L1	CD274 molecule
CDC42	Cell division cycle 42
CDK2	Cyclin dependent kinase 2
CDKN1A/p21/Waf1/Cip1	Cyclin-dependent kinase inhibitor 1A
CDKN2B-AS1/ANRIL	CDKN2B antisense RNA 1
ciRNA	Circular intronic RNAs
circRNA	Circular RNA
COL4A	Collagen type IV alpha
CYBB/NOX2	Cytochrome b-245 beta chain
DDOST/AGE-R1	Dolichyl-diphosphooligosaccharide–protein glycosyltransferase non-catalytic subunit
DHX9	DExH-box helicase 9
DKD	Diabetes-related kidney disease
DM	Diabetes mellitus
DN	Diabetic nephropathy
E2F1	E2F transcription factor 1
EC	Endothelial cell
EcircRNAs	Exonic circRNAs
EDN	Endothelin
EIciRNAs	Exon-intron circRNAs
EIF2AK3/PERK	Eukaryotic translation initiation factor 2 alpha kinase 3

EIF3A	Eukaryotic translation initiation factor 3 subunit A
EIF4G2	Eukaryotic translation initiation factor 4 gamma 2
ERBB4	Erb-b2 receptor tyrosine kinase 4
ERS	Endoplasmic reticulum stress
ERN1	Endoplasmic reticulum to nucleus signaling 1
ESRD	End-stage renal disease
FN1	Fibronectin 1
GAS5	Growth arrest specific 5
GBM	Glomerular basement membrane
GFR	Glomerular filtration rate
GH	Growth hormone
GMCs	Glomerular mesangial cells
GSDMD	Gasdermin D
GZMB	Granzyme B
GSDMD-N	Cleaved amino-terminal GSDMD
HG	High glucose
HIF1A/HIF-1α	Hypoxia inducible factor 1 subunit alpha
HMGB1	High mobility group box 1
ICAM1	Intercellular adhesion molecule 1
ID1	Inhibitor of DNA binding 1
IL1B	Interleukin 1 beta
IRAK	Interleukin 1 receptor-associated kinase
IRES	Internal ribosome entry site
IRS1	Insulin receptor substrate 1
JAK	Janus kinase
KCNQ1OT1	KCNQ1 opposite strand/antisense transcript 1
KL	Klotho
LGALS3/AGE-R3	Galectin 3
lncRNA	Long non-coding RNA
m6A	N6-methyladenosine
MALAT1	Metastasis-associated lung adenocarcinoma transcript 1
MAPK	Mitogen-activated protein kinase
MBNL	Muscleblind-like splicing regulator
MC	Mesangial cell
MEFV/pyrin	MEFV innate immunity regulator, pyrin
miRNA	MicroRNA
MPO	Myeloperoxidase
MREs	MiRNA response elements
MYD88	MYD88 innate immune signal transduction adaptor
NCF1/p47phox	Neutrophil cytosolic factor 1
ncRNA	Non-coding RNA
Neat1	Nuclear paraspeckle assembly transcript 1
NFE2L2/NRF2	NFE2 line bZIP transcription factor 2
NFKB	Nuclear factor kappa B
NLRC4	NLR family CARD domain containing 4
NLRP1	NLR family, pyrin domain containing 1
NOS2/iNOS	Nitric oxide synthase 2
NOX	NADPH oxidase
nt	Nucleotides
ORFs	Open reading frames
OS	Oxidative stress
PI3K	Phosphoinositide 3-kinase
POLR3	RNA polymerase III
PRF1	Perforin 1
PRKC	Protein kinase C
PRL	Prolactin
PTECs	Proximal tubular epithelial cells
PTGS/cyclooxygenase	Prostaglandin-endoperoxide synthase
PTK2B/FAK	Protein tyrosine kinase 2 beta
PWARSN	Prader Willi/Angelman region RNA, SNRPN neighbor
PYCARD/ASC	PYD and CARD domain containing
QKI	QKI, KH domain containing RNA binding
RAC	Rac family small GTPase
RBMX	RNA-binding motif protein X-linked
RBP	RNA-binding protein
RHOA	Ras homolog family member A
RIPK3	Receptor interacting serine/threonine kinase 3
RN7SK	RNA component of 7SK nuclear ribonucleoprotein
RN7SL1	RNA component of signal recognition particle 7SL1
ROCK	Rho-associated coiled-coil containing protein kinase
ROS	Reactive oxygen species, ribosomal RNAs
RTECs	Renal tubular epithelial cells

SGK1	Serum/glucocorticoid regulated kinase 1
siRNA	Small interfering RNA
rRNAs	SOD Superoxide dismutase
STAT	Signal transducer and activator of transcription
STZ	Streptozotocin
SYK	Spleen-associated tyrosine kinase
TGFB	Transforming growth factor beta
TLR2	Toll-like receptor 2
TNF	Tumor necrosis factor
TP53/p53	Tumor protein p53
TXN	Thioredoxin
TXNIP	Thioredoxin interacting protein
UAE	Urinary ALB (albumin) excretion
UTRs	Untranslated regions
VCAM1	Vascular cell adhesion molecule 1
XIST	X inactive specific transcript
YTHDF3	YTH N6-methyladenosine RNA-binding protein F3

Introduction

The primary and perhaps the most prevalent complication of diabetes mellitus (DM) is diabetic nephropathy (DN), which is linked to higher rates of morbidity and death in these patients [1, 2]. In the USA, the pooled prevalence of nephropathy among diabetic patients is approximately 24.2% (95% CI: 13.8–34.5), and although the number of diabetic patients beginning therapy for end-stage renal disease (ESRD) increased from 40,000 in 2000 to more than 50,000 in 2014, recent data indicate the incidence rate has stabilized while prevalence continues to rise [3]. China has also experienced a significant rise in the prevalence of DN during recent decades. Currently, China has an estimated 141 million adults with diabetes, accounting for 25% of the global diabetic population, with approximately 24.3 million diabetics suffering from chronic kidney disease (CKD), and diabetes-related CKD has become the leading cause of CKD in the country [4]. Globally, the prevalence of diabetes is rising quickly, particularly in emerging nations**.** As of 2022, over 537 million adults worldwide live with diabetes, a number projected to reach 781 million by 2045, with nearly 30 to 40% of these individuals developing CKD, underscoring the growing global burden of DN [5]. If the therapeutic approach for DN prevention does not improve immediately, it is anticipated that the incidence of DN will continue to rise along with the prevalence of diabetes [6, 7].

The complexity and incomplete understanding of the etiology of DN lead to poor therapy results. The current standard treatment, which calls for stringent blood pressure and blood sugar management, is insufficient to halt the development of DN to ESRD or reduce the death rate associated with DN [8, 9]. Developing innovative treatment approaches for DN requires a deeper comprehension of the disease's pathogenic underpinnings [2].

The term pyroptosis is frequently used to describe a pro-inflammatory process of regulated cell death that controls the innate immune system [10, 11]. It is primarily a pro-inflammatory cell death event dependent on GSDMD (gasdermin D), a key protein that forms pores in the cell membrane, facilitating the release of cellular contents during pyroptosis**.** According to recent research, pyroptosis is definitive in DN promotion. Furthermore, growing evidence has shown that activating the NLRP3 (NLR family, pyrin domain containing 3) inflammasome promotes DN by facilitating pyroptotic cell death. Researchers and medical professionals have begun to pay close attention to inhibiting inflammasome-mediated cell death. Current research indicates that certain pharmacological agents may inhibit pyroptosis-associated signaling, presenting promising therapeutic options for the treatment and management of various disorders, including DN [10]. Research indicates elevated circulating IL1B/IL-1β (interleukin 1 beta) and inflammasome levels in people and animals affected by DN. However, kidney damage is reduced, and disease progression is slowed when the expression of essential inflammasome components is diminished [12].

Circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs) are subclasses of non-coding RNAs (ncRNAs) that do not encode proteins but play essential roles in regulating gene expression. LncRNAs are typically larger than 200 nucleotides and can influence transcriptional and post-transcriptional processes, whereas circRNAs are characterized by their covalently closed-loop structure and are increasingly recognized for their regulatory functions in cellular pathways. Recently, circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs) have been found to be involved in various pathological processes, including kidney diseases. Their emerging importance in disease mechanisms provides a promising area for exploration in medical research. We think that exploring the regulatory mechanisms of pyroptosis through the lens of these novel RNA species offers a unique opportunity to identify potential therapeutic targets. The expression of non-coding RNAs (ncRNAs) and protein-coding RNAs makes up the transcriptome profile, which in an individual cell is responsible for the complicated characteristics of the cellular molecules [12]. As the fundamental tenet of biology, DNA information is transcribed and

translated into RNA and proteins, respectively. However, new research indicates that the human genome contains more ncRNAs than protein-coding RNAs. It is worth noting that the majority of such ncRNAs are functional [13]. The results obtained from the analysis of ncRNAs present a novel paradigm for understanding the regulation and expression of genes, especially the many levels of molecular control that exist inside a single gene [14, 15]. Different categories of ncRNAs have been identified thus far. The majority of ncRNAs are often categorized according to their sizes. These include small ncRNAs (less than 200 nucleotides), which comprise microRNAs (miRNAs), and some circRNAs [16–18], as well as big ncRNAs, such as lncRNAs [17]. These ncRNAs have previously been shown to be dysregulated in people and animals affected by DN. Significantly, these ncRNAs interact in certain ways to control important phases in the evolution of DN [19].

One recently identified process in DN is dysregulated pyroptosis, whose regulatory mechanism involves various signaling pathways and molecular processes. Still, few studies have focused on the role of ncRNAs in the pyroptosis regulatory mechanism. In this area of study, lncRNAs and circRNAs have been found to have a significant role in pyroptosis modulation during DN [20]. This review synthesizes current experimental evidence and theoretical frameworks, with the goal of identifying promising therapeutic targets for future clinical investigation. While many of the mechanisms discussed show potential in preclinical studies, their translation into clinical practice will require extensive validation through human trials. The findings presented here should be considered primarily as foundational research that may inform future therapeutic developments rather than providing immediate clinical applications.

Diabetic nephropathy

Pathophysiology of diabetic nephropathy

Diabetes patients' progression to DN is a highly complex process resulting from various circumstances (Fig. 1) [21–23]. Pathologically, glomerular lesions as well as tubular damage are the major injuries involving diabetic kidneys. In glomerular lesions, the glomeruli undergo several alterations that are classified into thickening the glomerular basement membrane (GBM) leading to impaired filtration, mesangial expansion that further disrupt the filtration process, nodular glomerulosclerosis (a.k.a., Kimmelstiel-Wilson nodules) that are principally seen in advanced DN, and hyalinosis of afferent arterioles which involves hyaline accumulation inside the arterioles resulting in further glomerular damage [24, 25].

The tubules also suffer damage in DN in the form of proximal tubular injury that is a key factor in the progression of DKD, tubulointerstitial inflammation and fibrosis which can lead to inflammation and fibrosis in the surrounding interstitial tissue further impairing kidney function, and activation of tubular epithelial cells also leading to further damage and inflammation [26–28].

Metabolic dysregulation in diabetic environments leads to glomerulosclerosis, tubulointerstitial inflammation, fibrosis, and changes in kidney hemodynamics. Renal hypertension and hyperglycemia are the main mediators of diabetic nephropathy [29]. Hyperglycemia activates pathways involving hexosamine, polyol, and PRKC/PKC (protein kinase C), causing the build-up of advanced glycation end products [30], glomerular hyperfiltration, and hypertension [31, 32]. The REN (renin)-angiotensin system is activated, leading to renal and glomerular hypertrophy, increased intraglomerular pressure, and renal injury [33, 34]. Reactive oxygen species (ROS) further damage podocyte and tubular cells, and are stimulated by high levels of angiotensin II (AngII)-aldosterone [33]. Hyperglycemia-induced increased glucose metabolism results in excess ROS, harming mitochondria and DNA [32]. Growth factors and inflammatory cytokines are activated, leading to kidney lesions and fibrosis [32]. Unchecked renal impairments eventually result in renal failure [19].

Impact of hyperglycemia

Chronic hyperglycemia is a primary cause of diabetic nephropathy. Patients with DN are managed with blood pressure and blood glucose control [35]. Not all short-term hyperglycemia is harmful; transient self-limited hyperglycemia can be beneficial in non-acute diseases [36]. Fasting hyperglycemia in diabetic patients is often due to hormonal imbalances that increase hepatic glucose transport [37]. Normally, glucose is converted to pyruvate and then to acetyl CoA, entering the tricarboxylic acid cycle to release energy. In high-glucose environments, glycolysis is saturated, activating alternative metabolic routes such as the sorbitol and polyol processes, leading to metabolic imbalance and kidney damage [38]. Hyperglycemia primarily damages glomerular endothelial cells (ECs), mesangial cells [39], podocytes, and endothelial cells, with podocytes being highly susceptible [8, 40].

High glucose levels lead to the development of advanced glycation end products (AGEs), contributing to DN [41]. Four main mechanisms explain hyperglycemia-induced complications in diabetes: the polyol pathway, the hexosamine pathway, AGEs synthesis, and PRKC, all linked by excess superoxide production from the mitochondrial electron transport chain [35, 42].

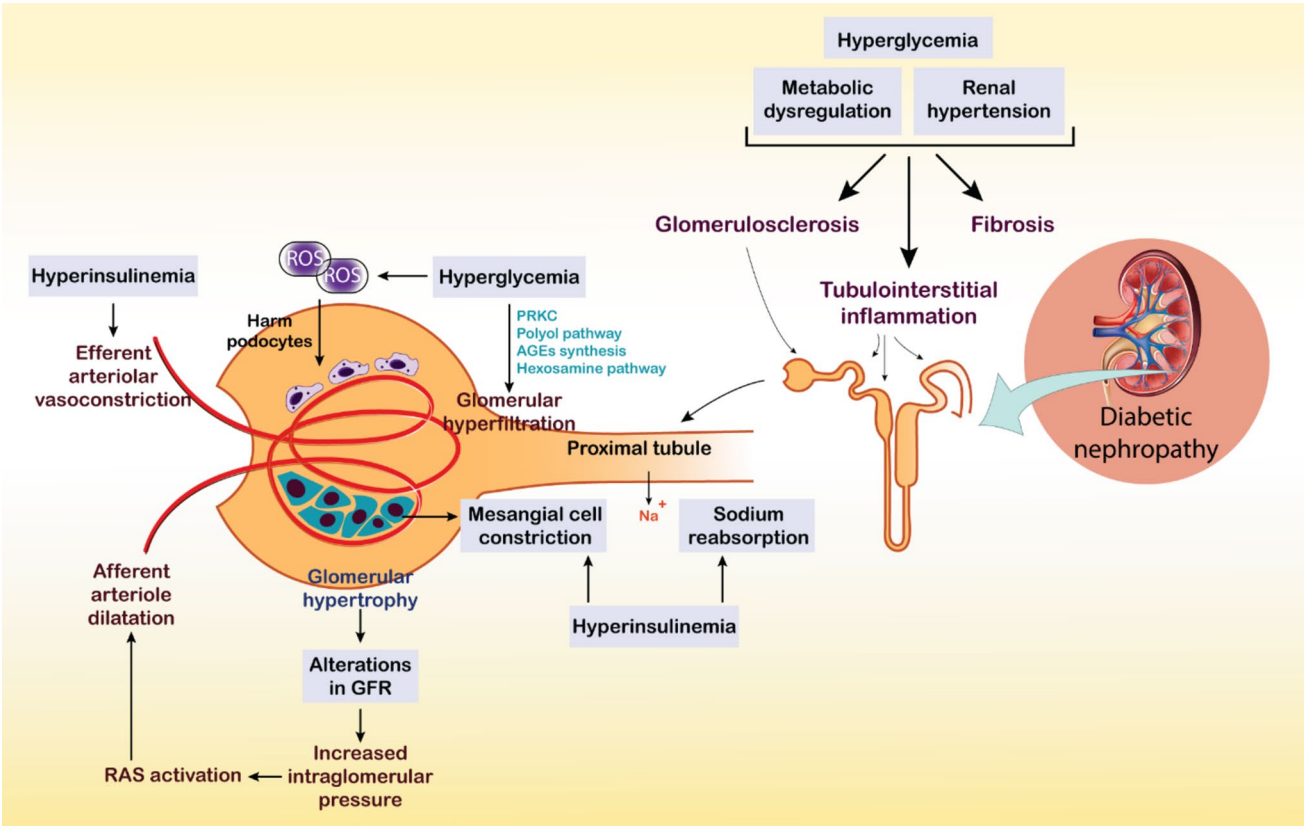


Fig. 1 Pathophysiological mechanisms underlying the progression of diabetic nephropathy. Chronic hyperglycemia and hyperinsulinemia initiate a cascade of renal alterations that contribute to diabetic nephropathy. Hyperinsulinemia promotes efferent arteriolar vasoconstriction, while hyperglycemia induces afferent arteriolar dilation via activation of the renin-angiotensin system/RAS, collectively leading to increased intraglomerular pressure, glomerular hyperfiltration, and hypertrophy. Hyperglycemia further generates reactive oxygen species (ROS), damaging podocytes and contributing to mesangial cell constriction and sodium reabsorption within the proximal tubule. Dysregulated metabolic pathways, including PRKC activation, polyol pathway flux, advanced glycation end-product (AGE) formation, and hexosamine pathway activation, exacerbate glomerular injury. The combined effects result in glomerulosclerosis, tubulointerstitial inflammation, and fibrosis, ultimately progressing to diabetic nephropathy. Despite compensatory mechanisms, alterations in glomerular filtration rate (GFR) and structural damage to the nephron underlie the progressive renal dysfunction characteristic of the disease

Inflammatory responses

The activation of the innate immune system and chronic low-grade inflammation are crucial in the development of diabetes mellitus [43, 44]. Patients with diabetes have elevated levels of inflammatory parameters [45], which indicate the onset of the disease [46, 47]. Inflammation, along with hemodynamic abnormalities, metabolic disturbances, and elevated neurohumoral factors such as AngII, plays a major role in developing diabetic nephropathy, as do oxidative stress and fibrosis [48].

Various immune system elements, such as pro-inflammatory cytokines, chemokines, and adhesion molecules, are involved in DN. Patients with DN have higher concentrations of inflammatory molecules and cells in their renal tissue [49, 50]. As nephropathy worsens, these substances increase [48, 51], leading to higher urinary ALB (albumin) excretion (UAE) and glomerular and tubulointerstitial damage [51, 52].

Immune mechanisms, including innate immune cells and pro-inflammatory molecules, play a substantial role in DN [53]. Adhesion molecules including VCAM1 (vascular cell adhesion molecule 1) and ICAM1 (intercellular adhesion molecule 1) are crucial in renal inflammation and are found in high concentrations in DN patients' kidneys [54]. Deleting the *Icam1* gene reduces renal inflammation in mouse models, indicating ICAM1's role in DN [55].

Chronic kidney disease (CKD) progression is linked to monocyte and macrophage accumulation in the kidneys [56], leading to decreased glomerular filtration rate (GFR), histological alterations, and unfavorable outcomes in DN patients [56, 57]. Pro-inflammatory factors, growth factors, metallopeptidases, and ROS from infiltrating cells intensify and prolong inflammation and renal injury [58].

Inhibiting inflammatory cell recruitment can protect against DN in experimental models [59, 60]. Mouse models with deletions for genes encoding macrophage receptors show increased resistance to DN by reducing albuminuria, mesangial matrix expansion, and inflammation [61].

Macrophages are polarized to M1 (pro-inflammatory) or M2 (tissue repair) phenotypes. In ongoing inflammation, both coexist, disrupting the sequence of events. In streptozotocin (STZ)-induced DN, M1 macrophages predominate [57, 62]. Transitioning from M1 to M2, induced by *tlr2* (toll-like receptor 2) deletion, inhibits renal alterations and UAE [62]. The role of M2 macrophages in slowing DN progression and promoting kidney repair is unknown.

Cytokines and chemokines, along with metabolic pathways and factors like NFKB (nuclear factor kappa B), ROCK (Rho-associated coiled-coil containing protein kinase), JAK (Janus kinase)-STAT (signal transducer and activator of transcription), and NFE2L2/NRF2 (NFE2 like bZIP transcription factor 2), play roles in systemic and local inflammation in DN [45, 63].

Cellular damage and dysfunction

Diabetes mellitus leads to significant complications, including microvascular (small vessel) and macrovascular (large vessel) impairments [64]. Microvascular complications, such as nephropathy, often go unnoticed due to DN's "silent phase," a prolonged period during which renal damage occurs insidiously without clear clinical manifestations. During this phase, patients may remain asymptomatic, while subtle pathological changes such as glomerular hypertrophy and basement membrane thickening progress. This latency makes early detection challenging, often delaying diagnosis until more advanced and symptomatic stages emerge [65].

DN, a worsening microvascular complication from diabetes types 1 and 2, starts with hyperfiltration and microalbuminuria, progressing to ESRD. Microalbuminuria, the earliest renal problem indicator, can develop into overt albuminuria, affecting about 25% of type 2 diabetics, with a 2–3% annual increase [64, 66, 67]. Albuminuria results from higher intraglomerular pressure and GBM permeability, influenced by ECs' interactions with MCs and podocytes [68]. Endothelial dysfunction in type 2 diabetes, even with normal UAE, suggests it may be a major etiological factor [64, 69].

Hyperfiltration, caused by afferent glomerular arteriole dilation, raises intraglomerular pressure and renal blood flow [70, 71]. This response is linked to early diabetes vascular dysfunction, leading to renal dysfunction, tubulointerstitial fibrosis, and glomerulosclerosis [72–74]. Endothelial dysfunction reduces ECs' antiatherogenic potential, contributing to abnormal renal function [64].

DN's pathological features include mesangial expansion, global glomerulosclerosis, Kimmelstiel-Wilson lesions, and GBM thickening due to extracellular matrix accumulation [48, 49]. Endothelial cell dissociation may break the GBM-mesangial area link. In later DN stages, nodular sclerosis or global glomerulosclerosis occur. DN-related vascular lesions show arteriolosclerosis in both afferent and efferent vessels, with efferent arteriole hyalinosis being more specific to DN [75, 76]. Afferent medial thickness is also seen in other contexts, possibly linked to concurrent hypertension [77, 78]. Both glomerular arterioles can constrict or relax, but the efferent arteriole may be more vulnerable to AngII, leading to higher glomerular capillary pressure and increased glomerular filtration rate [79].

Molecular characteristics of diabetic nephropathy

The activation of the REN-angiotensin-aldosterone system/RAAS, the accumulation of AGEs, and the epithelial-mesenchymal transition/EMT in renal cells (including podocytes, MCs, endothelial cells, and epithelial cells) are associated with cellular stress, inflammation, apoptosis, pyroptosis, and autophagy in the diabetic state (Fig. 2) [80].

Vasoconstriction, aldosterone secretion, increased myocardial contractility, and the excitation of the sympathetic nervous system are just a few of the cardiovascular events that are directly attributed to the REN-angiotensin-aldosterone system; if left unchecked, the system can result in hypertension, fluid retention, thrombosis, and atherosclerosis [22]. ACE (angiotensin I-converting enzyme) transforms angiotensin I into angiotensin II, which acts on AGTR1 (angiotensin II receptor type 1) or AGTR2 receptors to cause pathological effects in the kidney, heart, and vasculature [22, 81]. Furthermore, ACE contributes to the metabolism of bradykinin, which causes dysregulation and angioedema [82]. There is evidence that patients with DN have higher than normal levels of pro-REN, REN, ACE, and AngII [83]. Notably, the two main renal toxins are aldosterone and AngII. First, by upregulating EDN (endothelin) expression, blocking nitric oxide synthesis, and turning on PTGS/cyclooxygenase (prostaglandin-endoperoxide synthase) and PRKC, excess AngII and aldosterone directly cause endothelial dysfunction [84]. Second, increased ROS production and upregulation of NFKB, TGFB (transforming growth factor beta), and TNF (tumor necrosis factor) can facilitate the development of fibrosis due to elevated AngII and aldosterone levels [80].

The complicated and diverse category of substances named AGEs has been linked to complications associated with diabetes [85]. Under hyperglycemia, nonenzymatic glycation products, primarily N-carboxymethyllysine, methylglyoxal-derived hydroimidazolone, and glucosepane, are responsible for this effect. When AGEs

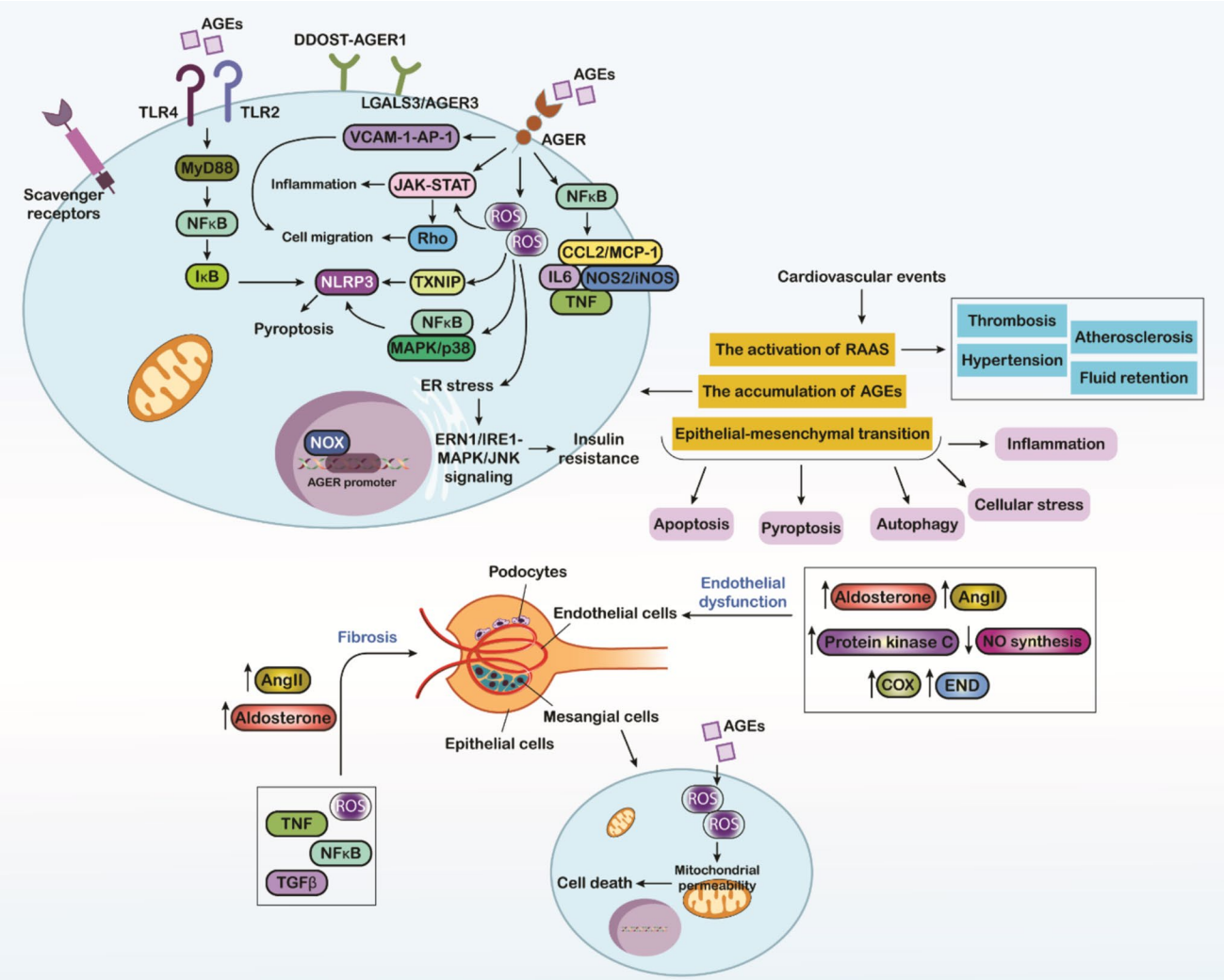


Fig. 2 Molecular and cellular mechanisms of diabetic nephropathy. Advanced glycation end-products (AGEs) interact with pattern recognition receptors, including toll-like receptors (TLR2, TLR4) and scavenger receptors, as well as specific AGE receptors including AGER, DDOST-AGER1, and LGALS3/AGER3. These interactions activate intracellular signaling cascades, including NFKB, JAK-STAT, MAPK/p38, and ER stress pathways, leading to inflammation, oxidative stress (via NOX activation), insulin resistance, and mitochondrial dysfunction. Activation of the NLRP3 inflammasome promotes pyroptosis, further exacerbating cellular injury. The cumulative effects contribute to epithelial-mesenchymal transition/EMT, apoptosis, autophagy dysregulation, and increased cellular stress. These processes are major drivers of diabetic complications, including cardiovascular events (such as thrombosis, hypertension, atherosclerosis, and fluid retention) through activation of the renin–angiotensin–aldosterone system (RAAS) and AGE accumulation. In the kidney, AGEs and oxidative stress damage podocytes, mesangial cells, and endothelial cells, promoting fibrosis, endothelial dysfunction and mitochondrial permeability, ultimately leading to cell death. Key mediators include TNF, TGFB/TGF-β, NFKB, ROS, and alterations in nitric oxide (NO) synthesis pathways

bind to their receptor, AGER/RAGE (advanced glycation end-product specific receptor), they trigger multiple intracellular signaling cascades, leading to aberrant cellular responses including autophagy, apoptosis, and inflammation. Other receptors that bind to AGEs include DDOST/AGE-R1 (dolichyl-diphosphooligosaccharide–protein glycosyltransferase non-catalytic subunit), LGALS3/AGE-R3 (galectin 3), and scavenger receptors, ensuring that AGEs are endocytosed and degraded [86].

In an AGER-dependent manner, AGEs elevate oxidative stress through the NOX (NADPH oxidase) enzymes, mediating the generation of intracellular ROS [87, 88]. A NOX enzyme attaches to the *AGER* promoter and increases AGER expression; one of its key downstream targets is the NFKB-dependent pathway [89]. When NFKB is transferred to the nucleus, it increases the synthesis of pro-inflammatory cytokines such as CCL2/MCP-1 (C–C motif chemokine ligand 2), IL6, TNF, and NOS2/iNOS (nitric

oxide synthase 2). NOX enzymes are activated by NFKB stimulation, which also upregulates NOS2 and NO produced by NOS2 and superoxide anion. Important downstream pathways of the AGE-AGER axis are activated, including the phosphoinositide 3-kinase/PI3K-AKT (AKT serine/threonine kinase) pathway, the MAPK (mitogen-activated protein kinase) pathway, and the JAK-STAT pathway, in addition to NOX-mediated oxidative stress [90]. Inflammation is mediated in part by JAK-STAT signaling that is triggered by AGEs [91]. Additionally, ROS produced during the AGE-AGER interaction stimulate JAK-STAT signaling, which stimulates cell migration via activation of the Rho family small GTPases CDC42 (cell division cycle 42) and RAC (Rac family small GTPase). Conversely, by controlling the expression of VCAM1-AP-1 transcription factor, activated AGER encourages cell migration [92]. Through the inhibition of JAK2-STAT1 and JAK2-STAT3 signaling, the induction of the anti-senescence protein KL (klotho) expression, and the suppression of CDKN1A/p21/Waf1/Cip1 (cyclin dependent kinase inhibitor 1A)-COL4A (collagen type IV alpha)-AGER expression, AGEs cause renal tubular hypertrophy [93]. Furthermore, in renal cells, AGEs can activate AKT. AGEs cause endothelial dysfunction and increased podocyte permeability by mediating the activation of MAPK/p38 and MAPK1/ERK2-MAPK3/ERK1, which decreases NOS3/eNOS expression and increases oxidative stress [94]. Moreover, the AGE-AGER interaction triggers oxidative stress and NFKB activation via the CDKN1A-renin-angiotensin system protein and MAPK signaling pathway, which drives the production of pro-inflammatory cytokines and other molecules associated with inflammatory processes as DN progresses [95]. Exogenous AGE exposure can increase the formation of cytosolic ROS in MCs, which disrupts the mitochondrial membrane's potential with a shift in mitochondrial permeability, ultimately leading to death of MCs [96]. AGER causes cells to undergo apoptosis by triggering the production of TP53/p53 (tumor protein p53)-BAX (BCL2-associated X, apoptosis regulator) and encouraging the activation of caspase cascades which depends on calcium [97].

Multiprotein complexes called inflammasomes act as a molecular switch during pyroptosis. Inflammasomes of several kinds, principally those lacking in melanoma 2, MEFV/pyrin (MEFV innate immunity regulator, pyrin), HIN-200 proteins, and nod-like receptors, switch during pyroptosis. For example, NLRP1 (NLR family pyrin domain containing 1), NLRP3, NLRP6, NLRP7, and NLRC4 (NLR family CARD domain containing 4) are NLRs associated with pyroptosis. The molecule most closely linked to the development of pyroptosis is the NLRP3 inflammasome [98, 99]. The most significant factors upstream of NLRP3 inflammasome activation appear to be overproduced AGEs, which also cause an increase in ROS generation [100]. The NLRP3 inflammasome, which primarily causes inflammation and cell pyroptosis, is activated by ROS [101]. Upstream of the NLRP3 inflammasome activation, ROS facilitates the separation of TXNIP (thioredoxin interacting protein) and TXN (thioredoxin) [101]. Moreover, ROS deactivates PTEN (phosphatase and tensin homolog), stimulating the phosphoinositide 3-kinase and extracellular MAPK/ERK pathways ahead of pyroptosis. ROS can also trigger the NLRP3 inflammasome through the NFKB and MAPK/p38 signaling pathways [102]. TXNIP activates the NLRP3 inflammasome in response to oxidative stress, which starts pyroptosis. TLRs are also crucial parts of the molecules that control pyroptosis. AGEs interact with TLR2 and TLR4, which facilitates the activation of MYD88 (MYD88 innate immune signal transduction adaptor) [103]. Following this, MYD88 engages with the IκB-NFKB complex, facilitating the transcription of pro-inflammatory cytokines such as NLRP3, pro-IL1B, and pro-IL18. Under high-glucose (HG) conditions, the increased expression of TLR4 and GSDMD is correlated with renal tubular damage and renal resident cell pyroptosis via the TLR4-NFKB signaling pathway [104].

ROS generation mediated by AGE-AGER-activated NOX is the primary cause of ER stress in renal cells [105]. The NOX enzymes are made up of catalytic and regulatory subunits, which together function as the enzyme complex. NOX4 is involved in both prosurvival and proapoptotic responses, whereas CYBB/NOX2 (cytochrome b-245 beta chain) is upstream of the unfolded protein response's proapoptotic signaling under ER stress conditions [106]. Because NOX4 is constitutively activated, it requires CYBA/p22phox for regulation, whereas CYBB/NOX2 needs CYBA, NCF1/p47phox (neutrophil cytosolic factor 1), and NCF2/p67phox. CYBB/NOX2 at the ER and cell membranes and NOX4 at the ER membrane are activated by AGEs through their interaction with AGER [107]. In addition, ER stress modifies insulin signaling, leading to insulin resistance through MAPK/JNK-dependent IRS1 (insulin receptor substrate 1) serine phosphorylation and ERN1/IRE1 (endoplasmic reticulum to nucleus signaling 1)-MAPK/JNK signaling. ER stress also induces kidney inflammation, glomerular hypertrophy, podocyte damage, proteinuria, and renal fibrosis [108]. Three key unfolded protein response sensors—EIF2AK3/PERK (eukaryotic translation initiation factor 2 alpha kinase 3), ATF6 (activating transcription factor 6), and ERN1—can mediate certain microRNAs (miRNAs) to regulate secretory pathway proteins and preserve ER homeostasis under conditions of ER stress. Conversely, in DN, *MIR200A*, *MIR25*, and *MIR93* are repressed. *MIR146A* inhibits AGE-induced inflammation through NFKB, TNF, and IRAK (interleukin 1 receptor-associated kinase) [109]. Furthermore, RHOA (ras homolog family member A)-ROCK2 signaling and AGE-induced endothelial cell damage are inhibited by *MIR200B* and *MIR200C* [110].

Pyroptosis as a regulated cell death process

The initial research on pyroptosis began in 1986 (Fig. 3), when Friedlander observed rapid release of cell content and death in primary mouse macrophages treated with anthrax lethal toxin/LT [111, 112]. The 1989 discovery of CASP1/ICE (caspase 1) revealed its role in converting precursor IL1B to mature IL1B**,** as reported by Cerretti and Thornberry [113, 114]. Pyroptosis was identified in 1992 by Zychlinsky et al., who noted macrophage suicide during *Shigella flexneri* infection [115]. In 1996, Chen et al. found Shigella's invasion plasmid antigen B (ipaB) directly attached to CASP1, activating the enzyme in infected macrophages [116]. Initially misclassified as apoptosis due to similarities like DNA damage and caspase dependency, further research demonstrated its uniqueness. The term "pyroptosis" was coined in 2001 by D'Souza et al. to describe a pro-inflammatory programmed cell death distinct from apoptosis [117]. This term was specifically coined to highlight the differences between pyroptosis and apoptosis, the latter being a non-inflammatory process of cell death [117]. In 2002, the theory emerged explaining how inflammatory caspases process pro-IL1B [118]. Petr et al. later discovered that CASP4/CASP11, during Salmonella infection, induces cell death independently of CASP1 [119].

Pyroptosis was thought to involve CASP1-induced monocyte death [11, 120]. Subsequently, it was found that CASP1, CASP4, or CASP5 cleave GSDMD, forming membrane pores that rupture the cell [121]. Recent studies identified CASP3 and CASP7 cleaving GSDMD at Asp87 to inactivate its pyroptotic function [122]. GSDMD pores may be removed by ESCRT machinery, reducing cell death and IL1B secretion [123]. Fumarate and dimethyl fumarate inhibit pyroptosis via succinizing GSDMD's cysteine to prevent activation [124]. Fumarate and dimethyl fumarate inhibit pyroptosis via succinizing GSDMD's cysteine to prevent activation [124]. Chemotherapeutic drugs like CASP3-stimulating agents cleave GSDME, promoting pyroptosis**,** as shown by Wang and Rogers [125, 126]. CASP8 also regulates inflammasome activity and induces pyroptosis [127]. GZMB (granzyme B) directly cleaves GSDME, enhancing antitumor immunity [128]. Recent findings show GZMA hydrolyzes GSDMB after PRF1 (perforin 1) infiltration into target cells [129]. According to Hou et al., nuclear CD274/PD-L1 (CD274 molecule) translocation via phosphorylated (p)-STAT3 under hypoxic conditions increases GSDMC production**,** which CASP8 cleaves at D365 to promote pyroptosis [130].

Role of pyroptosis-associated signaling pathways in DN progression

GSDMD-regulated pyroptosis

Common symptoms of DN include sterile inflammation, renal damage, and loss of intrinsic renal parenchymal cells. Researchers and physicians have taken note of the role that pyroptosis-signaling pathways play in developing diabetic neuropathy. According to the most recent research, renal cell death brought on by pyroptosis accelerates DN pathogenesis.

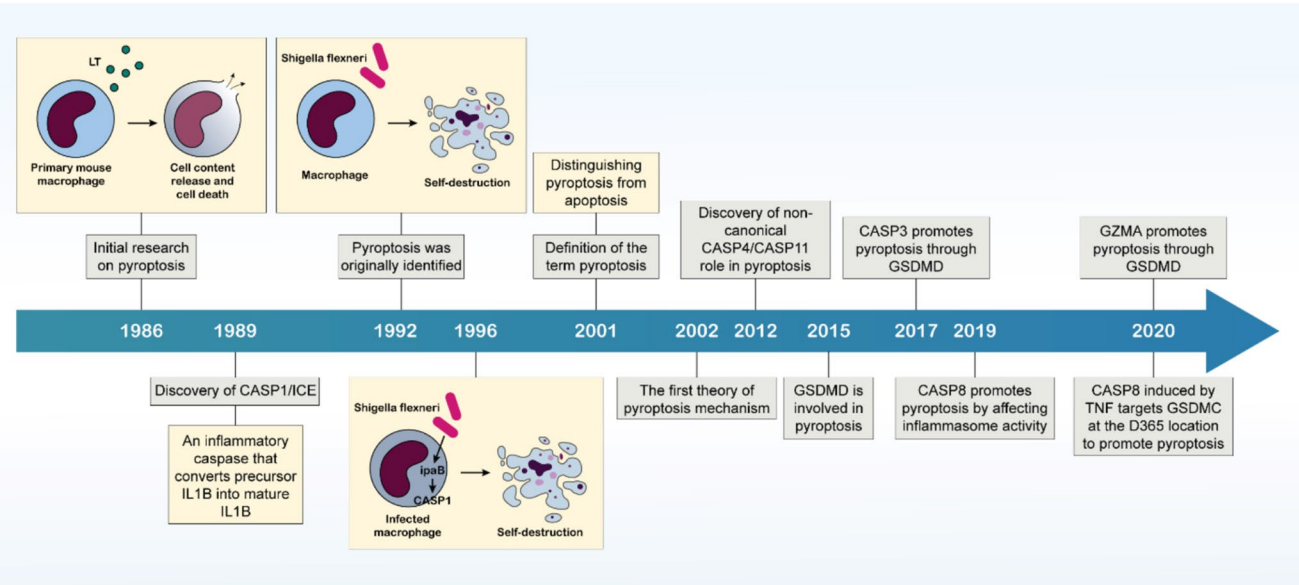


Fig. 3 Timeline of key discoveries and advancements in pyroptosis research

Pyroptosis is a so-called planned cell death [131, 132]. Li et al. showed that renal tubules upregulate proteins related to pyroptosis, such as GSDMD, NLRP3, CASP1, and IL1B [133]. Current research has revealed that the pathophysiology of diabetes late sequelae, such as DN, is accelerated by pyroptosis-dependent cell death [134–137]. The GSDMD protein molecule stimulates cell death regulated by pyroptosis in mouse podocytes subjected to HG [138]. Human podocyte cells exposed to HG have higher levels of GSDMD protein and mRNA expression, as shown by western blot and RT-PCR analyses. *GSDMD* gene silencing inhibits MAPK/JNK phosphorylation and mitochondrial ROS production, substantially reducing HG-mediated inflammation and apoptosis. Furthermore, GSDMD-dependent cell death facilitates renal inflammation, suggesting that GSDMD-dependent pyroptosis plays a critical role in DN pathogenesis advancement. Cheng et al. previously observed that HG circumstances significantly upregulate CASP4/CASP11 and cleaved amino-terminal GSDMD (GSDMD-N) protein expression levels in podocytes. Pyroptosis has shown a significant impact on several clinical disorders connected to the kidneys [139]. Prior research has demonstrated a considerable increase in the expression levels of GSDMD-N and CASP4/CASP11 in STZ-induced diabetic mouse models [140]. Pyroptosis may thus be linked to tubular damage in diabetes.

CASP1- and CASP4-dependent pyroptosis

In podocytes exposed to HG, CASP4 protein expression is markedly increased. Early research had shown that in cultured human podocytes, HG conditions significantly increase *CASP4* mRNA and protein expression levels. Furthermore, the findings using the ELISA test showed that HG therapy might raise the IL1B levels. In HG-stressed human podocytes, CASP4 knockdown using small interfering RNA (siRNAs) effectively reduces increased levels of IL1B release. *CASP4* and *GSDMD* gene silencing enhances renal function and glomerular and podocyte morphological features. Chronic inflammation is yet another important component that fosters the development of DN [10]. Numerous studies have demonstrated that inflammation in renal tissue accelerates the formation of scars and renal impairment [141]. In the kidney tissues of diabetic mouse models, the production of inflammatory mediators is markedly increased. By suppressing the release of high inflammatory factor levels, *CASP4* and *GSDMD* gene-silencing demonstrates that pyroptosis results in immunogenic cell death, hence connecting it to the induction of an inflammatory response. The essential component for starting the conventional pyroptotic signaling cascade is CASP1. Immunofluorescence labeling revealed that CASP1 colocalizing with the GSDMD-NLRP3 signaling axis is significantly boosted in DN and notably enhanced in tubules. In diabetic animal models, CASP1 gene silencing prevents inflammasome activation and prevents DN advancement [142]. These findings suggest that pyroptosis may play a significant role in developing DN. Prior research has indicated a possible correlation between DN inflammation and pyroptosis. It has also been demonstrated that one of the key drivers of DN pathogenesis is CASP1 activation, which is reliant on an inflammatory response.

NLRP3 inflammasome-mediated pyroptosis

When it comes to a variety of illnesses, such as diabetes mellitus, heart disease, and liver disease, the NLRP3 inflammasome has been highly intensively examined. However, this review focuses on the novel role of ncRNAs in modulating NLRP3-mediated pyroptosis, providing insights that are less explored in prior studies. NLRP3 inflammasomes trigger pyroptosis in a variety of pathological damage scenarios. Numerous studies have shown that the NLRP3 inflammasome activation is essential for advancing DN [143–145]. In diabetic rat models, the NLRP3 inflammasome and markers related to pyroptosis, such as cleaved-CASP1 and IL1B expression levels, are markedly elevated. In bone marrow-derived cells, *Nlrp3* and *Casp1* gene restriction may inhibit the development of DN [143]. Renal inflammation is dramatically reduced in *Nlrp3* gene-silencing mouse models, suggesting that activating the NLRP3 inflammasome may be a major driver of the pathophysiology of DN. In STZ-induced diabetic mouse models, Wu et al. reported that *Nlrp3*-gene restriction successfully reduces oxidative stress, inhibited kidney inflammation and fibrosis, and enhanced renal function [145]. The inflammatory response mediated by NLRP3-PYCARD/ASC (PYD and CARD domain containing) stimulates the production of CASP1 and the release of IL1B, both essential elements in the progression of DN pathogenesis. A unique aspect of this review is its discussion of how ncRNAs, such as circular RNAs (circRNAs) and long non-coding RNAs (lncRNAs), regulate NLRP3-mediated pyroptosis. These ncRNAs open new avenues for therapeutic interventions, as explored further in the review.

D-ribose is a monosaccharide biomolecule present in living organisms, is widely used in various foods, and is advised when implementing metabolic treatment. A growing body of data indicates that the production and activation of the NLRP3 inflammasome in podocytes in response to several clinical stimuli, such as obesity syndrome, and diabetes mellitus, might promote glomerular inflammation and progressive glomerular sclerosis. Persistent degenerative diseases are caused by an intracellular inflammatory inducer provided by the NLRP3 inflammasome [146–148]. Hong et al. demonstrated that mouse D-ribose-induced podocyte damage and glomerular sclerosis are linked to NLRP3 inflammasome activation and

enhanced IL1B release. Such results reveal that NLRP3 inflammasome activation is crucial in podocyte damage caused by D-ribose and the progressive development of glomerular sclerosis [149].

According to groundbreaking research, SYK (spleen-associated tyrosine kinase) may also have contributed to the progression of DN by activating the NLRP3 inflammasome. In human renal tubular epithelial (HK-2) cells and rat glomerular mesangial cells (GMCs), the HG-stimulated MAPK/JNK pathway, NLRP3 inflammasome, and mature IL1B are reduced by SYK blocker and *SYK*-siRNA [150]. Moreover, the SYK inhibitor BAY61–3606 markedly inhibits the HK-2 cell death mediated by CASP3 in response to HG stimulation. Consequently, the SYK-MAPK/JNK signaling pathway activation induces the HG-mediated NLRP3 inflammasome and subsequently promotes the level of pro- and mature IL1B protein production.

The SYK-MAPK/JNK-NLRP3 signaling axis has been demonstrated in earlier research to potentially play a crucial role in advancing the pathogenesis of DN. Conversely, TLRs control the innate immune response, which initiates an inflammatory response by sensing and identifying molecules linked to risk. Pro-inflammatory factors are formed via signaling pathways associated with TLR2 and TLR4. In DN, TLR4 signaling promotes inflammatory responses and results in significant tissue damage [151]. Liu et al. discovered that HG circumstances increase the frequency of TUNEL-positive cells, impair podocyte viability, raise intracellular ROS levels, and elevated IL1B, IL18, TNF, and TGFB1 levels in mouse podocytes in a dose-dependent manner. In HG-conditioned podocytes, *Tlr4* gene-silencing decreases the production of IL1B, IL18, TNF, and TGFB1, lowers the intracellular ROS level, and limits HG-mediated CASP3 activation [152].

TLR4 activation promotes HG-exposed podocyte damage by initiating the NLRP3/NALP3-PYCARD-CASP1 signaling pathway, suggesting that TLR4 is essential for advancing DN pathogenesis [152]. RIPK3 (receptor interacting serine/threonine kinase 3) is a multipurpose regulator of inflammatory responses and cell death. Shi et al. noted that RIPK3 stimulates the NLRP3 inflammasome, a critical inducer in the progression of renal fibrogenesis, to control cellular signaling [153]. In the renal cortex of DN animal models, RIPK3 activity and NLRP3 expression levels are elevated, and fibrotic responses are encouraged. Moreover, it has been documented that RIPK3 activates the NLRP3 inflammasome, which plays a major role in developing renal fibrosis in diabetes-related kidney disease (DKD) [153]. Deactivating the NLRP3 inflammasome to suppress RIPK3 has significant renoprotective benefits. As a result, RIPK3 could be a good target and offer fresh insights into the underlying pathogenesis of DN [10].

TXNIP-induced pyroptosis

In HFD + STZ animal models, pyroptosis is essential for the progression of DN because it activates the TXNIP-NLRP3-CASP1-GSDMD signaling axis [98]. To advance DN, the TXN-TXNIP signaling axis generates a crucial mediator. Renal inflammation and dysfunction are mostly promoted by activation of the TXNIP-mediated inflammasome [100]. An et al. recently showed that pyroptosis induced by the TXNIP-NLRP3 pathway has a pathogenic role in DN promotion [98]. For pyroptosis-mediated cell death, activation of the ROS-TXNIP-NLRP3-IL1B inflammasome signaling axis is an essential stimulus. Based on the groundbreaking study by Feng and colleagues, HG and lipopolysaccharide activate the glomerular MCs' ROS-TXNIP-NLRP3-IL1B inflammasome signaling axis, indicating that NLRP3-mediated inflammation can also contribute to the pathogenesis of DN [154].

One of the most important factors in developing DKD is intrarenal oxidative stress (OS) activation. A few NADPH components mostly mediate the generation of ROS in renal tissue diabetes. It is commonly recognized that DN pathogenesis advances when OS is stimulated. The NLRP3 inflammasome is stimulated by hyperglycemia, hyperlipidemia, and hyperuricemia, which further promotes the development of DN [144, 155]. Numerous studies have shown that the NLRP3 inflammasome in DN is further activated by ROS production [156, 157]. Mainly known as a cellular mediator of OS, TXNIP decreases TXN's antioxidant action and promotes processes leading to cell death. Overactivation of TXNIP increases inflammation by activating the NLRP3 inflammasome, which in turn promotes kidney damage [158]. According to Masson et al., mice with diabetes display higher levels of TXNIP expression, but mouse models with *txnip* gene deletion are shielded against STZ-stimulated diabetes. Conversely, in some pathological conditions, increased ROS production can help TXN and TXNIP dissociate. The detached TXNIP promotes the NLRP3 inflammasome by attaching itself to NLRP3 protein molecules. ROS production upregulates TXNIP expression in HG-stimulated HK-2 cells.

NADPH oxidase decreases HG-mediated podocyte damage and increases NLRP3 inflammasome activation and IL1B production, as demonstrated by Gao et al. [159]. It is commonly recognized that the anti-oxidant-dependent defense mechanisms are regulated by TXNIP, as a TXN blocker. The pathophysiology of DN may be further aided by the activation of the TXNIP-NOX pathway [159]. TXNIP may significantly upregulate the expression of associated inflammatory variables and activate the NFKB signaling pathway. It is widely known that producing pro-inflammatory factors, including IL1B and IL18 by inflammasomes, aids in developing DN. The kidneys of STZ-induced diabetes mouse models show elevated TNF and IL1B secretion

together with activation of the NFKB pathway. In DN mouse models, activation of inflammasome components causes pyroptosis by stimulating the TXNIP-NLRP3 signaling axis. Previous research has demonstrated that HG settings can enhance the expression levels of cleaved-CASP1, TXNIP, NLRP3, PYCARD, and GSDMD-N, all activated by ERN1/IRE1α (endoplasmic reticulum to nucleus signaling 1) phosphorylation. Furthermore, a remarkable rise in cell death has been shown by TUNEL labeling, suggesting that HG increases endoplasmic reticulum stress (ERS) and initiates pyroptosis in NRK-52E cells. Pyroptosis in HG-stimulated NRK-52E cells is inhibited by TXNIP inhibition through blocking the NLRP3-PYCARD-CASP1-GSDMD-N signaling pathway. The connection between TXNIP and NLRP3 is significantly limited when TXNIP is suppressed, as demonstrated by the co-immunoprecipitation of TXNIP and NLRP3.

According to recent research, endoplasmic reticulum stress (ERS) signals are activated in diabetic nephropathy (DN) rats. ERN1 can upregulate the production of *Mir200a* by inhibiting its RNase activity [99]. Moreover, overactivation of ERN1 and EIF2AK3/PERK (eukaryotic translation initiation factor 2 alpha kinase 3) leads to NLRP3 inflammasome activation by inducing the TXNIP molecule, resulting in cell death mediated by pyroptosis. A new study showed that the ERN1-*Mir200a*-TXNIP-NLRP3 signaling axis, along with EIF2AK3 activation, may play a critical role in pyroptosis regulation [99]. Consequently, EIF2AK3 has emerged as a key focus of investigation to examine its potential role in pyroptosis and its impact on DN pathogenesis. Emerging studies also reveal increased TXNIP-NLRP3 colocalization in cultured cells, indicating that inflammasome activation mediated by TXNIP significantly contributes to DN progression by enhancing IL1B production under hyperglycemic conditions [160, 161]. Consequently, the findings underscore ERS-mediated pyroptosis as a novel mechanism driving DN [10].

Figure 4 summarizes key pyroptosis-related signaling pathways and molecular mechanisms, which are involved in DN progression.

Long non-coding RNAs and circular RNAs: molecular contributors to biological processes

Long non-coding RNAs

Definition and classification

Long non-coding RNAs (lncRNAs) are typically defined as non-coding RNA transcripts longer than 200 nucleotides (nt). This size cut-off is practical for biochemical and biophysical RNA purification techniques aimed at removing most small structural RNAs (< 200 nt), such as 5S ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs/snRNAs, and small nucleolar RNAs/snoRNAs, along with microRNAs (miRNAs), small interfering RNAs (siRNAs), and PIWI-interacting RNAs/piRNAs [162]. Interestingly, this definition excludes several other well-known short RNAs, including vault RNAs, which range from 88–140 nt and play a role in translating external signals into cellular responses [163]; promoter-associated RNAs; non-canonical small RNAs that arise from post-transcriptional modifications [164, 165]; and primate-specific small RNAs/snaRs, approximately 80–120 nt in length, which interact with nuclear factor 90. Additionally, Y RNAs, which are shorter than 100 nt and function as scaffolding for ribonucleoprotein [166] complexes, are also not encompassed within this definition [167]. Near the 200-nt boundary are other non-coding RNAs, such as *RN7SK* (RNA component of 7SK nuclear ribonucleoprotein; ~ 330 nt in vertebrates), that regulate transcription initiation and culmination, including enhancers [168, 169], and *RN7SL1* (RNA component of signal recognition particle 7SL1; ~ 300 nt), which is a crucial member of the signal recognition particle that directs proteins to cell membranes [170], and the evolutionary progenitor of the short interspersed nuclear elements/SINEs of rodent B1 (~ 135 nt) and ubiquitous primate Alu (~ 280 nt.) [171–173]. In light of this ambiguous range of sizes, we endorse the proposal to categorize ncRNAs into three groups [174]: (i) short RNAs (less than 50 nt) [175], which are mostly transcribed by RNA polymerase III (POLR3) and include small RNAs such as tRNAs, 5S rRNA, 7SK RNA, 7SL RNA, Alu RNAs, vault RNAs (VTRNA), and Y RNAs. Additionally, some very short RNAs can also be derived from RNA polymerase II (POLR2) transcripts, including certain microRNAs and other small regulatory RNAs [176]; (ii) Pol V transcripts in plants, and small POLR2 transcripts (~ 50–500 nt), including (most) small nuclear RNAs and intron-derived small nucleolar RNAs [177, 178]; and (iii) lncRNAs (more than 500 nt), the majority of which are produced by POLR2.

The term "mRNA-like" refers to many lncRNAs being polyadenylated and spliced. A more ambiguous term, "transcripts of uncertain function," refers to additional lncRNAs that are not polyadenylated or 7-methylguanosine capped [179–181]; instead, they are produced from POLRI (*RNA5-8S/5.8S*, *RNA28S*, and *RNA18S* rRNAs) or POLR3 promoters; alternatively, they are processed from precursors, including from introns and repetitive elements. [182]. LncRNAs can be "intergenic," "antisense," or intronic about genes that code for proteins. Additionally, they originate from "pseudogenes," often found in metazoan genomes [183]. The mouse genome and the human genome include over 10,000 and almost 15,000 pseudogenes, respectively, some of which are functional [183–186]. Circular RNAs produced

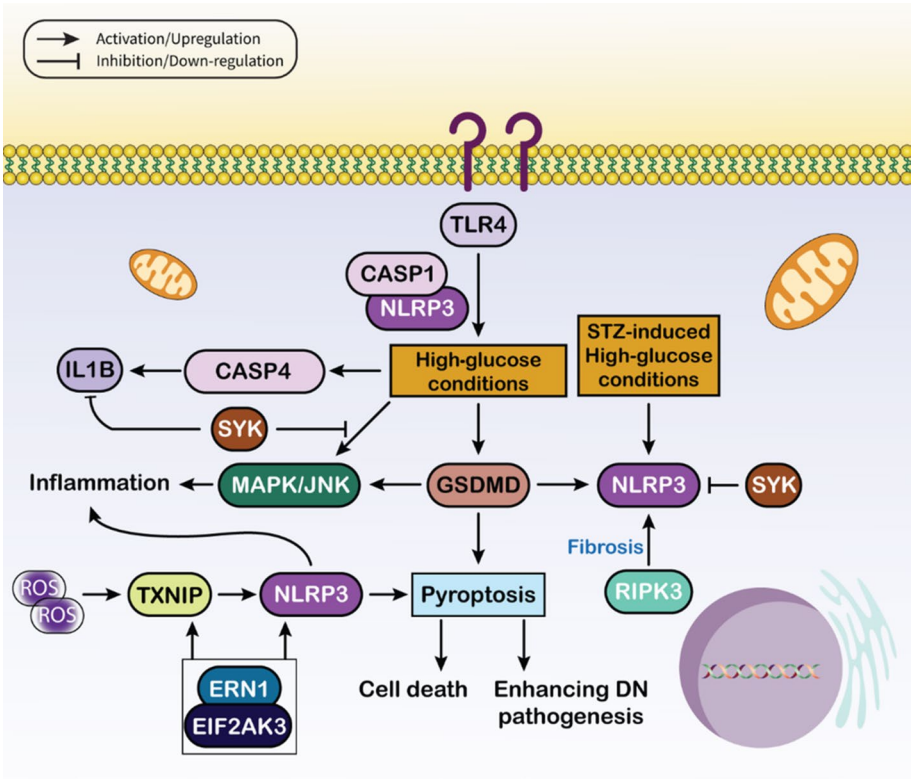


Fig. 4 Pyroptosis-related signaling pathways and molecular mechanisms in diabetic nephropathy. Under high-glucose conditions, TLR4 (toll-like receptor 4) activation can trigger the NLRP3 inflammasome, leading to CASP1 activation and subsequent GSDMD-mediated pyroptosis, a highly inflammatory form of cell death. Similarly, STZ-induced high glucose can directly activate the NLRP3 inflammasome. CASP4, activated by intracellular factors, can also contribute to inflammation, potentially through SYK and MAPK/JNK signaling. Reactive oxygen species (ROS) promote TXNIP activation, which in turn activates NLRP3, further driving pyroptosis. Endoplasmic reticulum stress, indicated by ERN1 and EIF2AK3 activation, also contributes to NLRP3 activation. Notably, GSDMD-driven pyroptosis leads to cell death and enhances DN pathogenesis, potentially contributing to fibrosis through RIPK3 activation. The diagram highlights the complex interplay of various cellular stress pathways converging on inflammasome activation and pyroptosis, independent of canonical NFKB signaling, in the development of the diabetic complication affecting kidneys

by back-splicing coding and non-coding transcripts, which also have roles, and trans-acting regulatory RNAs made from sequences that typically function as the 3′ untranslated regions (UTRs) of mRNAs are further examples of lncRNAs [187, 188].

Biological functions

Empirical evidence has demonstrated that RNAs engage in nearly every aspect of genome architecture, cellular structure, and gene expression via interactions between RNA-RNA, RNA-DNA, and RNA–protein [162]. These interactions frequently include repeat elements [189, 190], such as small interspersed nuclear elements in 3′ UTRs [191]. The control of chromatin architecture and transcription (discussed below), splicing (particularly by antisense lncRNAs) [192–194], protein translation and localization [195, 196], and further RNA processing, editing, localization, and stability are all affected by these interactions [197, 198].

In both plants and animals, many lncRNAs are engaged in the control of cell differentiation and development [199–202]. Additionally, they play a part in physiological processes such as the TP53-mediated response to DNA damage in mammals [203], V(D)J recombination and class switch recombination in immune cells [204], cytokine expression (205), endotoxic shock [206], inflammation and neuropathic pain [207–209], cholesterol biosynthesis and homeostasis [210, 211], GH (growth hormone) and PRL (prolactin) production [212], glucose metabolism [213, 214], cellular signal transduction and transport pathways [215–218], and synapse function [219, 220], and play a part in how plants react to different biotic and abiotic stresses [200, 221]. Additionally, a growing body of research links lncRNAs to ribozymes and the cell membrane [222, 223].

Currently, many lncRNAs have narratives of their own, the literature is a rich source of information for these. However, several converging themes—including the connection of lncRNAs with chromatin-modifying proteins, the

expression of lncRNAs from developmental "enhancers," and the production of RNA-nucleated phase-separated coacervates—emerge that account for lncRNA prevalence and relevance in differentiation and development [162].

Circular RNAs

Characteristics and biogenesis

CircRNAs are a significant category of ncRNAs produced from pre-mRNA by processes called back-splicing or exon skipping, which deviate from canonical splicing and have covalently closed-loop structures lacking 5′-to-3′ polarity. Exons, introns, UTRs, antisense RNAs, and intergenic regions can all be used to create circRNAs. Based on their inner elements, these molecules are divided into three main subtypes: circular intronic RNAs (ciRNAs), which are produced from introns, exon–intron circRNAs (EIciRNAs), which are created from both exons and introns, and exonic circRNAs (EcircRNAs), which include only exons. The majority of circRNAs are called EcircRNAs, mostly identified in the cytoplasm. Conversely, most ciRNAs and EIciRNAs are found in the nucleus [224].

Two speculative theories are widely recognized in the case of circRNA biogenesis. The first is called lariat-driven circularization, in which one or more exons are skipped because pre-mRNA is exposed by incomplete splicing, and it is near the exon-donor site and various exon-acceptor sites in the same places [225, 226]. This procedure forms a lariat intermediate with an ample number of exons and introns more quickly. Exon-derived circRNAs are created when an upstream and downstream exon connect to another after splitting the introns [227]. Also, intronic sequences are preserved in specific circumstances, producing EIciRNA [228]. Additionally, this strategy uses a C-rich 11-nucleotide motif near the 3' branch point and a GU-rich 7-nucleotide sequence near the 5' splice site to promote the synthesis of ciRNA [225]. The second method is called "intron-pairing driven circularization," which produces various circRNAs, such as EcircRNAs and EIciRNAs, by complementary pairing on both sides of the introns. This circular composition comprises repeating sequences such as the Alu [229].

Similar to linear RNAs, RNA-binding proteins (RBPs) such as nuclear helicase DHX9 (DExH-box helicase 9), MBNL (muscleblind-like splicing regulator), QKI (QKI, KH domain containing RNA binding), and the double-stranded RNA editing enzyme ADAR (adenosine deaminase RNA specific) regulate the synthesis of circular RNAs [230]. CircRNAs are produced when MBNL and QKI bind to pre-RNA, bringing the splicing sites close together [231, 232]. To stop circRNA production, ADAR can convert adenine to inosine, reduce RNA complementarity, and unwind the stem [233, 234]. In a similar vein, DHX9 also inhibits the formation of circRNAs. This is because this RBP, which consists of an RNA-binding domain and a helicase RNA domain, may open RNA pairs and prevent the production of circRNAs. As a result, concurrent reduction of DHX9 and ADRA can increase circRNA expression (233).

Biological functions

Remarkably, it has been shown that specific miRNA response elements (MREs) are present in circRNAs. These MREs provides these molecular sponges a structural foundation. Additionally, the MREs stop the interaction between miRNAs and mRNAs, which indirectly affects target genes downstream and the ensuing synthesis of proteins [235, 236]. "Super sponges" are circRNAs with a high affinity for binding to miRNAs. *LINC00632/ciRS-7*, a super sponge with over 70 binding sites for *MIR7*, is one of the well-studied instances. Consequently, *LINC00632/ciRS-7* functions as a miRNA sponge and influences the target mRNA transcripts of *MIR7* [235, 237]. Numerous additional circRNAs, including *circHIPK3*, *circPVT1*, *cir-ZNF609*, *circ-MMP9*, etc., can also function as miRNA sponges [238–242].

CircRNAs can selectively bind to certain proteins and function as protein sponges to alter the proteins' activity because they include unique binding sites for RBPs [243]. For example, the *circ-FOXO3* has a high affinity for several transcription factors linked to aging and stress, including PTK2B/FAK (protein tyrosine kinase 2 beta), E2F1 (E2F transcription factor 1), ID1 (inhibitor of DNA binding 1), and HIF1A/HIF-1α (hypoxia inducible factor 1 subunit alpha). Heart aging is caused by cardiac stress, which can be mitigated by *circ-FOXO3* by reducing the nuclear translocation of ID1, E2F1, and HIF1A, as well as the mitochondrial translocation of PTK2B [244]. In addition, as seen with *circ-FOXO3*, which may bind to CDK2 (cyclin dependent kinase 2) and CDKN1A to enable CDKN1A-induced inhibition of CDK2 and limit cell cycle progression through the G_1 phase, circRNAs also serve crucial functions as protein scaffolds for the assembly of two or more proteins via their binding sites [245].

CircRNAs were originally categorized as ncRNAs that could not be translated into proteins because they lacked a 3' poly (A) tail and a 5' cap structure. Surprisingly, it has been demonstrated that certain circRNAs, including *circ-SHPRH*, *circ-ZNF609*, and *circ-MBNL/MBL*, are able to be translated [236]. Critical components for the translation of circRNAs include those needed to start the translation process, such as the open reading frames (ORFs), N6-methyladenosine (m6A), and the internal ribosome entry site (IRES) [246, 247]. IRES elements recruit ribosome 40S subunits cap-independently to induce protein translation [248]. With an IRES, the *circ-ZNF609*'s ORF can be translated into a protein in a cap-independent and

splicing-dependent manner [249]. Additionally, the *circ-SHPRH* is expressed in healthy human brains to inhibit glioma carcinogenesis and possesses an ORF driven by an IRES that can translate into a functional protein [250, 251]. For some circRNAs, m6A alteration speeds up the protein synthesis process when an IRES is not present. According to Yang et al., there are several consensus m6A motifs inside the circRNAs, and the reader protein YTHDF3 (YTH N6-methyladenosine RNA-binding protein F3) can identify a specific m6A site that can interact with the initiation factors EIF4G2 (eukaryotic translation initiation factor 4 gamma 2) and EIF3A (eukaryotic translation initiation factor 3 subunit A) to start the translation process [246].

Long non-coding RNAs and circular RNAs in association with pyroptosis during diabetic nephropathy

Exploring the complex relationships between lncRNAs, circRNAs, and pyroptosis in the context of DN could pave the way for innovative diagnostic and treatment strategies. Long non-coding RNAs and circular RNAs have the ability to interact with each other, thereby creating complex regulatory networks [10, 19]. These types of RNAs can have a significant impact on pyroptosis, either encouraging or suppressing it. In essence, the interplay between lncRNAs, circRNAs, and pyroptosis in diabetic nephropathy is a promising area of study that could lead to the development of

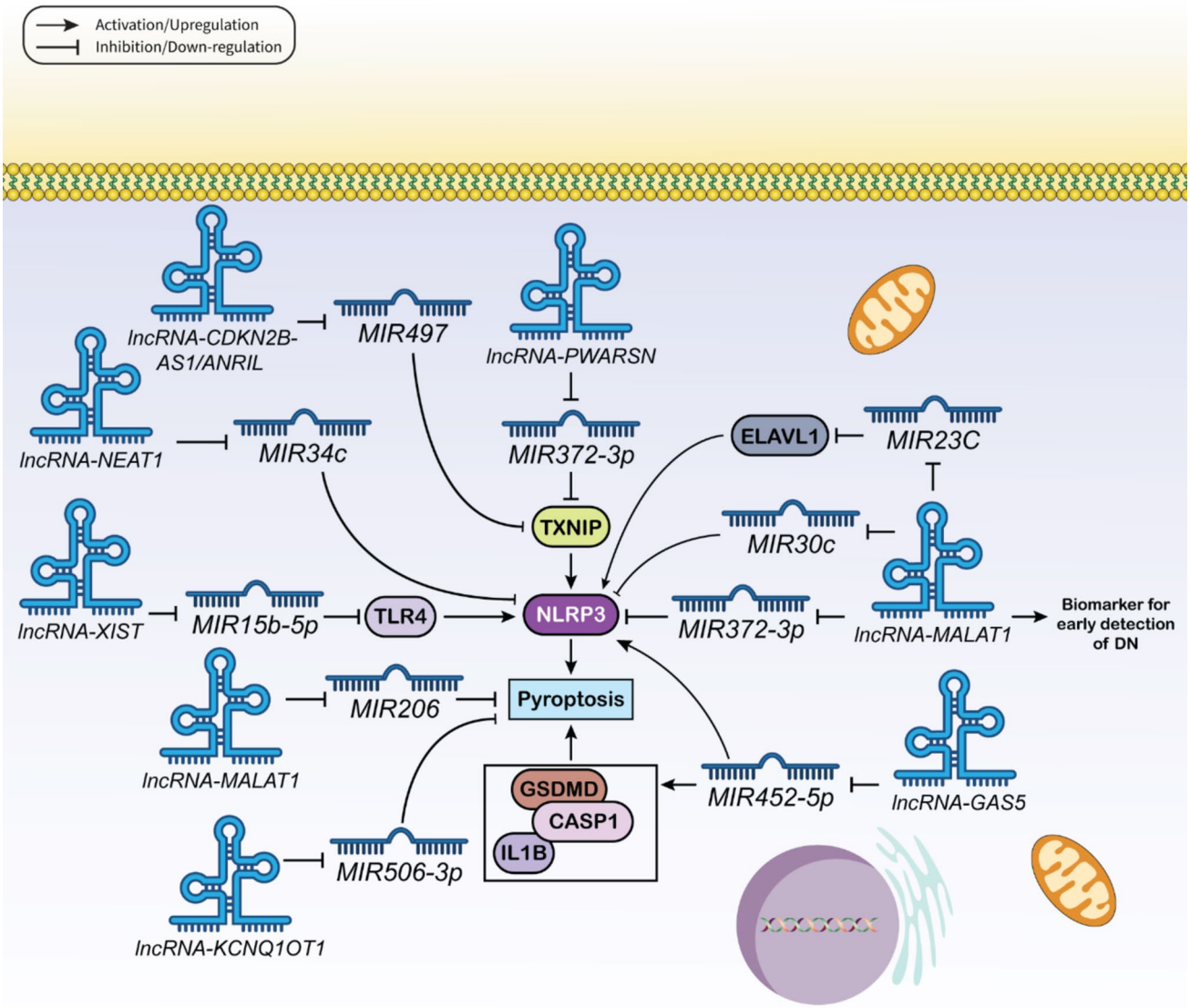


Fig. 5 Long non-coding RNAs in correlation with pyroptosis through diabetic nephropathy

new diagnostic tools and treatments (Figs. 5 and 6) [252]. By understanding how these RNAs interact and influence pyroptosis, we can potentially improve patient outcomes and prevent kidney damage in individuals with diabetes. This concept underscores the importance of future research in this area.

Major long non-coding RNAs, influencing pyroptosis through diabetic nephropathy

PWARSN

The pathophysiology of diabetes-related kidney disease is influenced by elevated TXNIP-induced pyroptosis. Proximal tubular epithelial cells (PTECs) show high expression of a novel long non-coding RNA, which is named *PWARSN* (Prader Willi/Angelman region RNA, SNRPN neighbor), under high-glucose conditions. Both diabetic mice and kidney tubules from DKD patients exhibit activated PTEC pyroptosis and the TXNIP-NLRP3 inflammasome. Pyroptosis in PTECs caused by TXNIP is improved by *PWARSN*. To increase TXNIP expression, cytoplasmic *PWARSN* sponges *MIR372-3p*. Furthermore, by reducing H3K9me3 enrichment at the *TXNIP* promoter, nuclear *PWARSN* acts on and enables the ubiquitination of RBMX (RNA-binding motif protein X-linked), which in turn initiates *TXNIP* transcription. The results of the study suggest that *PWARSN* is a promising therapeutic target for DKD because it can modulate TXNIP and PTEC pyroptosis in DKD through two different molecular approaches. *PWARSN* may prove to be a possible biomarker for DKD [253].

MALAT1/NEAT2 and NEAT1

Early diagnosis and treatment of DN hinders the further progression of the disease. Recent groundbreaking research has established that the early detection and development of DN are associated with non-coding RNA and pyroptosis. In a novel clinical study, 60 patients with type 2 DM were divided into normoalbuminuria and microalbuminuria groups based on their urine ALB/creatinine ratio/uACR. The unprecedented findings revealed that the microalbuminuria group exhibits notably higher levels of *MALAT1* (metastasis-associated lung adenocarcinoma transcript 1) expression, serum CASP1 and IL18 level, MPO (myeloperoxidase) activity, and protein carbonyl level compared to the normoalbuminuria group. Conversely, catalase (CAT) activity is significantly reduced. These results provide the first comprehensive evidence that the fundamental mechanisms underlying the development of DN may encompass

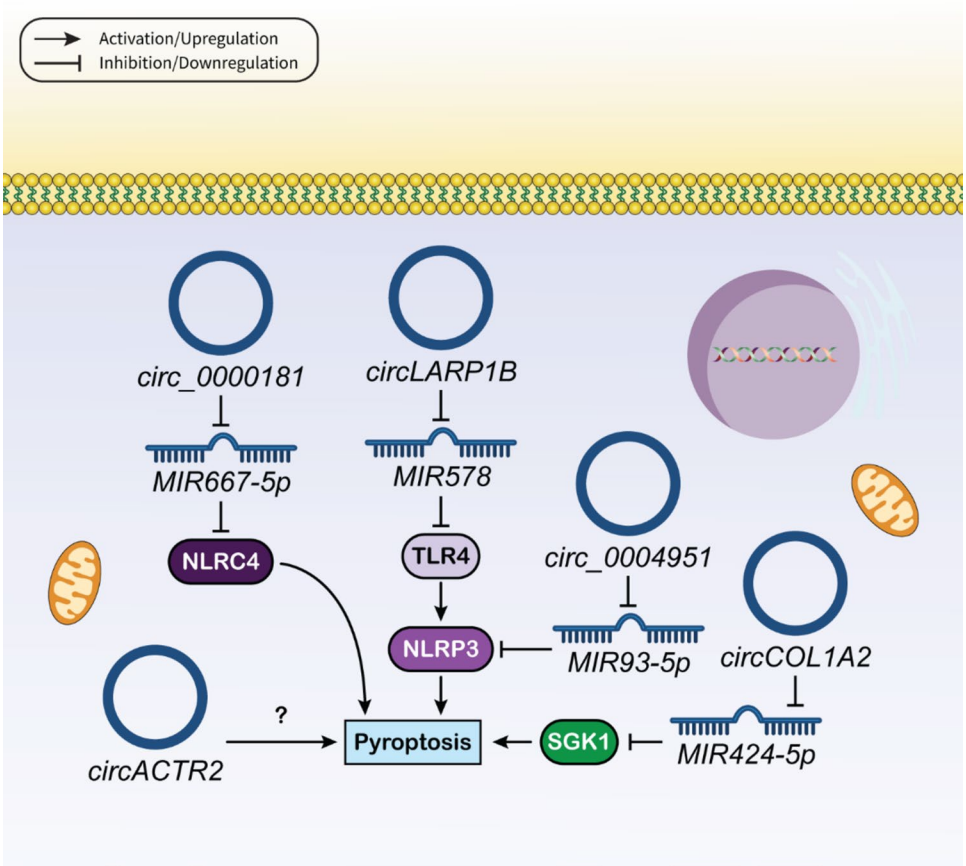


Fig. 6 Circular RNAs in correlation with pyroptosis during diabetic nephropathy

pyroptosis, diminished redox, and altered MALAT1 expression. Most significantly**,** the levels of CASP1, IL18, and the expression of MALAT1 may serve as valuable biomarkers in the timely identification of DN. In a major diagnostic breakthrough**,** IL18 has been identified to possess the greatest sensitivity and diagnostic precision, with CASP1 and MALAT1 coming in as subsequent contenders [254].

In an in vitro study on a cellular model of a kidney disorder, researchers scrutinized the levels of various crucial molecules, such as *NLRP3*, *MIR30C*, *MALAT1*, *CASP1*, *IL1B*, and *IL18*, by employing quantitative polymerase chain reaction on the treated HK-2 cells. Furthermore, they gauged the activity of LDH (lactate dehydrogenase) with the assistance of a commercially available kit designed specifically for this purpose and evaluated the frequency of pyroptosis using flow cytometry analysis. The principal discoveries included the increased expression of *MALAT1* and the reduced expression of *MIR30C*, which in turn led to the enhanced expression of NLRP3 and ultimately resulting in pyroptosis of the cells. The investigation demonstrated that pyroptosis induced by HG is averted in HK-2 cells by means of either upregulating *MIR30C* or downregulating *MALAT1*. Additionally, it was discovered that *MALAT1* promoted the expression of NLRP3 by sequestering *MIR30C*. The protective impact of *MIR30C* on HG-induced pyroptosis was nullified by co-transfection of the *MIR30C* inhibitor and sh-*MALAT1*. The workers concluded that *MALAT1* regulates pyroptosis in HK-2 cells by obstructing *MIR30C's* targeting of NLRP3. This information regarding the pathophysiology of DN may potentially contribute to the advancement of efficacious treatments for this ailment [255].

The pathophysiology of DN is influenced by the interplay of the long non-coding RNA *MALAT1*, microRNA *MIR23C*, and its target gene *ELAVL1*. In diabetic rats and HK-2 cells treated with high glucose, there was an observed downregulation of *MIR23C* and an upregulation of *MALAT1* expression (256). As above, the process of pyroptosis could be inhibited by either downregulating *MALAT1* or upregulating *MIR23C*. The inhibition of *MALAT1* expression resulted in the downregulation of NLRP3, CASP1, ELAVL1, and the pro-inflammatory cytokine IL1B. This effect could also be achieved by upregulating *MIR23C*. *MIR23C*, identified as a target of *MALAT1*, directly suppressed the expression of ELAVL1. This, in turn, led to a reduction in the expression of NLRP3, a downstream protein of ELAVL1. The downregulation of ELAVL1 induced by *MIR23C* was counteracted by the expression of *MALAT1*, which also served to inhibit hyperglycemia-induced cell pyroptosis. These findings may enhance our understanding of the pathophysiology of diabetic nephropathy and pave the way for the development of novel therapeutic strategies for this condition.

Another investigation was conducted on the participation of the lncRNA *MALAT1/NEAT2-MIR206* in the inflammatory processes associated with DN [257]. Additionally, the study explored the impact of oxidative stress and cell death in renal tubular epithelial cells (RTECs) induced by high glucose. The study established an HG-induced DN cell model using HK-2 cells. Various RNAs and proteins involved in pyroptosis were analyzed using qRT-PCR and western blot, including *MALAT1*, NLRP3, CASP1, IL1B, and GSDMD-N. A dual-luciferase assay was also used to detect interactions between *MALAT1*, *MIR206*, and other factors including TNF, IL6, CCL2/MCP-1, and NLRP3. The findings showed that *MIR206* binds to *MALAT1* in HG-treated HK-2 cells. Knockdown of *MALAT1* leads to decreased levels of inflammatory cytokines TNF, IL6, and CCL2. This result is consistent with the overexpression of *MIR206* under HG conditions. Furthermore, *MALAT1* augmentation mitigates HG-induced pyroptosis and inflammation in these cells through interaction with *MIR206*.

There is growing evidence that the pathophysiology of diabetic neuropathic pain involves pyroptosis and the ensuing inflammatory response. To study this, researchers took advantage of a DN model using GMCs exposed to high glucose in vitro and a rat DN model in vivo. The study found that increased pyroptosis observed in DN models is linked to upregulation of the lncRNA RNA *Neat1* (nuclear paraspeckle assembly transcript 1). *Neat1* modulates pyroptosis by regulating *miR34c*, which in turn controls the expression of pyroptosis genes including *Casp1*, *Il1b*, and *Nlrp3*. In in vitro DN model, overexpressing NLRP3 or inhibiting miR-34c can counteract the increase in pyroptosis and inflammation driven by *Neat1* [258].

KCNQ1OT1

To determine the role of the lncRNA *KCNQ1OT1* (KCNQ1 opposite strand/antisense transcript 1) in the development of DN, plasma samples were collected from DN patients and HG-induced HK-2 cells were found to have higher levels of *KCNQ1OT1* [259]. Notably, pyroptosis, oxidative stress, and inflammation in these cells were reduced when *KCNQ1OT1* was inhibited. Furthermore, the downregulated *MIR506-3p* and HG-induced HK-2 cells from DN patients are directly targeted by *KCNQ1OT1*. In HG-induced HK-2 cells, overexpression of *MIR506-3p* further reduces inflammation, pyroptosis and oxidative stress. These results suggest that DN treatment may benefit from modulating *MIR506-3p* and *KCNQ1OT1* expression.

XIST

Understanding the function of *XIST* (X inactive specific transcript), a long non-coding RNA, in the process of pyroptosis in RTECs in the setting of diabetic nephropathy was the main goal of a recent study [260]. By inhibiting *Xist*'s

expression in a rat model of DN, the researchers hoped to assess the function of this lncRNA. The research discovered that blocking *Xist* had a number of advantageous outcomes, such as bettering renal metabolic and biochemical parameters, lowering renal damage, and averting RTEC pyroptosis. These changes were mediated by the NLRP3-CASP1 pathway. Furthermore, the investigation revealed that the control of NLRP3-CASP1-mediated RTEC pyroptosis by *Xist* involves the *Mir15b-5p*-TLR4 axis. *Mir15b-5p* is upregulated by *XIST* suppression, which inhibits TLR4 and protects the kidneys from damage in diabetic kidney disease. This study indicates that *XIST* may be a viable therapeutic target for kidney diseases and offers important insights into the regulatory function of *XIST* in DN.

ANRIL

A study was carried out to find out how *ANRIL* (LncRNA-antisense non-coding RNA in the INK4 locus), *MIR497*, thioredoxin-interacting protein (TXNIP) and pyroptosis are related to diabetic nephropathy [261]. HK-2 cells and kidney tissues from DN patients were used as models. Western blot and qPCR measured levels of *ANRIL*, *MIR497*, TXNIP, and pyroptosis-related markers such as CASP1, IL1B, IL18 and NLRP3. CASP1 activity, LDH release, cell viability, and cytokine levels were also assessed. Results show DN tissues/cells exposed to high glucose have increased *ANRIL* and TXNIP, but decreased *MIR497* levels. *MIR497* directly binds and targets TXNIP by binding to *ANRIL*. Inhibiting *ANRIL* decreases CASP1 activation, LDH leakage, and IL1B and IL18 release. Overexpressing TXNIP or inhibiting MIR497 counteracts the effects of *ANRIL* knockdown. *MIR497* mimetics' inhibitory effect on pyroptosis is reversed by co-overexpressing TXNIP in HG-treated cells (Table 1).

GAS5

The impact of the long non-coding RNA *GAS5* (growth arrest specific 5)-*MIR452-5p* on the processes of pyroptosis, oxidative stress, and inflammation within renal tubular cells subsequent to exposure to elevated levels of glucose have been examined [262]. Researchers administered vectors containing enhanced lncRNA *GAS5* or reduced *Mir542-3p* expression to db/db mice. They monitored glucose levels in blood and protein content in urine through biochemical testing. Kidney tissue analysis included HE staining for cell structure, TUNEL assay for cell death, and Masson staining to evaluate fibrotic changes. Inflammatory markers (IL1B, IL6, TNF) were quantified using ELISA, while oxidative stress was assessed by measuring superoxide dismutase (SOD), catalase (CAT), and malondialdehyde (MDA) activity. The interactions between lncRNA *GAS5*, *Mir542-3p*, and ERBB4 (erb-b2 receptor tyrosine kinase 4) were confirmed using computational analysis, dual-luciferase testing, and RNA-immunoprecipitation/RIP assays. Analysis of DN mouse kidney tissue revealed decreased levels of lncRNA *GAS5* and ERBB4, alongside elevated *Mir542-3p* expression. Enhancing lncRNA *GAS5* or reducing *Mir542-3p* expression helps reduce kidney fibrosis associated with DN. The study demonstrated that lncRNA *GAS5* interacts directly with *Mir542-3p*, which in turn regulates ERBB4 expression. Increased *Mir542-3p* levels reverse the protective effects of enhanced lncRNA *GAS5* expression, while reduced ERBB4 expression counteracts the benefits of decreased *Mir542-3p* on kidney fibrosis in DN mice [263].

Circular RNAs as modulators of pyroptosis in diabetic nephropathy

CircLARP1B

In DN patients and cells treated with high glucose, researchers assessed the expression levels of *circLARP1B*, *MIR578*, and TLR4. They found that *MIR578* has low expression, while *circLARP1B* and TLR4 have high expression. The workers also reported that lowering *circLARP1B* levels in HG-treated cells inhibits inflammation and triggers cell death via pyroptosis, while promoting cell proliferation and cell cycle progression. *circLARP1B* functions as a "sponge" for *MIR578*, effectively reducing *MIR578's* ability to target TLR4. Reduction of *circLARP1B* has the opposite effect in rescue experiments when *MIR578* is inhibited, and the opposite effect is observed when TLR4 is overexpressed. In conclusion, in renal MCs stimulated by high glucose, the *circLARP1B-MIR578*-TLR4 axis inhibits cell proliferation, blocks the cell cycle in the G_0-G_1 phase, promotes pyroptosis, and releases inflammatory factors. According to these results, *circLARP1B* may be a viable DN therapeutic target [264].

CircCOL1A2

A recent study investigated the expression of *circCOL1A2* in plasma from DN patients and HK-2 cells exposed to HG [265]. Both DN patients and HG-treated HK-2 cells exhibit elevated *circCOL1A2* levels. Silencing *circCOL1A2* after HG treatment diminishes oxidative stress and pyroptosis. Additionally, suppressing *circCOL1A2* enhances *MIR424-5p* expression while reducing SGK1 (serum/glucocorticoid regulated kinase 1) levels. Strikingly, the protective effects of *circCOL1A2* knockdown on HG-induced oxidative stress and pyroptosis are counteracted by SGK1 overexpression or *MIR424-5p* inhibition. These findings support the notion that *circCOL1A2* modulates the *MIR424-5p*-SGK1 axis to regulate HG-induced pyroptosis and oxidative stress in DN.

Table 1 Mechanisms of lncRNA-mediated regulation of pyroptosis in diabetic nephropathy

LncRNA	Sample/cell line studied	Key findings	Target mRNAs/proteins	Effect of modulation	Potential role	Ref
PWARSN	Diabetic mice, kidney tubules from DKD patients, PTECs	*PWARSN* expression is higher under HG; this modulates TXNIP and PTEC pyroptosis in DKD through cytoplasmic sponging of *MIR372-3p* and nuclear interaction with RBMX to initiate *TXNIP* transcription	*TXNIP*	Inhibition reduces TXNIP and pyroptosis	Therapeutic target for DKD	[253]
MALAT1	Type 2 DM patients divided into normoalbuminuria and microalbuminuria groups	Microalbuminuria group shows higher *MALAT1* expression, serum CASP1 level and IL18 level, MPO activity, and protein carbonyl level. CAT activity is reduced	N/A	N/A	Biomarker for early detection of DN along with CASP1 and IL18 levels. Altered expression may be involved in DN development	[254]
MALAT1	HK-2 cells treated with high glucose	*MALAT1* expression increases and *MIR30C* expression decreases, leading to increased NLRP3 expression and cell pyroptosis	*MIR30C*, NLRP3	Upregulating *MIR30C* or downregulating *MALAT1* protects cells from HG-induced pyroptosis	Contributes to knowledge of DN pathophysiology and potential treatment development	[255]
MALAT1	Diabetic rats, HK-2 cells treated with high glucose	*MALAT1* expression upregulated, *MIR23C* expression downregulated	*MIR23C*, ELAVL1	Downregulating *MALAT1* or upregulating *MIR23C* inhibit pyroptosis	Contributes to knowledge of diabetic nephropathy pathophysiology and therapeutic development	[256]
MALAT1/NEAT2	HK-2 cells treated with high glucose	*MALAT1* upregulation induces pyroptosis by interacting with *MIR206*. *MALAT1* knockdown reduces inflammation	Interaction with *MIR206*	Inhibition decreases pyroptosis and inflammation	Therapeutic target for DN	[257]
NEAT1	GMCs, DN rat models	*Neat1* modulates pyroptosis through *Mir34c* targeting of NLRP3	*Mir34c*, NLRP3	Overexpression of NLRP3 or inhibition of *Mir34c* counters *Neat1*-induced increases in pyroptosis	Regulator of pyroptosis in DN	[258]
KCNQ1OT1	Plasma samples from DN patients and HK-2 cells treated with high glucose	*KCNQ1OT1* inhibition reduces pyroptosis, oxidative stress and inflammation by directly targeting *MIR506-3p*	*MIR506-3p*	Overexpression of *MIR506-3p* likewise reduces pyroptosis and inflammation	Therapeutic target for DKD	[259]
GAS5	HK-2 cells treated with high glucose	*GAS5* overexpression inhibits pyroptosis and oxidative stress by downregulating *MIR452-5p* and targeting NLRP3, CASP1 and IL1B	*MIR452-5p*, NLRP3 CASP1, IL1B	Inhibition of *MIR452-5p* recapitulates the effects of *GAS5* overexpression	Regulatory role in kidney diseases	[262]

Table 1 (continued)

LncRNA	Sample/cell line studied	Key findings	Target mRNAs/proteins	Effect of modulation	Potential role	Ref
XIST	Rat model of DN	*Xist* inhibition improves renal function by preventing NLRP3-CASP1-mediated RTEC pyroptosis through the *MIR15B-5p*-TLR4 axis	*Mir15b-5p*, TLR4	*Xist* suppression upregulates *MIR15b-5p*, inhibiting TLR4 and protecting kidneys	Therapeutic target for kidney diseases	[260]
ANRIL	HK-2 cells treated with high glucose and kidney tissue from DN patients	*ANRIL* promotes pyroptosis by acting as a sponge for *MIR497* to disinhibit TXNIP expression	*MIR497*, TXNIP	Inhibition of *ANRIL* suppresses CASP1 activation and pyroptosis	Underlying mechanisms in DN pathogenesis	[261]

This result further suggests that *circCOL1A2* silencing holds promise as a therapeutic strategy for DN treatment.

Circ_0000181

Investigations of DN have found elevated levels of the NLRC4 inflammasome in renal tissue [266] and also identified two potential targets for NLRC4 regulation, *circ_0000181* and *MIR667-5p*. To further investigate the role of these molecules, these workers utilized STZ-induced DN mouse models and employed a range of techniques, including immunohistochemical analysis, western blot, and qPCR, to identify marker expressions associated with pyroptosis. Next-generation sequencing was used to assess gene expression changes in circRNAs, miRNAs, and mRNAs. Dual-luciferase and functional rescue experiments confirmed that *circ_0000181* stimulates the release of IL1B and IL18, promotes pyroptosis, and activates the NLRC4 inflammasome by competing with *MIR667-5p* for binding sites. These findings indicate that *circ_0000181* regulates the *MIR667-5p*-NLRC4 axis, facilitating the progression of pyroptosis in DN.

CircACTR2

CircRNA microarray analysis was used to identify dysregulated circRNAs in DKD model HK-2 cells exposed to glucose stress [267]. Under these conditions *circACTR2* is upregulated and is associated with both inflammation and pyroptosis, an inflammation-related type of cell death. *CircACTR2* effectively regulates inflammation and cell death, as its suppression significantly reduces pyroptosis, the release of the pro-inflammatory cytokine IL1B, and the synthesis of COL4 and FN1 (fibronectin 1). In summary, research has found a new circRNA called *circACTR2* that controls pyroptosis, inflammation and fibrosis in proximal tubule cells caused by high glucose levels. This suggests new treatment approaches and provides novel insights into the pathophysiology of DKD.

Circ_0004951

CircRNA expression levels in HK-2 cells exposed to high levels of glucose and in kidney biopsy samples from DKD patients have been examined [268]. The findings revealed that *circRNA_0004951* is significantly upregulated in both HK-2 cells exposed to high glucose levels and in the kidneys of DKD patients. Likewise, pyroptosis is dramatically reduced by blocking *circRNA_0004951*. *CircRNA_0004951* contains binding sites where *MIR93-5p* can interact with NLRP3 according to bioinformatics analysis. This result was further confirmed by a dual-luciferase reporter assay. Rescue experiments showed that the anti-pyroptosis and

anti-inflammatory effects of *circRNA_0004951* are significantly reduced in HK-2 cells after knockdown. This observation was explained by higher expression of NLRP3 and lower levels of *MIR93-5p*. The results of the study suggest that *circRNA_0004951* stimulates renal tubular epithelial cells to undergo pyroptosis via the *MIR93-5p*-NLRP3 inflammasome pathway in diabetic kidney disease. These results may have implications for the clinical diagnosis and treatment of DKD (Table 2).

Clinical implications

LncRNAs and circRNAs are increasingly recognized as potential biomarkers for diverse pathologies due to their tissue-specific expression patterns and dysregulation as observed in various disease states [252, 269, 270]. For instance, lncRNAs such as *CARMN* (cardiac mesoderm enhancer-associated non-coding RNA) have been identified as biomarkers and therapeutic targets in diseases such as breast and colorectal cancer, while circRNAs have shown promise in cardiology for their roles in regulating cardiac function and response to stress [271, 272]. The detailed study of their molecular actions offers exciting prospects for the creation of new diagnostic techniques, prognostic markers, and therapeutic strategies. The role of these molecules in disease mechanisms can lead to breakthroughs in how conditions are detected, monitored, and treated. The critical discoveries and their potential implications for clinical practice are detailed in Table 3, providing a clear overview of how these biomarkers could transform patient care.

It is worth emphasizing that the findings presented are still in the early stages within the scientific community, requiring further research to verify these insights and translate them into effective clinical applications. Despite being preliminary, these studies highlight the potential of lncRNAs and circRNAs as promising targets for novel therapeutic strategies for DN. This underscores the need for ongoing research to explore these RNA molecules in greater depth, which could lead to the development of innovative treatment approaches that could significantly affect the management of DN. The continuing investigation into the roles of lncRNAs and circRNAs will not only deepen our understanding of their biological functions but also enhance our ability to devise more targeted and effective therapeutic interventions.

Future directions and conclusions

The future implications for lncRNAs and circRNAs as regulators of pyroptosis in diabetic nephropathy (DN) are multifaceted and warrant deeper investigation. Our search results highlight the complex and dynamic interplay between these

Table 2 Role of circRNAs in modulating pyroptosis in diabetic nephropathy

CircRNA	Sample/cell line studied	Key findings	Target mRNAs/proteins	Effect of modulation	Potential role	References
CircLARP1B	DN patients, renal MCs treated with high glucose	*circLARP1B* and *TLR4* high expression, *MIR578* low expression	*MIR578*, *TLR4*	Reduction inhibits inflammation and pyroptosis	Understanding DN pathology and identification of novel therapeutic target	[264]
CircCOL1A2	Plasma from DN patients, HG-treated HK-2 cells	Elevated *circCOL1A2* levels	*MIR424-5p*, SGK1	Reduction diminishes oxidative stress and pyroptosis	Potential DN treatment strategy via *circCOL1A2* silencing	[265]
Circ_0000181	Kidney tissue from DN patients, STZ-induced DN mouse models	Elevated NLRC4 inflammasome levels	*MIR667-5p*, NLRC4	Promotes pyroptosis progression	Facilitates understanding of DN pathophysiology	[266]
circACTR2	HG-treated HK-2 cells	Upregulated *circACTR2* is associated with inflammation and pyroptosis	N/A	Reduction inhibits pyroptosis, inflammation and fibrosis	Identification of novel circRNA in DN pathology and treatment approaches	[267]
Circ_0004951	DKD patient kidney biopsies, HG-treated HK-2 cells	Upregulated in DKD and HG conditions, reduces inflammation	*MIR93-5p*, NLRP3	Reduction inhibits pyroptosis	Implications for clinical DKD diagnosis and treatment	[268]

Table 3 Clinical implications of lncRNA- and circRNA-mediated pyroptosis in diabetic nephropathy[a]

RNA type	Name	Function	Potential clinical implications	References
lncRNA	*PWARSN*	Modulates TXNIP-mediated pyroptosis in PTECs	Inhibition may protect PTECs and slow DN progression	[253]
lncRNA	*MALAT1*	Associated with increased pyroptosis and early DN development	Targeting *MALAT1* or upregulating *MIR30C* could serve as diagnostic and therapeutic strategies	[255]
lncRNA	*KCNQ1OT1*	Contributes to pyroptosis, oxidative stress, and inflammation in DN	Modulating the expression of *KCNQ1OT1* might offer therapeutic potential	[259]
lncRNA	*ANRIL*	Promotes pyroptosis and kidney damage	Inhibiting *ANRIL* or upregulating *MIR497* could be potential therapeutic interventions	[261]
circRNA	*circLARP1B*	Promotes pyroptosis and inhibits cell proliferation	Silencing *circLARP1B* or upregulating *MIR578* might be beneficial for DN patients	[264]
circRNA	*circCOL1A2*	Aggravates oxidative stress and pyroptosis	Inhibiting *circCOL1A2* or upregulating *MIR424-5p* could be potential therapeutic strategies	[265]
circRNA	*circ_0000181*	Promotes pyroptosis	Targeting *circ_0000181* or upregulating *MIR667-5p* could be explored as therapeutic options	[266]
circRNA	*circ_0004951*	Induces pyroptosis via the *MIR93-5p*-NLRP3 inflammasome pathway	Targeting this axis could hold potential for clinical diagnosis and treatment of DN	[268]

[a]Studies in this table were carried out in cells or using mouse models; no clinical data are currently available.

non-coding RNAs and the pyroptotic cell death pathway in the context of DN. One key future direction is to elucidate the specific mechanisms by which lncRNAs and circRNAs regulate pyroptosis in DN. Our findings indicate that these non-coding RNAs can modulate pyroptosis through various pathways, such as by targeting components of the NLRP3 inflammasome or influencing the expression of pyroptosis-related genes such as *GSDMD* and *GSDME*. Unraveling the intricate regulatory networks involving lncRNA-miRNA-mRNA and circRNA-miRNA-mRNA interactions will be crucial to understanding how these non-coding RNAs exert control over the pyroptotic machinery in DN. Additionally, the therapeutic potential of targeting lncRNA- and circRNA-mediated regulation of pyroptosis in DN warrants further exploration. Our search results suggest that restoring the dysregulated expression of specific lncRNAs and circRNAs could potentially stimulate pyroptosis in a controlled manner, thereby enhancing the clearance of damaged or dysfunctional cells and mitigating disease progression. Developing targeted delivery systems or small molecule modulators to manipulate the activity of these non-coding RNAs may pave the way for novel therapeutic interventions in DN. Furthermore, these findings highlight the importance of understanding the broader implications of lncRNA- and circRNA-mediated regulation of pyroptosis in the context of the tumor microenvironment and cancer progression. Elucidating the cross-talk between these non-coding RNAs, pyroptosis, and other cell death pathways, such as ferroptosis, may uncover new avenues for therapeutic exploration in DN, as well as in related conditions where pyroptosis plays a significant role. In conclusion, the discovery of lncRNAs and circRNAs as regulators of pyroptosis in DN represents a significant advancement in our understanding of the molecular mechanisms underlying this complex disease. Future research should focus on delineating the specific functions and regulatory mechanisms of these non-coding RNAs, as well as exploring their therapeutic potential through targeted modulation. Advancing our knowledge in this area could lead to the development of innovative, effective therapies for DN and other related conditions.

Author contribution A.AIF, D. JK, and N.F were involved in the conceptualization, original drafting, visualization, and writing—review and editing. R.JR, AR.A, and M.A contributed to the review and editing. K.H assisted in the supervision and writing—review and editing. All authors have reviewed and approved the final manuscript for publication.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication All authors have read the review and given their consent to publish.

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