

Role of Pyroptosis in Diabetes and Its Therapeutic Implications

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Abstract: Pyroptosis is mainly considered as a new pro-inflammatory mediated-programmed cell death. In addition, pyroptosis is described by gasdermin-induced pore formation on the membrane, cell swelling and rapid lysis, and several pro-inflammatory mediators interleukin-1 β (IL-1 β) and interleukin-18 (IL-18) release. Extensive studies have shown that pyroptosis is commonly involved by activating the caspase-1-dependent canonical pathway and caspase-4/5/11-dependent non-canonical pathway. However, pyroptosis facilitates local inflammation and inflammatory responses. Current researches have reported that pyroptosis promotes the progression of several diabetic complications. Emerging studies have suggested that some potential molecules targeting the pyroptosis and inflammasome signaling pathways could be a novel therapeutic avenue for managing and treating diabetes and its complications in the near future. Our narrative review concisely describes the possible mechanism of pyroptosis and its progressive understanding of the development of diabetic complications.

Keywords: diabetes, pyroptosis, GSDMD, NLRP3, caspase-1, IL-1 β , IL-18

Introduction

Diabetes mellitus (DM) is an immunological disease characterized by metabolic dysregulation and chronic inflammation.¹ However, hyperglycemia is commonly associated with the generation of ROS and the formation of AGEs.^{2–4} Chronic and low-grade inflammation has been related to hyperglycemia in diabetes. Programmed cell death plays a significant role in the hosts' advancement and survival in the body's defensive mechanism against several microbial infections.^{5–8} Apoptosis, necrosis, pyroptosis, ferroptosis, autophagy, and efferocytosis are the most common cell death mechanisms.^{9–14} Apoptosis is the most widely studied, while the research of pyroptosis is neither comprehensive nor concrete. Apoptosis-mediated cell death regulates multicellular organism development.⁹ Notably, the apoptosis-mediated cell death mechanism predominantly impairs single cells and appears without any inflammatory responses.¹⁵ Apoptosis is induced by the cell surface death-receptor stimulation, exogenous, mitochondrial, and ER stress-regulated signaling pathways facilitating caspases initiation.^{16–19} In apoptosis-mediated cell death, cells shrink and are fragmented into apoptotic bodies engulfed by surrounding macrophages, leading to cell death's non-inflammatory nature.²⁰ Inhibiting the apoptotic caspase-8 due to pro-apoptotic stimulus initiates necroptosis-regulated cell death through the receptor-interacting serine/threonine-protein kinase 1 (RIPK1)–RIPK3-mixed lineage kinase domain-like (MLKL)

axis.²¹ Mounting evidence shows that RIPK3-phosphorylated MLKL changes to the membrane to accomplish membrane rupture, promoting cell swelling as well as lysis.^{22–25}

Pyroptosis is programmed necrosis, which regulates a common innate immune effector mechanism in invertebrates.^{26,27} Significantly, the innate immune response depends on PRRs to sense and recognize several microbial products or endogenous danger signals.²⁸ Stimulating cytokine transcription and inducing PRRs cause pyroptosis to promote inflammatory response.²⁹ Pyroptosis's immune defense functions are increased by disrupting the pathogen replication niche and directly invading intracellular bacteria through pore-stimulated intracellular traps.^{30,31} For a long time, pyroptosis has been described as a caspase-1-dependent monocyte cell death mechanism.³² Caspase-1 belongs to the inflammatory caspase family group, which processes pro-IL-1 β and IL-18 into mature IL-1 β and IL-18 pro-inflammatory factors.^{33,34} These pro-inflammatory factors nature discriminate pyroptosis from apoptosis despite the dependency on caspases.^{35,36} Indeed, pyroptosis is lytic, attributing cell rupture and swelling and many bubbles blowing on the plasma membrane.^{28,37,38}

Our narrative review highlights the current understanding and knowledge of the molecular mechanism of pyroptosis-mediated cell death and the potential role of inflammasome and pyroptosis in diabetes mellitus and its complications. More in-depth research of pyroptosis-mediated cell death may produce novel insight into the pathogenesis and development of diabetes and its complications.

History of Pyroptosis

In 1986 Friedlander AM first notated cellular components' rapid release in mouse macrophages after treatment with lethal anthrax toxin.³⁹ Furthermore, Zychlinsky et al in 1992 observed *Shigella flexneri* induced mouse macrophage cell death through an apoptosis-mediated cell mechanism.⁴⁰ Regrettably, both pieces of research demonstrated the secretion of cellular contents that are stimulated by classical apoptosis. Cookson performed a combination of Greek roots to establish a novel term, "pyroptosis." The novel term pyroptosis "pyro" and "ptosis" indicate fire and falling, respectively, to describe a newly discovered inflammatory-mediated programmed cell death.⁴¹ Pyroptosis was first described to be a caspase-1-mediated pro-inflammatory programmed cell death.⁴² Many researchers have identified the

GSDMD protein molecule is the primary substrate of caspase-1 and caspase-4/5/11.^{43,44} In addition, accumulating studies have documented that gasdermin-mediated proteins commonly induce pyroptosis, and the gasdermin family groups can be cleaved by inflammatory caspases, which are essential for the activation of pyroptosis-mediated cell death.¹¹ Shao et al have suggested that pyroptosis is a gasdermin family-mediated programmed necrotic cell death.⁴⁵ The Nomenclature Committee on Cell Death (NCCD) in 2018 recommended that pyroptosis is considered a programmed cell death characterized by the formation of gasdermin mediated pores on the membrane, often but not always as the results of inflammatory caspases induction.⁴⁶

Canonical Inflammasome Signaling Pathways

Pyroptosis is a novel pro-inflammatory mediated-programmed cell death mechanism that involves innate immune response.³² The innate immune response depends on PRRs to recognize PAMPs and DAMPs.^{47,48} The PRR family members comprise NLRs and membrane-bound TLRs, mainly observed in immune and inflammatory cells, including monocytes, macrophages, and neutrophils.⁴⁷ PAMPs or DAMPs activate PRRs, leading to the initiation of inflammatory response, which secretes pro-inflammatory factors, including IL-1 β and IL-18.⁴⁹ DAMPs-induced inflammation regulates inflammatory diseases.⁵⁰ Inflammasomes are multi-molecular complexes containing PRRs family members, including TLRs, NLRs, and AIMs like receptors.^{51,52} Under several intracellular and extracellular stimulations, inflammasomes regulate the molecular signal platform to trigger caspase-1, leading to the stimulation of cell death and inflammatory responses.⁵¹ Mounting research has demonstrated several stimuli, including bacterial flagellin, lethal anthrax toxin, double-stranded DNA activates NLRs (NLRP4, AIM2, NLRP1, and Pypin), which trigger the canonical inflammasome pathways.^{53–56} Then the canonical inflammasomes convert pro-caspase-1 to caspase-1, which stimulates GSDMD protein molecule. GSDMD induces pores formation on the cell membrane and secretes the inflammatory cytokines, including IL-1 β , IL-18, and HGRB1, leading to pyroptosis-mediated cell death initiation.^{57,58} Inflammasomes, including NLRP1, NLRP3, NLRP4, AIM2, and pypin, can form inflammasome complex with the adaptor protein ASC to caspase initiation and recruitment domain ASC and stimulate caspase-1.^{35,59,60}

NLRP3 inflammasome components include sensor molecules, such as NLRP3, ASC, and pro-caspase-1.^{52,61}

Extensive studies have shown the following two steps activate the NLRP3 inflammasome. The first is regarded as the initiation phase, and the second one is the inflammasomes initiation phase.^{62,63} The initiation phase triggers NLRP3 and pro-IL-1 β and IL-18 expression in response to several microbial molecules or endogenous factors. Accumulating evidence suggests that three types of stimulators activate the NLRP3 inflammasome.^{59,62,64,65} ROS produced by mitochondria activates the NLRP3 inflammasome.⁶⁶ In addition, lysosomal membrane disruption and lysosomal devastation can induce NLRP3 inflammasome. Growing evidence reports that phagocytosis of particles, including crystals, devastates the lysosomal membrane.⁶⁷ Besides, ion efflux, such as K⁺ efflux and Ca²⁺ mobilization, promotes NLRP3 inflammasome activation.⁶⁸

Current reports have documented that miRNAs stimulate the NLRP3 inflammasome.^{69,70} MiRNAs are commonly regarded as endogenous single-stranded non-coding RNA molecules involving 21–23 nucleotides and regulate RNA silencing.^{71,72} In addition, further research

indicates that miRNAs induce the NLRP3-mediated pyroptosis signaling pathway.⁷³

Non-Classical Inflammasome Signaling Pathways

In-classical inflammasome signaling pathways, LPS activates pro-caspase-4/5/11 (Figure 1).⁷⁴ Then, the pro-caspase-4/5/11 initiates pyroptosis-mediated cell death.⁷⁵ Caspase-4/5/11 binds to LPS and can cleave the 53-kDa precursor form of GSDMD protein molecule to form the N-terminal of mature GSDMD p30 fragment, leading to pore formation on the cell membrane.⁷⁶ Caspase-4/5/11 also stimulates NLRP3-mediated caspase-1 initiation by the cleaves of GSDMD and secretion of IL-1 β /IL-18.⁷⁵ Previous research has demonstrated that caspase-11 stimulates non-canonical caspase-1-mediated IL-1 β and IL-18 pro-inflammatory factors secretion with NLRP3 and ASC inflammasome, indicating caspase-4/5/11 triggers the non-classical NLRP3 inflammasome under several microbial-induced LPS stimulations.^{77,78} Surprisingly, activated caspase-4/5/11 can cleave pannexin-11 to promote

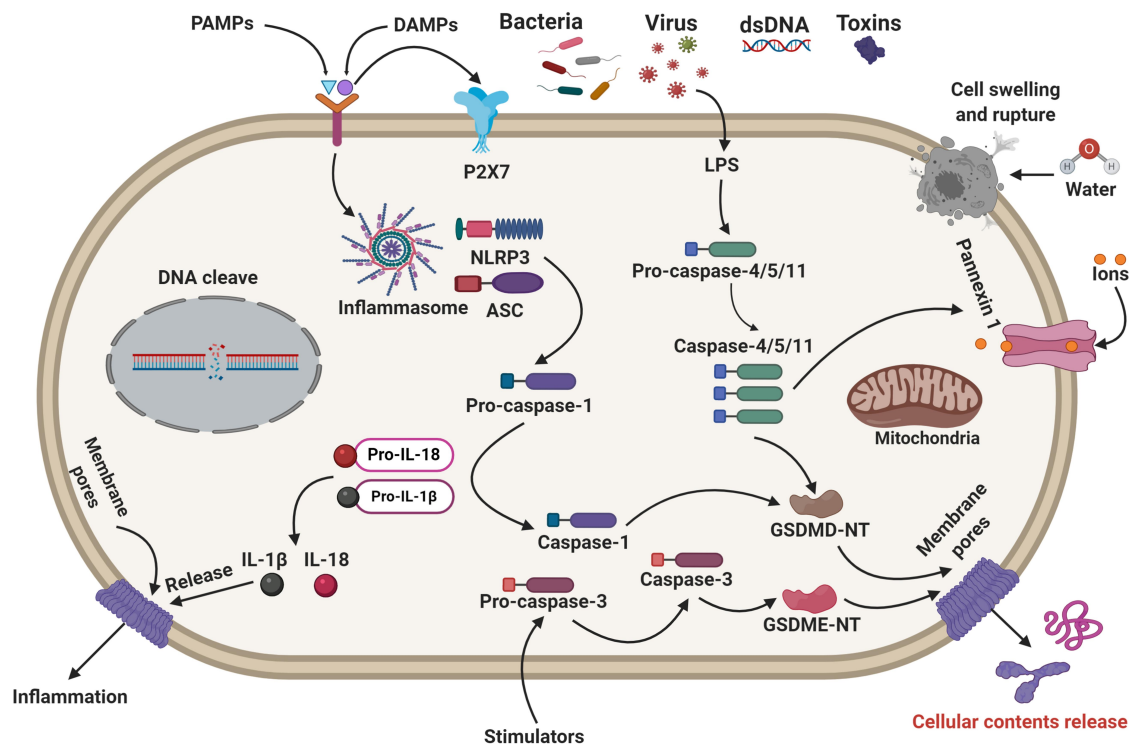


Figure 1 Molecular mechanisms of pyroptosis-regulated cell death. Pyroptosis-signaling pathways are generally activated by the stimulation of DAMPs or PAMPs triggering several inflammasomes. The stimulated inflammasome components trigger the cleavage of caspase-1. Caspase-1 can significantly cleave GSDMD to form GSDMD N-fragment and plasma membrane pores formation, leading to pyroptosis-regulated cell death. Stimulated caspase-1 leads to the maturation and secretion of IL-1 β and IL-18 inflammatory factors. Besides, LPS binds to the caspase-4/5/11 precursor; leading to the activation of pyroptosis-regulated cell death. Caspase-3/GSDME can also lead to pyroptosis-regulated cell death. Notably, mitochondrial and death receptor pathways can trigger caspase-3. Then, the activated caspase-3 cleaves GSDME to form GSDME N-fragments, leading to plasma membrane pores formation, cell swelling, and pyroptosis.

potassium efflux and ATP release. Then, the potassium ion efflux activates NLRP3-mediated pyroptotic cell death. Simultaneously, ATP-gated P2X7 receptors are initiated by new stimulators, inducing pore formation on the plasma membrane. Russo et al have reported that the non-canonical inflammasome triggers several secretory pathways, which play a significant role in Gram-negative bacterial infection.⁷⁹ Growing research has indicated that ROS can induce the non-canonical NLRP3 inflammasome by the JNK signaling pathway promoting *C. rodentium* infection-mediated colitis.⁸⁰ These findings strongly suggest that the non-canonical inflammasome signaling pathway's activation plays a critical role in multiple diseases, including cardiovascular, renal, spinal cord injury, inflammatory, and infectious diseases.

Other Signaling Pathways

Recently, emerging studies have reported that caspase-3 activation can cleave GSDME to promote a necrotic GSDME-N portion, causing pore formation on the plasma membrane.⁸¹ Particularly, caspase-3 can cleave GSDME protein molecules into N-terminal and C-terminal fragments. The N-terminal part of GSDME (GSDME-N) is generally similar to the GSDMD-N component, can stimulate pyroptosis-regulated cell death. It has been traditionally believed that caspase-3 promotes apoptosis-mediated cell death mechanisms.⁸² Moreover, the formation of the gasdermin-mediated pores promotes mitochondrial apoptotic pathways to trigger cytochrome c release. Notably, GSDME-N permeabilizes the mitochondrial membrane, which releases cytochrome c and initiates the apoptosome, indicating GSDMD-N has a similar activity.⁸² Intriguingly, Jing et al suggest that caspase-1, 3, and 7 can also cleave GSDME, leading to pyroptosis.⁸³ This finding indicates that caspase-1, 3, and 7-induced GSDME can create a prospective investigation of the pyroptosis-signaling pathways. A current study has documented that caspase-8 activates the NLRP3 inflammasome, demonstrating caspase-8 can also induce pyroptosis.⁸⁴ Recently, Oring and co-workers claimed that the tak-1 kinase suppression by the *Yersinia* effector protein molecule yopj induced caspase-8-mediated pyroptosis, illustrating caspase-8 could be another initiator of pyroptotic cell death.⁸⁴ The authors also showed that caspase-8 activation could significantly lead to GSDMD-mediated pores formation on the plasma membrane. In addition, Mandal et al have demonstrated that caspase-8 activation triggers an inflammatory response.⁸⁵

Role of Pyroptosis and Inflammasomes in the Development of Diabetes and Its Complications

The innate immune system plays a critical role in diverse pathological situations, such as autoimmune diseases. However, T1DM is an autoimmune disorder described by the destruction of the β -cell functions and reducing insulin levels. Insulin resistance and disrupted insulin secretion from pancreatic β -cells are the critical pathological conditions of T2DM. Growing research has reported that pyroptosis in β -cells promotes insulin resistance pathogenesis.^{86–88} In addition, pyroptosis plays a crucial role in developing obesity-associated inflammation and insulin resistance.⁸⁹ Recently, Ma et al also noted that the activation of pyroptosis-regulated cell death promotes β -cell destruction.⁹⁰ Carlos et al have indicated that mitochondrial DNA stimulates the NLRP3 inflammasome and predisposes T1D in a murine model.⁹¹ The authors showed that diabetic mice elevated NLRP3 and pro-IL-1 β mRNA expression levels in pancreatic lymph nodes. The NLRP3, ASC, and pro-IL-1 β mRNA expression levels were increased by multiple low doses of STZ administration in the C57BL/6 mice model.⁹¹ Elevated IL-1 β expression levels at day 7 and day 15 were notably found in the pancreatic tissue of diabetic mice. Furthermore, after STZ treatment, diabetic mice demonstrated the enhanced positive caspase-1 macrophages in the PLNs, which were remarkably downregulated in the NLRP3-gene knockout mice model. Interestingly, NLRP3- and IL-1R-gene knockout mice could tremendously improve insulin levels and downregulate hyperglycemia. NLRP3-mediated pyroptosis promotes the pathogenesis and progression of T1D.⁹¹ Recently, emerging research has reported that NLRP3 inflammasome activation promotes T2D progression and insulin resistance.^{92,93} Kursawe et al suggest that elevated NLRP3 inflammasome promotes inflammation in adipose tissues and reduces insulin sensitivity.⁹⁴ Previous studies have demonstrated the down-regulation of the NLRP3 inflammasome can considerably attenuate or prevent diet-treated insulin resistance and metabolic abnormalities.^{95,96} Kim et al have documented that over-expression of the NLRP3 inflammasome facilitates the progression of T2D in db/db mice.⁹⁷ Downregulation of the NLRP3 inflammasome can reduce immune cell accumulation to the white adipose tissue and preserve insulin sensitivity. The potential role of NLRP3 inflammasome in the pathogenesis of insulin resistance was verified in

human studies.^{98,99} TXNIP activates the caspase-1 inflammasome and regulates innate immune responses in pancreatic β -cell and macrophages.¹⁰⁰ Recent reports suggest that diabetes-mediated pyroptosis and inflammation are associated with myeloid or non-myeloid cells, which play a significant role in diabetic complications.¹⁰¹ Muller cells seem to be a prime candidate for this form of inflammation-driven cell death. Feenstra et al have documented that hyperglycemia leads to Muller cell death by introducing pyroptosis-like mechanisms.¹⁰² Therefore, these findings indicate that pyroptosis-regulated cell death plays a crucial role in the pathogenesis and development of diabetes and its complications.

Diabetic Cardiomyopathy

Diabetic cardiomyopathy (DCM) is a crucial complication of long-term chronic diabetes mellitus (DM) and is described by myocardial inflammation, fibrosis, and myocardial hypertrophy.¹⁰³ Growing evidence reports that DCM is closely related to pyroptosis associated with inflammation.^{104,105} Pyroptosis-regulated cell death plays a significant role in DCM development. Previous research has documented that pyroptosis-related proteins, including GSDMD, caspase-1, NLRP3 inflammasome, and IL-1 β expression levels are augmented in cardiac tissues.¹⁰⁶ Furthermore, immunohistochemistry staining reported that GSDMD-N, NLRP3, caspase-1, and IL-1 β expression levels were also augmented in diabetic mice models' cardiac tissues. A prior study also reported that NLRP3, caspase-1, and IL-1 β mRNA expression levels were substantially upregulated in the DM group.¹⁰⁷ Fu et al have documented that lncRNA Kcnq1ot1 regulates pyroptosis in the diabetic heart tissues.¹⁰⁶ Western blotting, qRT-PCR, and immunofluorescence staining confirm that kcnq1ot1 and pyroptosis are initiated in HG-stimulated cardiac fibroblasts. Luo et al have claimed the increased NLRP3, caspase-1, and IL-1 β expressions are closely associated with the pathogenesis of DCM progression.¹⁰⁸ Increasing research reports that non-coding RNAs (ncRNAs) play a significant role in DCM progression.¹⁰⁹ Non-coding RNAs can induce pyroptosis in DCM.^{110,111} Increased caspase-1 expression promotes DN progression via regulating miR-214-3p expression in cardiac fibroblasts. The authors transfected cardiac fibroblasts with si-Kcnq1ot1 with or without AMO-214-3p in HG conditions and found that HG promotes NLRP3 and IL-1 β expression levels.¹⁰⁶ Intriguingly, co-transfection with siKcnq1ot1 and AMO-214-3p could promote NLRP3 and IL-1 β

expression levels. Yang et al identified increased Kcnq1ot1 expression levels in diabetic patients, HG-stimulated cardiomyocytes, and diabetic cardiac tissues.¹¹¹ Silencing Kcnq1ot1 alleviates pyroptosis by targeting miR-214-3p and attenuating caspase-1 activation. Besides, silencing Kcnq1ot1 can significantly hinder cell death, cytoskeletal structure abnormalities, and higher calcium levels in vitro and improve cardiac functions and histopathological scores in the diabetic animal model. Increasing evidence reports that pyroptosis facilitates myocardial inflammation in DCM.¹⁰⁷ Wei et al have documented that hyperglycemia promotes cardiomyocyte pyroptosis via activating the AMPK-TXNIP signaling pathway in a high-fat diet-treated T2D mice model.¹¹² TXNIP overexpression leads to pyroptosis-mediated cardiomyocyte cell death.¹¹³ Therefore, TXNIP activation can play a significant role in the development of DCM. Prior research has reported that upregulation of the mir-30d can significantly promote pyroptosis in cardiomyocytes by enhancing caspase-1, IL-1 β , and IL-18 expression levels.¹¹⁴ The fundamental role of miRNAs regulating pyroptosis in DCM remains unknown. The authors evaluated the regulatory role of microRNA-30d on cardiomyocyte pyroptosis by directly targeting FoxO3a in STZ-induced diabetic rats and HG-stimulated cardiomyocytes.¹¹⁴ Cao et al have noted that NLRP3 inflammasome and pyroptosis promote HG-treated H9C2 cardiac cell injury.¹¹⁵ The author and colleagues have recently documented that NLRP3 inflammasome-dependent pyroptosis promotes the pathogenesis of non-ischemic DCM. Prior research has also reported that pyroptosis promotes DCM progression in DIC-induced cardiac dysfunction.¹¹⁶ The inflammasome markers, including TLR4 and NLRP3 inflammasome, pyroptotic indicators including caspase-1, IL-1 β , IL-18, and cell signaling proteins p-JNK, p-P38, and MyD88, M1 macrophages, and TNF- α mediator are significantly augmented in DCM experimental mice model.¹¹⁶ However, spleen tyrosine kinase-stimulated JNK-dependent NLRP3 inflammasome promotes DCM progression.¹¹⁷ Therefore, inflammasome-mediated cell death is a key player in the pathogenesis of DCM progression. Dargani et al have documented that pyroptotic indicators, such as caspase-1, IL-1 β , caspase-11, and GSDMD-N expression levels are markedly higher in doxorubicin (Dox)-induced H9c2 cell.¹¹⁸ Macrophage-derived miR-155-containing exosomes can increase cardiomyocyte pyroptosis and uremic cardiomyopathy changes, such as cardiac fibrosis and

hypertrophy by directly targeting FoxO3a in uremic mice. Wang et al have shown that AIM2 expression levels are elevated in diabetic heart tissues than in the control rats group.¹¹⁹ The authors have also shown that AIM2-gene silencing attenuates DCM progression in the T2D rat model. AIM2 promotes cell death and fibrosis via GSDMD pathway activation in HG-stimulated and ROS-mediated DCM.¹¹⁹ A recent study suggests that pyroptosis facilitates DCM progression via enhancing caspase-1 and NLRP3 inflammasome and IL-1 β pro-inflammatory mediator release.¹⁰⁷ Kar et al have documented that pyroptosis-mediated cell death can trigger cardiac dysfunctions in high-fat diet-treated diabetic C57BL6 mice.¹²⁰ Therefore, these reports illustrate that pyroptosis plays a significant role in contributing to the pathogenesis of DCM. Further exploring the essential role of pyroptosis in DCM can create a novel therapeutic avenue for treating DCM in the future.

Diabetic Nephropathy (DN)

Diabetic nephropathy (DN) is a severe complication of DM and is regarded as a sterile inflammatory disease. However, growing research suggests that pyroptosis and subsequent inflammation play a crucial role in DN progression.¹²¹ The exact molecular mechanism of pyroptosis in DN remains elusive. Zhang et al claimed that pyroptosis-regulated cell death facilitates DN's pathogenesis and progression.¹²² Previous studies also documented that pyroptosis-related proteins, including caspase-1, NLRP3, and IL-1 β expression levels, were considerably augmented in the STZ-treated diabetic rats.¹²³ The authors claimed that pyroptosis is another key player to DN progression via activating the NLRP3 inflammasome.¹²³ NLRP3 inflammasome activation promotes DN development in the diabetic mice model.¹²⁴ Shahzad et al have demonstrated that caspase-1-deficiency could hinder inflammasome activation and protect against DN in diabetic mice model, indicating pyroptosis contributes to DN progression. A recent study has documented that pyroptosis-associated proteins, including IL-1 β , caspase-1, GSDMD, and NLRP3 inflammasome expression levels are elevated in HFD/STZ diabetic mice model.¹²⁵ Numerous investigations have also reported that the NLRP3 inflammasome senses and recognizes endogenous risk signals, leading to the initiation of caspase-1 and IL-1 β , which promotes the inflammatory cascade induced-DN progression.¹²⁴ Immunofluorescence findings illustrated that pyroptosis-associated proteins, including GSDMD,

caspase-1, and NLRP3 expression levels, were augmented in diabetic renal tissues.¹²⁵ The authors evaluated the possible role of NLRP3 inflammasome and pyroptosis-signaling pathways in DN.¹²⁵ The Western blotting analysis showed that pyroptosis-associated proteins, such as GSDMD-N, NLRP3, cleave-caspase-1, p-NF- κ B, ASC, and cleaved-IL-1 β expression levels were tremendously augmented in high-fat diet/STZ diabetic mice and HG-induced podocytes.¹²⁶ In addition, the TUNEL assay and cell viability test confirm that pyroptosis-regulated cell death promotes DN progression. Extensive studies show that podocyte loss promotes DN progression.^{127,128} Cheng et al have reported that podocytes are nearly associated with pyroptosis in the diabetic kidneys.¹²² The author and colleagues have demonstrated that the caspase-11 and GSDMD-N expression levels in podocytes are augmented, escorted by decreased expression of the podocyte markers nephrin and podocin, loss and fusion in podocyte foot processes, promoted pro-inflammatory factors NF- κ B, IL-1 β , and IL-18, macrophage accumulation, glomerular matrix expansion and higher urinary albumin to creatinine ratio (UACR). Podocyte pyroptosis is characterized by inflammasome activation, which plays a crucial role in DN progression. These findings strongly indicate that pyroptosis and inflammasome activation play significant roles in podocyte loss, eventually leading to the pathogenesis of DN progression. Ding et al have recently documented that miR-21-5p in macrophage-derived EVs promote pyroptosis in podocytes by regulating A20 in DN.¹²⁹ The authors investigated whether miR-21-5p in macrophage-derived EVs could largely impact podocyte injury.¹²⁹ Flow cytometry and the Western blotting analysis indicated that pyroptosis-mediated cell death is involved in DN progression.¹²⁹ Intriguingly, caspase-11/GSDMD gene knockout can prevent pyroptosis-regulated cell death.¹²² Furthermore, the Western blotting analysis demonstrated that caspase-11, caspase-4, GSDMD-N, NF- κ B, IL-1 β , and IL-18 protein expression levels were considerably upregulated in HG-stimulated human and mouse podocytes.¹²² Caspase-4 or GSDMD knockdown by siRNA can considerably prevent notable changes.¹²² These findings report that caspase-4/11 and GSDMD-dependent pyroptosis under hyperglycemia promotes podocyte loss and DN progression. With DN research progression, the Trx-TXNIP signaling system's potential role is progressively acknowledged.¹³⁰ Current research has reported that TXNIP and inflammasome-related pathway activation promotes DN progression and the complex of NLRP3, and

TXNIP regulates the formation of NOX4-mediated NLRP3 inflammasome in hyperhomocysteinemia-stimulated glomerular damages.^{131,132} Accumulating studies report that NLRP3 inflammasome activation via TXNIP overexpression leads to DN progression (Figure 2).¹³³ The author and colleagues demonstrated severe metabolic abnormalities, disorganized ultrastructure, renal inflammation, fibrosis, cell death, and excessive stimulation of NLRP3, ASC, pro-caspase-1, activated caspase-1, and mature IL-1 β were noticeably found in diabetic rats. The author also showed the caspase-1-mediated pyroptotic cell death in vitro experiment. Long non-coding RNA MALAT1 has also been documented to be contributed to DN progression.¹³⁴ The authors evaluated the potential role of MALAT1 and miR-23c and its target gene ELAVL1 in renal tubular epithelial cells. They showed that MALAT1 expression was significantly enhanced, but miR-23c expression was lower levels in STZ-treated diabetic rats and HG-stimulated HK-2 cells.¹³⁵ Upregulation of MALAT1 or downregulation of miR-23c expression could significantly hinder pyroptosis in HK-2 cells.¹³⁵ Further research has documented that LncRNA MALAT1 can promote HG-stimulated pyroptosis in renal tubular epithelial cell by sponging miR-30c and targeting NLRP3 inflammasome.¹³⁶ The authors revealed the

downregulated MALAT1 and miR-30c expression levels in HG-induced HK-2 cells, leading to the activation of NLRP3 inflammasome and pyroptosis.¹³⁶ Intriguingly, MALAT1 knockdown or miR-30c overexpression could protect HK-2 cells from HG-stimulated pyroptosis.¹³⁶ In contrast, the authors found MALAT1 expression could significantly promote the NLRP3 inflammasome by sponging miR-30c through dual-luciferase reporter assay. Furthermore, sh-MALAT1 and miR-30c inhibitor's co-transfection could considerably invert the protective effects of the sh-MALAT1 on HG-stimulated pyroptosis. These notable findings verified that MALAT1 stimulated HK-2 cell pyroptosis by suppressing miR-30c and targeting NLRP3 inflammasome, facilitating to a better understanding of DN pathogenesis. Zhu et al have reported that lncRNA KCNQ10T1 promotes oxidative stress and pyroptosis in HG-treated renal tubular epithelial cells.¹³⁷ The authors have performed RT-qPCR analysis to determine the KCNQ10T1 expression levels in serum with DN and HG-treated HK-2 cells, analyze the GSDMD-N, NLRP3, cleaved-caspase-1, pro-caspase-1, IL-1 β , and p-IL-1 β expression in HG-treated HK-2 cells, and verify the transfection effects. ELISA analysis detected the increased TNF- α , IL-6, and MCP-1 serum levels. These findings indicate that pyroptosis-mediated inflammation promotes

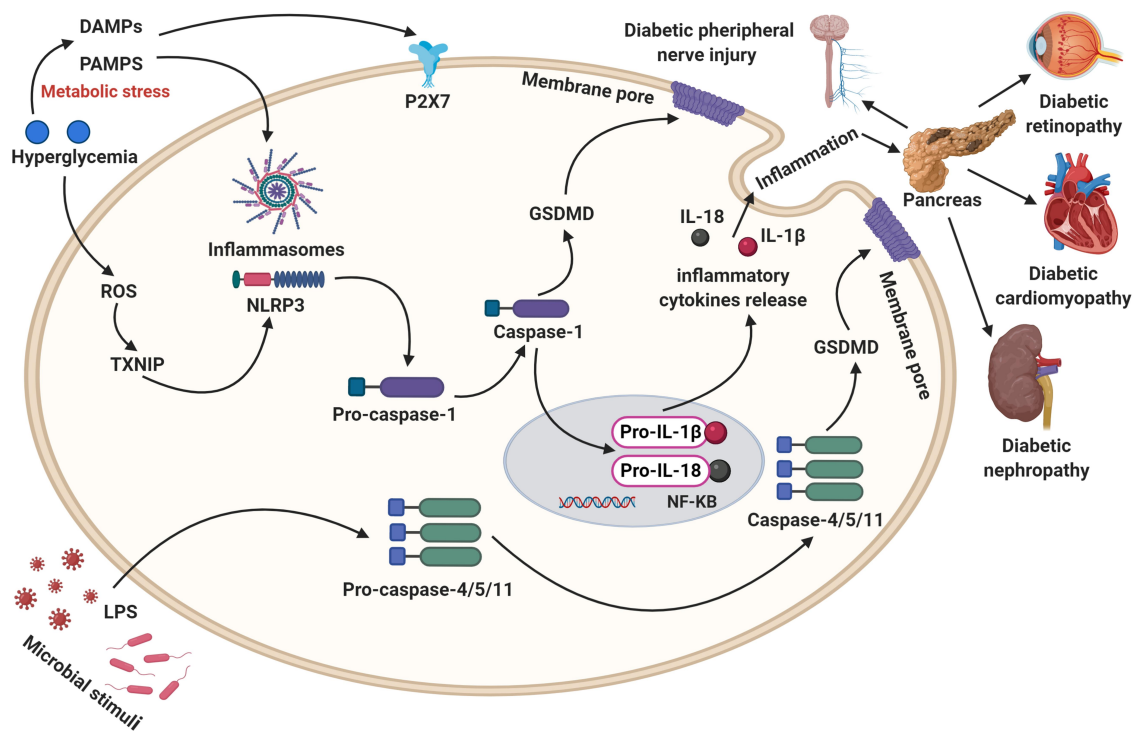


Figure 2 Activating the caspase-1/4/5/8/11 signaling pathways, inflammatory factors including IL-1 β and IL-18 release, and ROS generation, leading to GSDMD/GSDME-mediated pore formation as well as cell lysis and promote the development of diabetic complications.

DN pathogenesis. Song et al have reported long non-coding RNA LINC00339 can significantly facilitate renal tubular epithelial pyroptosis by regulating the miR-22-3p/NLRP3 signaling axis in calcium oxalate-stimulated diabetic kidney stone.¹³⁸ The author and colleagues determined the pyroptosis-regulated cell death by lactate dehydrogenase release and active caspase-1-propidium iodide double staining.¹³⁸ They performed luciferase reporter to confirm whether miR-22-3p could bind to LINC00339 or NLRP3 inflammasome. The authors reported enhanced LINC00339, downregulated miR-22-3p, NLRP3 inflammasome stimulation, and promoted cell pyroptosis in COM-induced HK-2 cells.¹³⁸ Furthermore, LINC00339 and NLRP3 overexpression can significantly promote pyroptosis in COM-induced HK-2 cells, whereas miR-22-3p mimics and NLRP3 knockdown provide the contrary effects. These findings suggest that NLRP3 inflammasome mediated pyroptosis death plays a significant role in DCM progression. Qiao et al have established the Syk/JNK/NLRP3 signaling axis might play a crucial role in DN.¹³⁹ A recent study documented that decreased GAS5 expression could promote TNF- α , IL-6, MCP-1, ROS expression levels in HG-stimulated renal tubular cells.¹⁴⁰ Besides, reduced GAS5 expression can significantly promote NLRP3, caspase-1, IL-1 β , and GSDMD-N expression levels, and the results of immunofluorescence confirmed the critical findings.¹⁴⁰ Notably, the miR-452-5p disruption could promote similar changes as GAS5 overexpression for HG-treated HK-2 cells, and GAS5 suppression could lead to opposite the potential effects of miR-452-5p disruption. Emerging research has reported increased pyroptosis-regulated proteins, including GSDMD, caspase-1, IL-1 β , and IL-18 expression and lowered serum levels of IL-1 β and IL-18, and enhanced catheter activities B and cathepsin L can promote DN progression in the diabetic SD rats.¹⁴¹

Diabetic Retinopathy

Diabetic retinopathy (DR) is one of the most critical causes of visual damage and accumulated blindness among adults worldwide. Retinal microvascular pericyte deficiency is one of the earliest pathological alterations associated with DR. However, long noncoding RNA MIAT regulates DR's microvascular dysfunctions. Accumulating research has demonstrated that pyroptosis and inflammasome activation leads to DR progression. The potential role of pyroptosis in retinal pericytes loss in DR remains elusive. Yu et al investigated pyroptosis's

role in primary HRPCs.¹⁴² The authors implemented advanced glycation end product modified bovine serum albumin (AGE-BSA) to induce DR progression and demonstrated that AGE-BSA triggered the cleavage of caspase-1 and GSDMD, release of IL-1 β , IL-18, and LDH, and decreased cell viability.¹⁴² Notably, Immunofluorescence staining indicated pyroptosis's phenotypic features, such as pyknosis, swelling, cellular disruption, and hyperpermeability in plasmalemma. The authors claimed that pyroptosis plays a critical role in DR progression.¹⁴² Loukovaara et al have reported that caspase-1, ASC, and IL-18 expression levels are increased in PDR eyes.¹⁴³ NLRP3 inflammasome activation can be associated with the pathogenesis of PDR.¹⁴³ Immunohistochemistry staining and RT-PCR analysis indicate that NLRP3, ASC, and cleaved-caspase-1 expression levels are upregulated in STZ-induced diabetes' retinas rats.¹⁴⁴ These notable findings indicate that inflammasomes-induced pyroptosis promotes DR progression. Previous studies have reported that HG can significantly induce the NLRP3-caspase-1-GSDMD axis and pore formation in the cell membrane in a dose- and time-dependent manner.¹⁴⁵ Furthermore, the GSDMD, GSDMD-N, NLRP3, caspase-1, cleaved-caspase-1, and cleaved-IL-1 β expression levels were remarkably augmented in lysates of HRP. Immunofluorescence staining also confirms the caspase-1-dependent pyroptosis promotes human ARPE-19 cell death.¹⁴⁶ Plasmids overexpressing human GSDMD-N with a GFP tag or pEGFP-C1 control plasmid were designed to measure the potential role of GSDMD-N overexpressed in HG-induced inflammation and HRP's pyroptosis cell death.¹⁴⁵ Immunofluorescence staining indicates increased GSDMD-N expression levels in HRP. Fluorometric plots also demonstrate PI uptakes over time to show the kinetics of pore appearance in HRP. These findings indicate that GSDMD-mediated HRP's cell death plays a significant role in DR progression. Chien et al have reported that caspase-1, IL-1 β , and IL-18 mRNA expression levels are considerably higher in MCMV-infected eyes of MAIDS-10 mice.¹⁴⁷ The authors have also documented that pyroptosis participates simultaneously in MAIDS-related MCMV retinitis. Growing research demonstrates that NLRP3 inflammasome activation promotes bystander cone-photoreceptor cell death in a P23H rhodopsin model of retinal degeneration.¹⁴⁸ Elevated NLRP3 and caspase-1, mature IL-1 β and IL-18 expression levels, and enhanced cell survival with N-acetylcysteine treatment suggest inflammasome

activation leads to cone cell death.¹⁴⁸ P2RX7 receptors induce the NLRP3 inflammasome and promote IL-1 β and IL-18 secretion, leading to pyroptosis cone cell death.¹⁴⁹ P2RX7 receptors respond to local extracellular ATP levels, and it has been reported that P23H retina tissue promotes ATP levels.^{150,151} Author and colleagues proposed that rod photoreceptors undergoing necroptotic cell death release their cellular components including ATP and HMGB1, which lead to inflammasome activation in cones.¹⁴⁸ Caspase-1-mediated pyroptosis triggers photoreceptor cell death in photo-oxidative damage-produced retinal degeneration.¹⁵² As a consequence, these outcomes report that P2RX7 plays a significant role in DN progression. Zha et al have documented that down-regulation of METTL3 promotes HG-treated RPE cell pyroptosis by regulating the miR-25-3p/PTEN/Akt signaling axis through DGCR8.¹⁵³ Therefore, METTL3 regulates the pathogenesis of DR.¹⁵³ Extensive reports have documented a potential role of pro-inflammatory and pro-apoptotic TXNIP in developing both T1 and T2D and its vascular complications.^{154,155} TXNIP is highly upregulated in diabetic retinal tissues and HG-treated retinal cell culture. Multiple non-mutually unique mechanisms of inflammasome initiation in DR have been projected.^{156,157} Hyperglycemia-mediated ROS synthesis promotes NLRP3 inflammasome activation through dissociation of TRX1-TXNIP and aggregation of AGEs and ALEs. Previous studies have also reported that the NLRP3 inflammasome activation via TXNIP overexpression promotes DR progression.^{156,158} Perrone et al showed that overactivation of TXNIP leads to DR progression.¹⁵⁹ TXNIP-induced inflammasome activation promotes diabetic ocular complications.¹⁵⁹ In a previous study, authors and colleagues have reported that ROS-TXNIP pathway mediates NLRP3 inflammasome activation promoting HRMECs death.¹⁶⁰ Decreased miR-590-3p activates pyroptosis by enhancing the NLRP1 inflammasome and inducing the NOX4/ROS/TXNIP/NLRP3 signaling pathway. These notable findings indicate that inflammasome-induced pyroptosis contributes to the pathogenesis and progression of DR.

Diabetic Peripheral Neuropathy (DPN)

Diabetic peripheral neuropathy (DPN) is a common and severe complication of DM. The early changes in patients with DPN include accumulation of the extracellular matrix

proteins, chronic inflammation, axonal degeneration, and loss of the unmyelinated fibers, leading to sensorimotor conduction delays and irreversible nerve damage. Current research has documented that pyroptosis and inflammasome play significant roles in DPN progression.¹⁶¹ However, Sun et al have reported pyroptosis-mediated proteins, including GSDMD, NLRP3, pro-caspase-1, cleaved-caspase-1, and IL-1 β expression levels, are substantially higher in STZ-induced diabetic rat peripheral tissues.¹⁶¹ ELISA analysis reported that serum IL-1 β and IL-18 levels are tremendously augmented in STZ-treated DPN injured experimental rats.¹⁶² Excessive ROS generation and NLRP3 inflammasome activation promote inflammation and pyroptosis in DPN.^{156,163} Author and colleagues have evaluated the potential effects of mediating TXNIP on pre-diabetic neuropathy and its actual molecular mechanism in HFD-treated diabetic mice and palmitate-stimulated neurons.¹⁶⁴ TXNIP activation is commonly associated with pre-diabetic neuropathy in the HFD-fed mice model. Zhou et al demonstrated that TXNIP/NLRP3 inflammasome activation could promote the pathogenesis of diabetes and regulate miR-23a mediated neuropathic pain in spinal glial cells.¹⁶⁵ Previous research has also reported that NLRP3 inflammasome activation plays a significant role in DPN progression.¹⁶⁴ Cheng et al have reported that Schwann cell pyroptosis further promotes DPN progression.¹⁶⁶ The authors evaluated pyroptosis-signaling pathways in HG-treated rat Schwann cell line RSC96. Importantly, they found higher cleaved-GSDMD, NLRP3, P2X7, TXNIP, ASC, caspase-1, IL-1 β , and IL-18 expression levels in HG-treated RSC96 cells. Immunofluorescence staining and quantitative RT-PCR confirmed that the pyroptosis-associated proteins are significantly enhanced in HG-stimulated RSC96 cells.¹⁶⁶ Furthermore, increased ROS generation and NF- κ B nuclear translocation are notably observed in HG-stimulated RSC96 cells. These findings strongly indicate that pyroptosis plays a significant role in DPN development.

Targeting Inflammasome and Pyroptosis for the Therapeutic Implications of Diabetic Complications

Metformin (MET) is an antidiabetic drug widely used for treating T2D. Current studies have documented that MET exerts powerful anti-aging, anti-tumor, and cardioprotective

effects.^{167,168} However, the actual mechanism of MET in regulating the NLRP3 inflammasome and pyroptosis in DCM remains elusive. Yang et al have demonstrated that MET administration can reduce mTOR, NLRP3, caspase-1, GSDMD-N, and IL-1 β protein expression levels in STZ-induced diabetic C57BL/6 mice models and HG-treated primary cardiomyocytes from neonatal mice.¹⁶⁹ Immunohistochemistry staining shows the NLRP3, caspase-1, and IL-1 β protein expression levels are considerably lower in the MET-treated DCM mice model.¹⁶⁹ In addition, immunofluorescence staining reports that MET treatment could hinder GSDMD-mediated pyroptosis in HG-treated primary cardiomyocytes. MET treatment could hinder the NLRP3 inflammasome activation via promoting the AMPK/mTOR signaling pathway in diabetic mice model. Besides, MET treatment can induce AMPK, thus promoting autophagy via hindering the mTOR signaling pathway and suppressing pyroptosis in DCM. A previous study has suggested that Ac-YVAD-CMK, BAY11-7082, or NAC attenuate HG- and H/R-stimulated H9C2 cell injury and suppress NLRP3 inflammasome-dependent pyroptosis.¹⁷⁰ Suppression of the NLRP3 inflammasome and ROS synthesis attenuates cell injury and pyroptosis in LPS-stimulated H9C2 cells under HG and H/R conditions.¹⁷⁰ BAY11-7082 and NAC treatment can hinder NLRP3 inflammasome by decreasing the NLRP3, ASC, and NF- κ B p65 protein expression levels in LPS and HG+H/R-stimulated H9C2 cells. In addition, Ac-YVAD-CMK and BAY11-7082 treatment can promote cell viability. These findings suggest that Ac-YVAD-CMK and BAY11-7082 can suppress pyroptosis for the novel therapeutic approach in treating DCM. Jeyabal et al have reported that treatment with miR-9 mimics can hinder hyperglycemia-stimulated ELAVL1 and suppress pyroptosis in cardiomyocytes.¹⁷¹ MicroRNA-9 suppresses HG-stimulated pyroptosis by targeting ELAVL1 in human ventricular cardiomyocytes.¹⁷¹ ELAVL1 knockdown also suppresses the canonical inflammasome pathway and pyroptotic cell death in mouse macrophage RAW 264.7 cells.¹⁷¹ MiRNAs are small endogenous non-coding RNAs that contribute to DCM progression. The knockdown of miR-30d can significantly suppress cardiomyocyte pyroptosis in DCM.¹¹⁴ The author and colleagues suggest that miR-30d may be a potential therapeutic target in treating DCM. RNA Kcnq1ot1 promotes several pathophysiological mechanisms of multiple diseases, including arrhythmia and acute myocardial damage. The potential role of Kcnq1ot1 regulating pyroptosis in HG-induced cardiac fibroblasts remains unclear. Kcnq1ot1 silencing by

a lentivirus-shRNA can promote cardiac function and inhibit pyroptosis-signaling pathways in the STZ-induced C57BL/6 mice models.¹⁰⁶ Growing evidence suggests that NLRP3-gene silencing ameliorates cardiac inflammation and pyroptosis in the STZ-induced T2D rat model.¹⁷² Furthermore, silencing of the NLRP3 inflammasome suppresses cardiomyocyte pyroptosis in HG-treated H9c2. Interestingly, ROS inhibition can reduce NF- κ B phosphorylation, TXNIP, NLRP3 inflammasome, and mature IL-1 β in HG-stimulated H9c2 cells. Importantly, NF- κ B inhibition attenuates the NLRP3 inflammasome activation. TXNIP-siRNA can significantly reduce the stimulation of caspase-1 and IL-1 β .¹⁷² Wei et al have reported that the TXNIP-gene silencing reduces the NLRP3 inflammasome expression and inhibits caspase-1 activation and IL-1 β secretion in HG-stimulated cardiomyocytes.¹¹² Therefore, inhibiting the TXNIP-induced NLRP3 inflammasome could be a novel therapeutic target in treating DCM in the future. AIM2-gene silencing alleviates cardiac dysfunctions, promoting a metabolic disorder and ventricular remodeling in the STZ-induced diabetic rat model.¹¹⁹ AIM2-siRNA suppresses GSDMD-N-associated pyroptosis in H9c2 cardiomyoblasts.¹¹⁹ Xie et al have reported that the silencing of CMKLR1 in DCM rats attenuates the NLRP3 and caspase-1 and IL-1 β protein expression levels.¹⁰⁷ The authors have demonstrated that the silencing of either CMKLR1 or NLRP3 can significantly suppress caspase-1 and IL-1 β expression levels. These findings show that CMKLR1-gene silencing can have a protective effect against DCM. The emerging study also reported that knockdown of the CACR in cardiomyocytes opposed HG-stimulated caspase-1 activation.¹⁷³ Intriguingly, miR-214-3p knockdown could partly abolish the favorable outcomes of CACR silencing on pyroptosis in cardiomyocytes.¹⁷³ These important findings suggest that CACR could be a promising therapeutic avenue via CACR/miR-214-3p/caspase-1 pathways in DCM. Exendin-4 is considered a GLP analog and has a prolonged half-life than GLP-1 by shirking removal through DPP-4. Exendin-4 is a potent pyroptotic blocker preserving against hyperglycemia-stimulated cardiomyocyte pyroptosis via regulating the AMPK-TXNIP signaling axis.¹¹² Ye et al reported that inhibition of the SGLT-2 with dapagliflozin could reduce the NLRP3/ASC inflammasome and attenuate DCM progression in the T2D diabetic mice model (Table 1).¹⁷⁴ The authors also reported that inhibition of the SGLT-2 with dapagliflozin could suppress the NLRP3, caspase-1, ASC, IL-1 β , IL-18, and TNF- α mRNA expression levels in

Table I Compounds Inhibiting Pyroptosis-Signal Pathway to Treat and Manage Diabetic Complications

Classification	Compounds	Complications	Mechanism of Pyroptosis Inhibition	References
Reagent	Metformin	DCM	NLRP3/caspase-1/GSDMD-N/IL-1 β and IL-18	169
	Ac-YVAD-CMK	DCM/DN	NLRP3/caspase-1/GSDMD-N/IL-1 β and IL-18	170,184
	BAY11-7082 and NAC	DCM	NLRP3/ASC/caspase-1/GSDMD-N/IL-1 β and IL-18	170
	Exendin-4	DCM	TXNIP/NLRP3/caspase-1 and GSDMD	112
	Dapagliflozin	DCM	NLRP3/caspase-1/ASC/IL-1 β and IL-18	174
	Rosuvastatin	DCM	TXNIP/NLRP3/ASC/pro-caspase-1 and caspase-1	108
	Sodium butyrate	DN	Cleaved-caspase-1/GSDMD-N/IL-1 β and IL-18	180
	TAK-242	DN	Caspase-1/GSDMD	181
	STF-083010	DN	NLRP3/ASC/cleaved-caspase-1 and GSDMD-N	182
	Glyburide or Ac-YVAD-CMK	DR	NLRP3/caspase-1 and GSDMD	184
MCC950	DR	Nek7/NLRP3/IL-1 β and IL-18	198	
Natural	H3 relaxin	DCM	NLRP3/IL-1 β and IL-18	176
	Vaspin	DCM	NLRP3/cleaved-caspase-1 and IL-1 β	177
	Gypenosides	DCM	ROS/NLRP3/caspase-1/IL-1 β and IL-18	178
	MSCs	DCM	NLRP3/ASC/caspase-1/IL-1 β and IL-18	179
	Geniposide	DN	NLRP3/ASC/cleaved-caspase-1/GSDMD-N and cleaved-IL-1 β	126
	Punicalagin	DN	NLRP3/caspase-1/GSDMD and IL-1 β	125
	Vitamin D3	DR	ROS/TXNIP and NLRP3	194
	Methylene blue	DR	NLRP3/ASC/pro-caspase-1/caspase-1/IL-1 β and IL-18	195
	Sulforaphane	DR	NLRP3/ASC/cleaved-caspase-1 p20/IL-1 β and IL-18	196
	Jinmaitong	DPN	TXNIP/NLRP3/cleaved-caspase-1/GSDMD/IL-1 β and IL-18	161
Loganin	DPN	NLRP3/ASC/caspase-1/IL-1 β and IL-18	166	

cardiac tissues of the T2D mice model. Li et al have shown that Klotho can improve DCM by inhibiting the NLRP3 inflammasome.¹⁷⁵ The authors documented that Klotho's protective effect on diabetes-mediated cardiac injury is intensively associated with the suppression of NLRP3 inflammasome, recommending its potential therapeutic effects in treating DCM. Zhang et al have suggested that H3 relaxin treatment for two weeks can protect against myocardial injury in experimental DCM by suppressing the NLRP3 inflammasome, IL-1 β , and IL-18 expression levels.¹⁷⁶ Thus, this study recommends that H3 relaxin could be a novel therapeutic agent for DCM treatment. Growing research shows that vaspin ameliorates myocardial injury in rats' DCM model by suppressing the NLRP3 inflammasome and reducing the cleavage of caspase-1 and maturation of IL-1 β in STZ-induced diabetic cardiac tissues and HG-stimulated H9C2 cells.¹⁷⁷ Gypenosides are the major ingredients of *Gynostemma pentaphyllum* that have exerted significant anti-hyperglycemia and anti-inflammation effects. Zhang et al have reported that Gypenosides treatment can improve DCM by hindering

ROS-mediated NLRP3 inflammasome activation.¹⁷⁸ Previous studies have documented that MSCs exert substantial cardioprotective effects in CVB3-stimulated myocarditis. MSCs can significantly hinder NLRP3 inflammasome in CVB3-triggered inflammatory DCM.¹⁷⁹ Rosuvastatin alleviates DCM by attenuating the NLRP3 inflammasome and MAPK pathway in a T2D rat model.¹⁰⁸ These findings suggest that inhibiting the pyroptosis and inflammasome factors might be a promising therapeutic avenue in treating DCM.

Sodium butyrate (NaB) has potential anti-inflammatory activities in the DN mice model and HG-stimulated mouse glomerular mesangial cells. Gu et al performed an investigation to explore the possible therapeutic effects of NaB regulating pyroptosis in HG-treated renal glomerular endothelial cells (GECs).¹⁸⁰ Exogenous NaB administration can suppress the pyroptosis-associated proteins, including GSDMD-N, caspase-1, and IL-18 expression levels in HG-induced GECs. Furthermore, caspase-1 blocker Ac-YVAD-CMK or GSDMD-gene silencing could significantly attenuate DN progression. The authors

also indicated that PI-positive cells were further promoted by hindering the caspase-1 and GSDMD pathway. Therefore, suppression of the pyroptosis-regulated cell death attenuates DN progression. Blocking the TLR4 prevents tubular cell injury by attenuating GSDMD-mediated pyroptosis in db/db mice model.¹⁸¹ TLR4 or NF- κ B inhibition reduces GSDMD-NT, p-p65, and caspase-1 p20 expression levels in HG-treated HK-2 cells.¹⁸¹ This study suggests that suppressing the pyroptosis-mediated cell death could be a novel therapeutic strategy for DN treatment. Accumulating results report that Geniposide (GE) can effectively suppress DN progression. Li et al have demonstrated that GE can significantly alleviate DN by suppressing pyroptosis-related proteins, such as p-NF- κ B, NLRP3, and ASC cleaved-caspase-1, GSDMD-N, and cleaved-IL-1 β expression levels in STZ-treated DN mice and HG-induced podocyte injury models.¹²⁶ GE alleviates renal dysfunctions by attenuating BUN, Scr, TNF- α , IL-1 β , and IL-6 expression levels. Histological findings indicate GE administration efficaciously attenuates renal damages, including glomerular basement membrane thickening and inflammatory cell accumulation. These remarkable findings recommend that GE could be a prospective therapeutic molecule targeting pyroptosis-signaling pathways for DN treatment. TUNEL staining indicates that administration of the TLR4 blocker TAK-242 can significantly suppress tubular cell death in the kidneys of diabetic mice model.¹⁸¹ These crucial findings suggest that the TLR4/NF- κ B signaling-pathway inhibition could be a promising therapeutic avenue to prevent and treat DN. A recent study has also reported that inhibiting TXNIP can attenuate NLRP3, ASC, cleaved-caspase-1, and GSDMD-N expression levels in DN rats.¹⁸² TUNNEL staining indicates that the ER-stress induced TXNIP molecule inhibition can tremendously reduce NRK-52E cell death.¹⁸² The current study also suggests that IRE1- α inhibitor STF-083010 treatment can inhibit pyroptosis-mediated renal tubular epithelial cell death. These findings suggest that inhibiting the ER-mediated pyroptosis could be another novel therapeutic strategy for managing and treating DN in the near future. Punicalagin (PU) has substantial anti-inflammatory properties and can alleviate DN progression. The Western blotting analysis has confirmed that PU administration can tremendously inhibit NLRP3, GSDMD, and caspase-1 expression levels in diabetic mice models.¹²⁵ PU administration can also inhibit the IL-1 β inflammatory factor secretion in the kidney tissues of HFD/STZ-treated diabetic animals. Suppressing the

pyroptosis-mediated inflammatory response plays a vital role in the protective effects of PU. These findings strongly conclude that the TXNIP/NLRP3 signaling axis is a crucial player promoting DN progression, and PU can be a potential therapeutic agent in treating DN. Previous studies have shown that caspase-4/11 or GSDMD knockdown by siRNA can considerably attenuate DN progression.¹²² lncRNAs improve DN by changing miRNAs expression. Xie et al demonstrated that GAS5 overexpression could considerably attenuate GSDMD-N, NLRP3, caspase-1, and IL-1 β expression levels.¹⁴⁰ Immunofluorescence also verified GAS5 overexpression could significantly decrease that pyroptosis-related protein expression levels. Wen et al have reported that circACTR2 knockdown inhibits pyroptosis and reduces IL-1 β secretion in HG-stimulated fibrosis in renal tubular cells.¹⁸³ The authors have detected a new circRNA, circACTR2, that modulates HG-stimulated fibrosis, inflammation, and pyroptosis in proximal tubular cells. Therefore, targeting the circRNAs can serve unique insight regulating pyroptosis into DN's pathogenesis and create a novel therapeutic strategy in the future.

Recent research has reported that caspase-1 blocker YVAD or NLRP3 blocker glyburide can significantly suppress GSDMD, NLRP3, caspase-1 protein expression levels in retinal pericytes.¹⁸⁴ Notably, the silencing of GSDMD can also inhibit HG-induced retinal pericytes. Studies have documented that miRNAs play a significant role in the pathogenesis of DR development by regulating cell proliferation, migration, and death.^{185–187} Gu et al have established miR-590-3 to suppress pyroptosis in DR by targeting the NLRP1 inflammasome and inhibiting the NOX4 signaling pathway in HRMECs.¹⁸⁸ The author and colleagues have demonstrated that the miR-590-3p overexpression or NLRP1 and NOX4 knockdown can promote cell activity and suppress HRMECs pyroptosis. Immunofluorescence staining and cell viability assay confirm that miR-590-3p overexpression can significantly suppress caspase-1-dependent pyroptosis in HRMECs. The authors claimed that targeting the miR-590-3 and NOX4/ROS/TXNIP/NLRP3 signaling axis could be a novel therapeutic avenue in treating DR. Previous reports indicate that METTL3 regulates multiple cell functions and diseases by modulating N⁶-methyladenosine (m⁶A) modifications.^{189–191} Upregulation of METTL3 and miR-25-3p can alleviate the cytotoxic effects of HG on RPE cells, and knockdown of METTL3 and miR-25-3p had a contrary impact.¹⁵³ Furthermore, METTL3

overexpression can promote miR-25-3p expression in RPE cells in a microprocessor protein DGCR8-dependent manner, and miR-25-3p removal abolishes the effects of overexpressed METTL3 on cell functions in HG-induced RPE cells.¹⁵³ More importantly, METTL3 overexpression can attenuate GSDMD, caspase-1, NLRP3, IL-1 β , and IL-18 pyroptosis-related proteins and mRNA expression levels in HG-stimulated RPE cells.¹⁵³ Flow cytometry and CCK-8 tests confirm that METTL3 overexpression levels can significantly suppress pyroptotic RPE cells in HG conditions. Therefore, METTL3 may help to discover a potential therapeutic gateway for DR treatment in the clinic. Zhang et al reported that the upregulation of miR-214 could remarkably attenuate pyroptosis. KCNQ1OT1 knockdown using a small interfering RNA can reduce pyroptosis-related markers expression.¹⁹² The authors suggest that the KCNQ1OT1/miR-214/caspase-1 signaling pathway shows a novel diabetic corneal endothelial keratopathy progression and can be a promising therapeutic target in the future.¹⁹² In addition, increasing evidence suggests that vitamin D3 has substantial therapeutic effects in treating DR.¹⁹³ Vitamin D3 administration can significantly protect against DR by inhibiting the HG-induced ROS/TXNIP/NLRP3 inflammasome signaling pathway.¹⁹⁴ Methylene blue (MB) administration can tremendously attenuate DR by impeding the NLRP3 inflammasome activation in STZ-treated diabetic rats.¹⁹⁵ Thus, MB treatment can be a potential therapeutic molecule in treating DR. Sulforaphane (SFN) is abundant in cruciferous plants, serving substantial protective effects against multiple chronic diseases. Previous research demonstrated that NLRP3, ASC, cleaved-caspase-1 p20, and IL-1 β expression levels were tremendously reduced in SFN-treated diabetic mice retinal tissues.¹⁹⁶ MCC950 is considered an effective and definite blocker of the NLRP3 inflammasome.¹⁹⁷ Zhang et al have investigated the substantial anti-inflammatory activities of MCC950 on HG-treated HRECs.¹⁹⁸ The authors have demonstrated that MCC950 can significantly inhibit Nek7, NLRP3 expression, and IL-1 β secretion in HG-induced HRECs. This study suggested that MCC950 could suppress HRECs dysfunction under HG conditions. This research can provide new insights for a future pharmacological therapeutic approach in treating DR in the future. PKR may regulate the NLRP3 inflammasome, and PKR deficiency can downregulate NLRP3, IL-1 β , and HMGB1 expression levels in macrophages.¹⁹⁹ Jiang et al have documented that Epacl1 attenuates PKR to downregulate the NLRP3 inflammasome in HG-induced RECs.²⁰⁰ These

shreds of evidence suggest that suppressing the NLRP3 inflammasome could be a promising therapeutic target in treating DR in the near future.

Jinmaitong (JMT) is regarded as a traditional Chinese medicine used in treating multiple diseases.^{201,202} Extensive studies have reported that JMT has significant clinical efficacy to prevent and treat DPN.^{202,203} However, Sun et al have documented that JMT treatment can significantly downregulate the GSDMDC1, NLRP3, TXNIP, cleaved-caspase-1, IL-1 β , and IL-18 expression levels in the STZ-treated rat model.¹⁶¹ Furthermore, immunohistochemical assay indicates that JMT treatment can also hinder TXNIP-induced NLRP3 inflammasome in SNs of diabetic rats. The authors suggest that JMT can be a potential therapeutic candidate targeting pyroptosis in treating and managing DPN. Loganin (LOG) is an iridoid glycoside extracted from the fruit *Cornus officinalis*. Previous investigations have reported that LOG has substantial antioxidant, anti-inflammatory, neuroprotective effects.^{204–206} Cheng et al documented that LOG treatment could significantly suppress pyroptosis-related proteins and mRNA expression levels in HG-induced rat Schwann cell line RSC96.¹⁶⁶ The authors demonstrated that LOG treatment could suppress Schwann cell pyroptosis by attenuating ROS synthesis and NLRP3 inflammasome. These findings suggest that LOG could be a novel therapeutic agent suppressing pyroptosis and inflammasome to treat DPN.

Conclusion and Future Prospectives

Pyroptosis is considered a pro-inflammatory programmed cell death mechanism. Studies have implicated that pyroptosis plays a crucial role in multiple diseases, such as liver disease, cardiovascular, cancer metastasis, immunological diseases, and CNS disorder. However, the activation of pyroptosis and its actual mechanism remains elusive in diabetes. Extensive reports have documented that pyroptosis plays a critical role in the development of diabetes and its complications. Targeting pyroptosis and inflammasome components has been exceptional attention to the researchers and clinicians. Recent research strongly suggests that some potential molecules can be applied to suppress the pyroptosis and inflammasome signaling pathways for a novel therapeutic target to treat diabetes in the near future. Our narrative review highlighted the significant role of pyroptosis and inflammasome in diabetic complications (Figure 3). Moreover, our article illustrated some potential agents that could be a possible therapeutic target for the management and treatment of diabetes and its complications. The studies on the fundamental role of pyroptosis-mediated cell death in

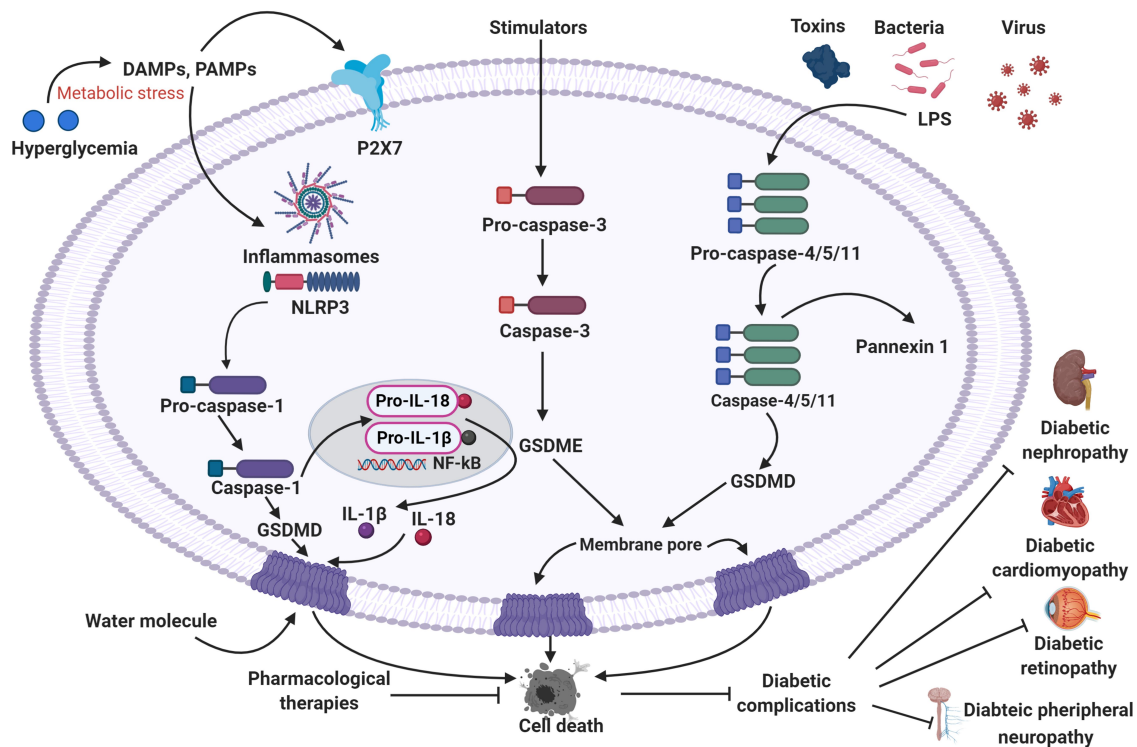


Figure 3 Summary of the pyroptosis in the development of diabetic complications and its therapeutic implications.

diabetes and its complications are still limited and challenging to experimental and clinical investigations. Further studies are highly essential to investigate and clarify the exact molecular mechanism and the fundamental role of pyroptosis in diabetic complications. Clinical studies of those potential agents targeting the pyroptosis-mediated cell death and inflammasome may create a new window to achieve a possible therapeutic avenue for managing and treating diabetes and its complications in the future.

Abbreviations

ROS, Reactive oxygen species; AGEs, Advanced glycation end products; ER, Endoplasmic reticulum; PRRs, Pattern recognition receptors; GSDMD, Gasdermin D; PAMPs, Pathogen-associated molecular patterns; DAMPs, Damage-associated molecular patterns; TLRs, Toll-like receptors; NLRs, NOD-like receptors; AIMs, Absent in melanomas; NLRP1, NOD-like receptor protein 1; NLRP3, NOD-like receptor protein 3; ASC, apoptosis-associated speck-like protein; miRNAs, MicroRNAs; HFD, High-fat diet; STZ, Streptozotocin; TXNIP, Thioredoxin-interacting protein; NF- κ B, Nuclear factor-kappa B; EVs, Extracellular vesicles; siRNA, Small interfering RNA; MALAT1, Metastasis associated lung adenocarcinoma transcript 1; HRPCs, human retinal progenitor cells; CMKLR1, Chemokine-Like Receptor 1;

GLP, Glucagon-like peptide; DPP-4, Dipeptidyl peptidase-4; SGLT-2, Sodium-glucose co-transporter-2; CCK-8, Cell counting kit-8; MCMV, Murine cytomegalovirus; CVB3, coxsackievirus B3; IRE1 α , Inositol-requiring enzyme 1 α ; MSCs, Mesenchymal stem cells; PKR, Protein kinase R.

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Disclosure

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