Review Article

Targeting Pyroptosis: New Insights into the Treatment of Diabetic Microvascular Complications

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Received 24 March 2022; Accepted 16 September 2022; Published 27 September 2022

Academic Editor: Jian-You Guo

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Pyroptosis is an inflammatory form of programmed cell death that is dependent on inflammatory caspases, leading to the cleavage of gasdermin D (GSDMD) and increased secretion of interleukin (IL)-1β and IL-18. Recent studies have reported that hyperglycemia-induced cellular stress stimulates pyroptosis, and different signaling pathways have been shown to play crucial roles in regulating pyroptosis. This review summarized and discussed the molecular mechanisms, regulation, and cellular effects of pyroptosis in diabetic microvascular complications, such as diabetic nephropathy, diabetic retinopathy, and diabetic cardiomyopathy. In addition, this review aimed to provide new insights into identifying better treatments for diabetic microvascular complications.

1. Introduction

Diabetes is a low-grade inflammatory disease that seriously affects the quality of life of 463 million adults aged 20–79 years [1]. Diabetic microvascular complications (DMCs), such as diabetic nephropathy (DN), diabetic retinopathy (DR), and diabetic cardiomyopathy (DC), are the main contributors to the morbidity and mortality associated with diabetes. However, the pathogenesis and pathophysiology of these DMCs are complex. Chronic inflammatory response induced by hyperglycemia is a common mechanism in DMCs. Further investigation of novel molecular mechanisms is required to develop new therapeutic approaches for DMCs.

Pyroptosis is a type of programmed cell death and its morphological characteristics are mainly caused by cell membrane rupture, chromatin condensation, nuclear fragmentation, and substantial release of cellular contents, including interleukin (IL)-1β, IL-18, and lactate dehydrogenase [2]. Pyroptosis is initially considered an innate immune and inflammatory response to invasion by external pathogens. Appropriate cell pyroptosis eliminates pathogens when they invade, but subsequent investigations suggest that pyroptosis is a double-edged sword, and that excess pyroptosis leads to a constant inflammatory response [3]. Recent studies have reported that a series of chronic inflammatory diseases, such as cardiovascular disease [4], rheumatoid arthritis [5], and nervous system diseases [6],
are associated with pyroptosis, and that blocking excessive pyroptosis is a promising strategy for delaying disease development. Evidence suggests that diabetes is closely associated with pyroptosis [7]. This review provided an overview of the role of pyroptosis in DMCs and the effects of inhibition of the pyroptosis pathway in DMCs.

2. Pyroptosis and Pyroptosis-Related Mechanisms

tZychlinsky et al. first discovered the phenomenon of pyroptosis in 1992, which was initially considered apoptosis in macrophages infected by *Shigella flexneri* [8]. Studies have shown that pyroptosis is caused by caspase-1-regulated etiology. Scholars called this the canonical pyroptosis pathway and named it “pyroptosis” in 2001 to contrast with other types of cell death, meaning “fire” [9]. Thereafter, a noncanonical pyroptosis pathway was observed [10]. In 2015, Kayagaki and Shi demonstrated that gsdemarin D (GSDMD) was the ultimate executor of pyroptosis [11, 12]. GSDMD is a gsdemarin family member that can be cleaved into GSDMD-N fragments by inflammatory caspases, including caspase-1 and caspase-4/caspase-5/caspase-11 (caspase-4/caspase-5 in humans and caspase-11 in mice) [13]. The GSDMD-N fragment of ring-shaped oligomers anchored on the cell membrane forms pores to induce cell death [14].

Inflammation is a complex process that reflects local and systemic responses to different immunological and nonimmunological stimuli. Pyroptosis, which is essentially an inflammatory reaction, has provided a new perspective for research on the pathophysiological mechanisms of DMCs. Pyroptosis mechanisms include canonical and noncanonical pathways. The difference between the two pathways is primarily due to their triggering factors. The two pathways are independently discussed below, and the details can be found in Figures 1(a) and 1(b).

2.1. Canonical Pyroptosis Pathway. The canonical pyroptosis pathway is caspase-1-dependent and is triggered by inflammasomes [15]. In this pathway, pattern recognition receptors including Nod-like receptor (NLR) proteins (NLRP1, NLRP3, NAIP/NLRC4), pyrin, and ALR proteins (AIM2 and IFI16) as sensors, first recognize pathogen-associated molecular patterns (such as bacteria, viruses, and DNA damage) or danger-associated molecular patterns (such as uric acid and extracellular adenosine 5′-triphosphate) [16]. During this process, NLRP1 and NLRC4 directly recruit pro-caspase-1, while binding between procaspase-1 and NLRP3/ pyrin/ALR, and the activation of caspase-1 must be accompanied by the adaptor protein ASC to form inflammasomes [17]. Thereafter, pro-IL-1β and pro-IL-18 are sheared to activate IL-1β and IL-18, respectively, by activating caspase-1, and GSDMD is cleaved into GSDMD-N to form pores on the cell membrane [18].

2.2. Noncanonical Pyroptosis Pathway. The noncanonical pyroptosis pathway is caspase-11- or caspase-4/caspase-5-dependent (caspase-11 in mice and caspase-4/5 in humans) [19]. In 2011, Kayagaki et al. reported that the secretion of IL-1β from macrophages was inhibited in Casp11−/− C57BL/6 or Casp1−/− Casp11129m1/129m1 mice infected with Gram-negative bacteria and that cell death induced by caspase-11 activation was independent of NLRP3 and ASC [20]. Therefore, they proposed this phenomenon as the noncanonical inflammasome-triggered caspase-11 or the noncanonical pyroptosis pathway [20]. The study has shown that lipopolysaccharide (LPS) initially activates the non-canonical pyroptosis pathway, and this process is independent of Toll-like receptor 4 (TLR4) [21]. Lipid A in LPS binds to caspase-11/caspase-4/caspase-5 through the CARD-CARD domain. Subsequently, inflammatory caspases are activated, and GSDMD is cleaved to GSDMD-N to induce cell death [22]. Notably, although activated caspase-11/caspase-4/caspase-5 can induce pyroptosis, they cannot directly cleave pro-inflammatory cytokines [23].

3. Pyroptosis in Diabetic Microvascular Diseases

Recently, although limited, studies have attempted to explore the relationship between pyroptosis and DMCs and their potential mechanisms. Studies on pyroptosis and its associated diseases are summarized in this review.

3.1. Pyroptosis in Diabetic Nephropathy. DN is one of the most prevalent and serious microvascular complications associated with diabetes. Its early pathological characteristics include basement membrane thickening, increased mesangial matrix production, and extracellular matrix accumulation, with the subsequent development of glomerulosclerosis and tubulointerstitial fibrosis, eventually leading to proteinuria and irreversible renal damage. The early clinical diagnosis of DN is based on canonical biochemical markers, such as glomerular filtration rate, urinary microalbumin, urinary microalbumin to urinary creatinine ratio, serum creatinine, urinary cystatin C, and serum β2 microglobulin. In addition, some biomarkers related to the pathogenesis of DN, such as kidney injury molecule 1 (Kim-1), neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases-2, insulin-like growth factor-binding protein 7 (IGFBP-7), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), monocyte chemoattractant protein-1(MCP-1), and inflammatory cytokines, such as tumor necrosis factor (TNF)-α, MCP-1, and ILs (IL-1α, IL-1β, IL-18, IL-10), have also attracted significant attention [24, 25]. However, the pathogenesis of DN remains unclear, and treatment strategies are limited. Recent studies have found that pyroptosis is involved in pathophysiological processes and may be a potential therapeutic target.

3.1.1. Glomerular Endothelial Cells. Glomerular endothelial cells (GECs) are located within the glomerulus and are the first layer to be involved in glomerular filtration. Recent findings suggest that both cell loss and
inflammation in GECs are important causes of DN [26], and that pyroptosis may be a pivotal link between them. Activation of NLPR3 inflammasomes has been observed in the glomeruli of patients with DN and in animal models [27]. An in vitro study has reported that LPS directly induces pyroptosis in vascular endothelial cells [28]. Because low-grade inflammation and hyperglycemia form a vicious circle that promotes the development of DN toward end-stage renal disease, inhibiting pyroptosis may be an ideal strategy to block it. Our previous study showed that high glucose levels could induce pyroptosis in GECs, which was alleviated by a caspase-1 inhibitor or sodium butyrate [29]. Another study reported that hirudin ameliorated DN by inhibiting GSDMD-mediated pyroptosis in GECs [30].

### Figure 1: Canonical and noncanonical pathway pyroptosis.

Pyroptosis mechanisms include canonical and noncanonical pathways. The left side of (a) shows the canonical pyroptosis pathway, which is caspase-1 dependent; the right side of (b) shows the noncanonical pathway, which is caspase-4/caspase-5/caspase-11 dependent; the cleavage of gasdermin D (GSDMD) (GSDMD-N domain) forms pores on the cell membrane, inducing pyroptosis.

#### 3.1.2. Podocytes.
Podocytes are the outer glomerular filtration barriers. Podocyte fusion and foot process effacement cause proteinuria, and cell death and inflammation are the underlying mechanisms [31]. Podocyte pyroptosis has gradually been elaborated upon. Previous studies have demonstrated the activation of NLRP3/caspase-1/IL-1β in podocytes derived from patients with DN, db/db mice, and streptozotocin (STZ)-induced mice/rats [27, 32]. High glucose [27], D-ribose [33], and visfatin [34] levels directly induce the activation and release of NLRP3/ASC/caspase-1/IL-1β in podocytes, whereas inhibition or knockdown [33] of NLRP3 [32], ASC [33], and caspase-1 [33] improves the function of podocytes. A previous study showed that inhibition of NLRP3 reduced the expression of podocin and ameliorated renal fibrosis [32]. Another study reported that...
the inhibition of caspase-1/IL-18 signaling in DN could reduce albuminuria [35]. Additionally, high glucose levels activate caspase-11/caspase-4 and GSDMD-mediated pyroptosis, resulting in podocyte loss and DN development [36]. Thus, the intervention of the podocyte pyroptosis pathway may be a new target for the treatment of DN. Given the targets of pyroptosis, the regulatory mechanism of the pyroptosis pathway is gradually being studied. TLR4 knockdown attenuates high glucose-induced podocyte injury via the NALP3/ASC/caspase-1 signaling pathway [37]. There is also an indication that thioredoxin interaction protein (TXNIP) is involved in activating the high-glucose-induced NALP3 inflammasome and podocyte injury [38]. Forkhead box protein M1 transcriptionally activates sirtuin 4 and inhibits nuclear factor kappa B (NF-κB) signaling and NLRP3 inflammasome to alleviate kidney injury and podocyte pyroptosis in DN [39]. Moreover, sublytic complement C5b-9 induces pyroptosis in podocytes via the KCNQ1 overexpressing transcript 1 (KCNQ1OT1)/miR-486a-3p/NLRP3 regulatory axis [40]. A recent study by Ding et al. showed that MiR-21-5p in macrophage-derived extracellular vesicles could regulate pyroptosis-mediated podocyte injury induced by A20 in DN [41]. Furthermore, unexpectedly, some drugs have been found to exert a protective effect against DN via an antipyroptosis mechanism. Geniposide inhibits pyroptosis via the AMPK/SIRT1/NF-κB pathway in podocytes in DN [42]. Atorvastatin protects podocytes via the metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)/miR-200c/nuclear factor-erythroid 2-related factor 2 (NRF2) signaling pathway from hyperglycemia (HG)-induced pyroptosis and oxidative stress [43]. Catalpol effectively inhibits oxidative stress and inflammation accompanied by pyroptosis in podocytes via the AMPK/SIRT1/NF-κB pathway [44]. The total flavones of Abelmoschus manihot (TFA) alleviate podocyte pyroptosis and injury by adjusting methyltransferase-like protein 3 (METTL3)-dependent m6A modification and regulating NLRP3-inflammasome activation and phosphatase and tensin homolog (PTEN)/phosphoinositide 3-kinase/protein kinase B (Akt) signaling [45]. As podocytes act as the last barrier against proteinuria, exploring agents that prevent damage to these cells is of special significance.

3.1.3. Glomerular Mesangial Cell. Glomerular mesangial cells (GMCs) play a pivotal role in maintaining the basic structure of the glomerulus. Increasing the mesangial matrix and GMCs proliferation promotes DN development. Inflammation is an important factor in GMC proliferation [46]. Previous studies have shown that high glucose level significantly induces the expression of pyroptosis markers, including NLRP3, caspase-1, pro-caspase-1, IL-1β, and pro-IL-1β, in GMCs [47, 48], whereas inhibiting NLRP3 with MCC950 suppresses NLRP3/caspase-1/IL-1β activation and decreases renal fibrosis [32]. Nuclear enriched abundant transcript 1 and its target gene miR-34c are also found to regulate pyroptosis by mediating NLRP3 on GMCs in DN [49]. Furthermore, naringin and ginsenoside compound K have been reported to exert potential effects against pyroptosis in GMCs [50, 51].

3.1.4. Renal Tubular Epithelial Cells. Renal tubular epithelial cells (RTECs) are more vulnerable to death because they are inevitably stimulated by various pathogenic factors, such as toxins, hypoxia, and metabolic disorders. In patients with diabetes, the expression of IL-18, an inflammatory cytokine released during pyroptosis in renal tubular cells, increases significantly (approximately 83%) [52], suggesting the potential involvement of pyroptosis in RTEC damage. The expression of NLRP3, caspase-1, and IL-1β increases significantly in both STZ-induced DN rats and high glucose-treated RTECs [53]. Inhibition of caspase-1 or GSDMD knockdown ameliorates RTEC pyroptosis and reduces kidney damage in vivo and in vitro [54, 55]. Moreover, upregulation of miR-23c inhibits RTEC pyroptosis by modulating MALAT1/ELAVL1 [53]. The TLR4/NF-κB signaling pathway also modulates GSDMD-mediated pyroptosis in RTECs [56]. Recent studies have reported that antisense noncoding RNA in the INK4 locus/miR-497/TXNIP and KCNQ1OT1/miR-506-3p are involved in the regulation of high glucose-activated HK2 cell pyroptosis [57, 58]. Moreover, circACTR2 regulates high glucose-induced pyroptosis, inflammation, and fibrosis in proximal tubular cells [59]. Specific inhibitors of pyroptosis in RTEC have not been well studied, and existing evidence suggests a potential function for an A1 adenosine receptor agonist [35] or hirudin [30]. In summary, the canonical pyroptosis pathway is associated with intrinsic damage to RTECs and plays an essential role in DN development. RTEC pyroptosis inhibition may be a novel target for ameliorating albuminuria and renal fibrosis.

3.2. Pyroptosis in Diabetic Retinopathy. DR is a hallmark complication of diabetes and a leading cause of vision loss in adults. Loss of retinal pericytes is one of the earliest changes associated with DR, and it has been postulated to initiate or trigger microaneurysm formation, abnormal leakage, edema, and ischemia, provoking proliferative neovascularization in the retina. Although the pathophysiological mechanisms of DR are complex, vascular endothelial damage, increased vascular permeability, and neovascularization are the most common phenomena. Hemoglobin A1c (HbA1c) is the only validated systemic biomarker for DR progression. However, only 6.6% of the variation in the risk of DR is explained by HbA1c levels [60]. In addition, there are some biomarkers for the pathogenesis of DR, including VEGF, pigment epithelium-derived factor, platelet-derived growth factor subunit B, photoreceptor-secreted retinol-binding protein 3, forkhead box protein O1, NRF2, atypical protein kinase C, and inflammatory cytokines, such as TNF-α, IL1β, IL-6, IL-8, chemokines, C-C motif ligand-2, intercellular cell adhesion molecule-1, and vascular cell adhesion molecule-1 [61]. Furthermore, long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) in whole blood can serve as novel non-invasive biomarkers for proliferative DR [62, 63]. However, there remains an
3.3. Pyroptosis in Diabetic Cardiomyopathy. DC is the main cardiovascular complication that occurs in approximately 60% of patients with well-controlled diabetes, resulting in systolic and diastolic dysfunctions, which are independent risk factors for any vascular disease or hypertension [74]. Increasing evidence suggests that hyperglycemia, lipotoxicity, and mitochondrial uncoupling contribute to cardiac inflammation, which plays an important role in the pathogenesis and progression of DC [75]. In this process, cytoplasmic calcium is increased, triggering mitochondrial changes, the production of ROS is increased, and activating ROS levels lead to oxidative damage in DC, among which oxidative stress and chronic inflammation are critical [75]. A broad spectrum of cardiovascular biomarkers that have been described in patients with DC includes brain natriuretic peptide (BNP), cardiac troponins (T, N, and I), and matrix metalloproteinases (MMPs), particularly MMP-9. Some biomarkers related to the pathogenesis of DR have been reported, such as cardiostatin-1, IGFBP7, TGF-β, activin A, ROS-induced inflammatory cytokines (TNF-α, IL-6), galectin-3, suppression of tumorigenicity 2 (sST2), IncRNAs, and microRNAs [76]. However, the predictive roles of these biomarkers in patients with DM remain unclear owing to limited evidence [77]. We hope to identify novel biomarkers for DC screening.

Due to the undefined pathophysiology of DC, several studies have attempted to investigate the role of pyroptosis in DC. In early 2014, Luo et al. [78] reported that the expressions of NLRP3, ASC, caspase 1, and IL-1β increased significantly in cardiomyocytes of STZ-treated diabetic rats and that NLRP3 silencing or inhibition of caspase-1 reduced their expression, alleviated left ventricular dysfunction, and ultimately reversed myocardial remodeling in DC. Similar findings were observed in a DC model developed from C57BL/6 mice [79, 80]. Apart from the caspase-1 modulated pathway, noncoding RNAs are also involved in this process. Upregulation of microRNA-30d directly modulates the downregulation of forkhead box class O 3a in STZ-treated rats or high glucose-induced cardiomyocytes [81]. The study has observed that knockdown of the long noncoding RNA KCNQ1OT1 inhibits high glucose-induced pyroptosis by upregulating miR-214-3p and reducing caspase-1 expression in AC16 cells and primary cardiomyocytes [82]. Similarly, another study suggested that lncRNA-MALAT1 targeted miR-141-3p to promote HG-induced H9C2 cardiomyocyte pyroptosis [83]. Moreover, activation of the transforming growth TGF-β1/Smads pathway in cardiac fibroblasts is repressed by KCNQ1OT1 knockdown [80]. A further study reported that hsa_circ_0076631, a caspase-1 related circRNA that suppresses miR-214-3p, increased in high-glucose-treated cardiomyocytes or serum from patients with diabetic [84]. Other noncoding RNAs, including AIM2 [85], miR-9 [86], GASS [87], and MIAT [88], are also potential modulators of pyroptosis in DC. A recent study demonstrated that the circRNAs circ_0071269 might promote the development of DC through the miR-145/GSDMA axis [89]. In addition, overexpression of mitochondrial aldehyde dehydrogenase 2 can reduce the high glucose-induced occurrence of pyroptosis in H9C2 cardiac cells [90].

Many drugs have been demonstrated to have some effects against pyroptosis (e.g., metformin [91], exendin-4 [92], pyrroloquinoline quinone (PQQ) [93], and skimm-ing) [94]. A natural coumarin derivative has been found to protect against experimental DC by inhibiting pyroptosis in cardiomyocytes [94]. Empagliflozin has also been confirmed to alleviate the activation of NLRP3 and subsequent cardiomyocyte pyroptosis in the diabetic heart [95]. Overall, these studies indicate that the role of pyroptosis in DC and inhibition of the pyroptosis pathway might have an advantage in their ability to protect DC.

Evidence-Based Complementary and Alternative Medicine
### Table 1: Summary of the effects of different methods or drugs on pyroptosis in vivo and in vitro.

| Methods/drugs                          | Intervention targets               | Cell type/animal model            | Effects                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------|------------------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ac-YVAD-CMK [29, 33]                   | Caspase-1 inhibitor                | GECs [29]                        | Reduce the expression of NLRP3, caspase-1, and IL-1β                                                                                           |
| VX-765 [51]                            | Caspase-1-GSDMD,                   | Immortalized mouse podocyte cell line [29, 33] | Ameliorate caspase-1-GSDMD-IL-1β/IL-18 canonical pyroptosis pathway and NF-κB/1b-α signaling pathway Inhibit IRF2-induced GSDMD Inhibit the NLRP3/caspase-1/IL-1β pathway Inhibit NALP3/ASC/caspase-1 signaling pathway Inhibits HG-induced NALP3 inflammasome activation, IL-1β production, and podocyte injury |
| Sodium butyrate [29]                   | NF-κB/1b-α                         | GECs                             |                                                                                                                                                                                                         |
| Hürudin [30]                           | IRF2-GSDMD                         | GECs, RTECs, and BMDMs           |                                                                                                                                                                                                         |
| MCC950 [32]                            | NLRP3 inhibitor                    | DB/db mice and rat mesangial cells |                                                                                                                                                                                                         |
| Knockdown TLR4 [37]                    | NALP3/ASC/caspase-1               | Mouse podocytes                  |                                                                                                                                                                                                         |
| Knockdown TXNIP [38]                   | TXNIP                              | Immortal human podocyte cell line |                                                                                                                                                                                                         |
| Overexpress FOXM1 [39] sC5b-9          | SIRT4                              | MPC5 cells                       |                                                                                                                                                                                                         |
| Knockdown KCNQ1OT1                     | NLRP3                              | MPC5 cells                       |                                                                                                                                                                                                         |
| Upregulate MiR-486a-3p [40]            | miR-21-5p/A20                      | MPC5 cells                       |                                                                                                                                                                                                         |
| Geniposide [42]                        | APMK/SIRT1/NF-κB                   | HFD/STZ-induced DN mice and podocyte |                                                                                                                                                                                                         |
| Catalpol [44]                          | miR-21-5p/A20                      | MPC5 cells                       |                                                                                                                                                                                                         |
| Atorvastatin [43]                      | MALAT1/miR-200c/NRF2               | MPC-5 cells                      |                                                                                                                                                                                                         |
| TFA [45]                               | PTEN/P13K/Akt                      | MPC-5 cells                      |                                                                                                                                                                                                         |
| Naringin [50]                          | NLRP3                              | Rat mesangial cells              |                                                                                                                                                                                                         |
| Ginsenoside compound K [51]            | NLRP3                              | HBZY-1                           |                                                                                                                                                                                                         |
| Downregulate MALAT1 [53]               | ELAVL1                             | HK-2 cells                       |                                                                                                                                                                                                         |
| Upregulate MiR-23c [53]                |                                    |                                  |                                                                                                                                                                                                         |
| TAK-242 [56]                           | TLR4 inhibitor                     | HK-2 cells                       |                                                                                                                                                                                                         |
| Downregulate KCNQ1OT1 [57, 65]         | NLRP3                              | HK-2 cells [57]                  |                                                                                                                                                                                                         |
| Upregulate MiR-214 [65]                |                                    | Corneal endothelial cells [65]   |                                                                                                                                                                                                         |
| Knockdown ANRIL [58]                   | TXNIP                              | HK-2 cells                       |                                                                                                                                                                                                         |
| Upregulate miR-497 [58]                |                                    |                                  |                                                                                                                                                                                                         |
| Resolvin D1 (RvD1) [66]                | NLRP3                              | STZ-induced diabetic retinopathy rats |                                                                                                                                                                                                         |

Evidence-Based Complementary and Alternative Medicine
| Methods/drugs | Target | Cell type/animal model | Effects |
|--------------|--------|-----------------------|---------|
| Upregulate miR-214-3p | H9c2 cells | Mice cardiomyocytes | Inhibit the NLRP3 inflammasome via the downregulation of TNFα |
| Overexpress MIAT | H9c2 cells | Primary cardiacomyocytes | Decrease the expression of NLRP3 inflammatory and reduce the expression of cleaved-caspase-1, IL-1β and IL-18 |
| Knockdown MALAT1 | MIAT | H9c2 cells | Decrease the expression of NLRP3 inflammatory and reduce the expression of cleaved-caspase-1, IL-1β and IL-18 |
| Overexpress HGF | AC16 cells and primary cardiacomyocytes | Rat cardiacmyocytes | Attenuate the expression of ELAVL1 and inhibit pyroptosis |
| Silence IRF2 | AC16 cells and primary cardiacomyocytes | Rat cardiacmyocytes | Inhibit pyroptosis via the downregulation of TNFα |
| Knockdown circ_0071269 | miR-145/GSDMA | H9c2 cells | Inhibit pyroptosis via the downregulation of GSDMA |
| Overexpress ALDH2 | NLRP3 | H9c2 cells | Inhibit NLRP3/caspase-1 dependent pyroptosis |
| Metformin | NLRP3 | STZ-induced diabetic mice | Inhibit pyroptosis via the downregulation of TXNIP |
| Exendin-4 | ROS/pAMPK/TXNIP | Primary cardiacomyocytes | Inhibit pyroptosis via the downregulation of TXNIP |
| PQQ | NF-κB/NLRP3 | AC16 cells | Decrease pyroptosis-related protein levels |
| Skimmin | NLRP3 | Primary neonatal cardiomyocytes | Decrease the expression of NLRP3 inflammatory |
| Empagliflozin | NLRP3 | db/db mice | Alleviate the activation of NLRP3 inflammasome and reduce the expression of cleaved-caspase-1, IL-1β and IL-18 |

NLRP: the nucleotide-binding oligomerization domain-like receptor family; caspase: a proteinase family containing the pyrin domain-containing 3; IL: interleukin; GSDMA: gasdermin A; GSDMD: gasdermin D; GSDM: gasdermin N-terminal domain; miRNA: microRNA; ASC: apoptosis-associated speck-like protein containing a caspase recruitment domain; IL-1β: interleukin-1β; TNFα: tumor necrosis factor alpha; MMPs: matrix metalloproteinases; PMA: phorbol 12-myristate 13-acetate; ERK: extracellular signal-regulated kinase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP: pyrin domain-containing protein; ASC: apoptosis-associated speck-like protein containing a caspase recruitment domain. The table includes various interventions and their corresponding effects on different cell types and animal models.
4. Conclusions and Prospects

In conclusion, the pathophysiological mechanisms underlying DMCs are complex and unclear. However, pyroptosis, a type of programmed cell death that triggers inflammatory reactions, provides a novel perspective for determining the mechanisms and therapeutic targets of DMCs (Table 1). These experiments have demonstrated the involvement of pyroptosis in the pathophysiological process of DMCs in vitro and in vivo. Based on an enhanced understanding of these existing results, we further explore how pyroptosis and inflammasome are activated, including some novel studies related to pyroptosis regulation and its relationship with DMCs, to provide a promising avenue for DMC prevention and treatment. Three new insights have been discovered regarding the regulation of pyroptosis in DMCs:

1. The important causes of DMCs are oxidative stress and inflammation resulting in pyroptosis. Based on the antioxidative stress and anti-inflammatory strategies, we determined effective drugs or small-molecule compounds against pyroptosis to improve DMCs and further explored the regulation of pyroptosis and its potential mechanisms, which will open up a new direction for the prevention and treatment of DMCs.

2. The pro-inflammatory effect of pyroptosis is a key factor in the development of DMCs. Some studies have found that several upstream regulatory signaling proteins, noncoding RNAs, and circRNAs play a role in the upregulation of pyroptosis. Furthermore, autophagy plays a protective role in the inhibition of NLPR3 overactivation [96]. Therefore, further clarification of the regulatory mechanism of pyroptosis and targeting these pathways will also be an effective means to prevent and treat DMCs.

3. The inflammatory response is an important factor in the development of DMCs. Pyroptosis maintains or expands inflammation by tightly controlling the inflammatory response via the release of IL-1β and IL-18. IL-1β and IL-18 are two essential pro-inflammatory cytokines that are upregulated in tissue-resident cells of patients and animals with diabetes and are further induced by positive feedback to pyroptosis to form inflammatory storms [97]. Based on the perspective of the upregulation of different pro-inflammatory factors triggered by metabolic and hemodynamic disorders, controlling the chronic inflammatory microenvironment of diabetes will provide potential insights into the prevention and treatment of DMCs.

Nevertheless, whether some promising pyroptosis biomarkers can be used as novel targets for diagnosing and treating DMCs requires further investigation, particularly in animal experiments and clinical studies. Further investigations into the exact molecular and regulatory mechanisms of pyroptosis are necessary for DMCs.

Furthermore, GSDMD, as the ultimate pyroptosis protein, should be investigated for its function in DMCs and to determine whether inhibiting GSDMD is a more valuable therapeutic target for these complications. Moreover, inhibition or activation of the pyroptosis pathway affects various aspects of physiology and can have different effects. It is necessary to consider the overall body balance when studying drugs that target the pyroptosis pathway in DMCs.

Data Availability

No data were used to support this study.

Conflicts of Interest

All authors declare no conflicts of interest.

Authors’ Contributions

J. G. researched the documents and wrote the manuscript. K. G. and M. G. revised the manuscript. Y. X. and YH. X. designed the study and reviewed the manuscript. W. H. and X. L. revised the manuscript for important intellectual content. All authors approved the final version of the manuscript. Junling Gu, Kang Geng, and Man Guo contributed equally to this work.

Acknowledgments

The work was supported by grants from the National Natural Science Foundation of China (Nos. 81970676, 81800741, and 82170834), and the Science and Technology Development Fund of Macau (Nos. 0006/2019/A and 0025/2019/AGJ), and the Science and Technology Department of Sichuan Province (No. 2019JY0697).

References

[1] H. Sun, P. Saeedi, S. Karuranga et al., "IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045," *Diabetes Research and Clinical Practice*, vol. 183, Article ID 109119, 2022.

[2] I. Jorgensen and E. A. Miao, "Pyroptotic cell death defends against intracellular pathogens," *Immunological Reviews*, vol. 265, no. 1, pp. 130–142, 2015.

[3] X. Liu and J. Lieberman, "A mechanistic understanding of pyroptosis: the fiery death triggered by invasive infection," *Advances in Immunology*, vol. 135, pp. 81–117, 2017.

[4] C. Zeng, R. Wang, and H. Tan, "Role of pyroptosis in cardiovascular diseases and its therapeutic implications," *International Journal of Biological Sciences*, vol. 15, no. 7, pp. 1345–1357, 2019.

[5] X. Y. Wu, K. T. Li, H. X. Yang et al., "Complement C1q synergizes with PTX3 in promoting NLRP3 inflammasome over-activation and pyroptosis in rheumatoid arthritis," *Journal of Autoimmunity*, vol. 106, Article ID 102336, 2020.

[6] Z. Liang, L. Han, D. Sun et al., "Chemerin-induced macrophages pyroptosis in fetal brain tissue leads to cognitive disorder in offspring of diabetic dams," *Journal of Neuroinflammation*, vol. 16, no. 1, p. 226, 2019.

[7] C. F. Lin, Y. T. Kuo, T. Y. Chen, and C. T. Chien, "Quercetin-rich guava (psidium guajava) juice in combination with..."
trehalose reduces autophagy, apoptosis and pyroptosis formation in the kidney and pancreas of type II diabetic rats, "Molecules, vol. 21, no. 3, p. 334, 2016.

A. Zychlinsky, M. C. Prevost, and P. J. Sansonetti, "Shigella flexneri induces apoptosis in infected macrophages," Nature, vol. 358, no. 6382, pp. 167–169, 1992.

B. T. Cookson and M. A. Brennan, "Pro-inflammatory programmed cell death," Trends in Microbiology, vol. 9, no. 3, pp. 113–114, 2001.

P. Broz, T. Ruby, K. Belhocine et al., "Caspase-11 increases susceptibility to Salmonella infection in the absence of caspase-1," Nature, vol. 490, no. 7419, pp. 288–291, 2012.

N. Kayagaki, I. B. Stowe, B. L. Lee et al., "Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling," Nature, vol. 526, no. 7575, pp. 666–671, 2015.

J. Shi, Y. Zhao, K. Wang et al., "Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death," Nature, vol. 526, no. 7575, pp. 660–665, 2015.

J. Shi, W. Gao, and F. Shao, "Pyroptosis: gasdermin-mediated programmed necrotic cell death," Trends in Biochemical Sciences, vol. 42, no. 4, pp. 245–254, 2017.

R. A. Aglietti, A. Estevez, A. Gupta et al., "Gsdmd P30 elicited by caspase-11 during pyroptosis forms pores in membranes," Proceedings of the National Academy of Sciences, vol. 113, no. 28, pp. 7858–7863, 2016.

A. Malik and T. D. Kanneganti, "Inflammasome activation and assembly at a glance," Journal of Cell Science, vol. 130, no. 23, pp. 3955–3963, 2017.

J. S. Roh and D. H. Sohn, "Damage-associated molecular patterns in inflammatory diseases," Immune network, vol. 18, no. 4, p. e27, 2018.

M. Lamkanfi and V. M. Dixit, "Mechanisms and functions of inflammasomes," Cell, vol. 157, no. 5, pp. 1013–1022, 2014.

W. T. He, H. Wan, L. Hu et al., "Gasdermin D is an executor of pyroptosis and required for interleukin-1β secretion," Cell Research, vol. 25, no. 12, pp. 1285–1298, 2015.

J. Shi, Y. Zhao, Y. Wang et al., "Inflammatory caspases are innate immune receptors for intracellular LPS," Nature, vol. 514, no. 7521, pp. 187–192, 2014.

N. Kayagaki, S. Warming, M. Lamkanfi et al., "Non-canonical inflammasome activation targets caspase-11," Nature, vol. 479, no. 7371, pp. 117–121, 2011.

C. E. Diamond, D. Brough, H. J. Khameneh, and A. Mortellaro, "Novel perspectives on non-canonical inflammasome activation," ImmunoTargets and Therapy, vol. 4, pp. 131–141, 2015.

X. Liu, Z. Zhang, J. Ruan et al., "Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores," Nature, vol. 535, no. 7610, pp. 153–158, 2016.

C. Ross, A. H. Chan, J. Von Pein, D. Boucher, and K. Schroder, "Dimerization and auto-processing induce caspase-11 protease activation within the non-canonical inflammasome," Life science alliance, vol. 1, no. 6, Article ID e201800237, 2018.

L. Pérez-López, M. Boronat, C. Melián, Y. Brito-Casillas, and A. M. Wängner, "Animal models and renal biomarkers of diabetic nephropathy," Advances in Experimental Medicine & Biology, vol. 1307, pp. 521–551, 2021.

W. R. Zhang and C. R. Parikh, "Biomarkers of acute and chronic kidney disease," Annual Review of Physiology, vol. 81, no. 1, pp. 309–333, 2019.

I. S. Daehn, "Glomerular endothelial cell stress and cross-talk with podocytes in early [corrected] diabetic kidney disease," Frontiers of Medicine, vol. 5, p. 76, 2018.
diabetic nephropathy by regulating A20,” Journal of Endo-
crinological Investigation, vol. 44, no. 6, pp. 1175–1184, 2021.

[42] F. Li, Y. Chen, Y. Li, M. Huang, and W. Zhao, “Geniposide alleviates diabetic nephropathy of mice through AMPK/ SIRT1/NF-κB pathway,” European Journal of Pharmacology, vol. 886, Article ID 173449, 2020.

[43] Y. Zhao, L. Chen, X. He et al., “Atorvastatin regulates MALAT1/miR-200c/NRF2 activity to protect against podo-
cyte pyroptosis induced by high glucose. Diabetes, metabolic syndrome and obesity: targets and therapy,” Diabetes, Met-
abolic Syndrome and Obesity: Targets and Therapy, vol. 14, pp. 1631–1645, 2021.

[44] J. Chen, Y. Yang, Z. Lv et al., “Study on the inhibitive effect of Catalpol on diabetic nephropathy,” Life Sciences, vol. 257, Article ID 118120, 2020.

[45] B. H. Liu, Y. Tu, G. X. Ni et al., “Total flavones of Abelmoschus manihot ameliorates podocyte pyroptosis and injury in high glucose conditions by targeting METTL3-dependent m(6)A modification-mediated NLRP3-inflammasome activation and PTEN/PI3K/Akt signaling,” Frontiers in Pharmacology, vol. 12, Article ID 667644, 2021.

[46] Y. M. Scindia, U. S. Deshmukh, and H. Bagavant, “Mesangial pathology in glomerular disease: targets for therapeutic in-
tervention,” Advanced Drug Delivery Reviews, vol. 62, no. 14, pp. 1337–1343, 2010.

[47] S. Tang, C. Gao, Y. Long et al., “Maresin 1 mitigates high glucose-induced mouse mesangial cell injury by inhibiting inflammation and fibrosis,” Mediators of In-
flammation, vol. 2017, Article ID 2438247, 11 pages, 2017.

[48] H. Feng, J. Gu, F. Gou et al., “High glucose and lipopoly-
 saccharide prime NLRP3 inflammasome via ROS/flipaseXin path in mesangial cells,” Journal of Diabetes Research, vol. 2016, Article ID 6973175, 11 pages, 2016.

[49] J. F. Zhan, H. W. Huang, C. Huang, L. L. Hu, and W. W. Xu, “Long non-coding RNA NEAT1 regulates pyroptosis in di-
abetic nephropathy via mediating the miR-34c/NLRP3 Axis,” Kidney & Blood Pressure Research, vol. 45, no. 4, pp. 589–602, 2020.

[50] F. Chen, G. Wei, J. Xu, X. Ma, and Q. Wang, “Naringin ameliorates the high glucose-induced rat mesangial cell in-
flammatory reaction by modulating the NLRP3 inflamma-
some,” BMC Complementary and Alternative Medicine, vol. 18, no. 1, p. 192, 2018.

[51] W. Song, L. Wei, Y. Du, Y. Wang, and S. Jiang, “Protective effect of ginsenoside metabolite compound K against diabetic nephropathy by inhibiting NLRP3 inflammasome activation and NF-κB/p38 signaling pathway in high-fat diet/strepto-
tozocin-induced diabetic mice,” International Immunophar-
macology, vol. 63, pp. 227–238, 2018.

[52] K. Miyachida, Y. Takiyama, J. Honjo, M. Tateno, and M. Haneda, “Upregulated IL-18 expression in type 2 diabetic subjects with nephropathy: TGF-β1 enhanced IL-18 expres-
sion in human renal proximal tubular epithelial cells,” Di-
abetes Research and Clinical Practice, vol. 83, no. 2, pp. 190–199, 2009.

[53] X. Li, L. Zeng, C. Cao et al., “Long noncoding RNA MALAT1 regulates renal tubular epithelial pyroptosis by modulated miR-23c targeting of ELAVL1 in diabetic nephropathy,” Experimental Cell Research, vol. 350, no. 2, pp. 327–335, 2017.

[54] N. Miao, F. Yin, H. Xie et al., “The cleavage of gasdermin D by caspase-11 promotes tubular epithelial cell pyroptosis and urinary IL-18 excretion in acute kidney injury,” Kidney Intern-
nal, vol. 96, no. 5, pp. 1105–1120, 2019.

[55] W. Tonnus and A. Linkermann, “Gasdermin D and pyro-
tosis in acute kidney injury,” Kidney International, vol. 96, no. 5, pp. 1061–1063, 2019.

[56] Y. Wang, X. Zhu, S. Yuan et al., “TLR4/NF-κB signaling induces GSDMD-related pyroptosis in tubular cells in di-
abetic kidney disease,” Frontiers in Endocrinology, vol. 10, p. 603, 2019.

[57] B. Zhi, X. Cheng, Y. Jiang et al., “Silencing of KCNQ1OT1 decreases oxidative stress and pyroptosis of renal tubular epithelial cells,” Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, vol. 13, pp. 365–375, 2020.

[58] J. Wang and S. M. Zhao, “LncRNA-antisense non-coding RNA in the INK4 locus promotes pyroptosis via mir-497/ thioredoxin-interacting protein axis in diabetic nephropathy,” Life Sciences, vol. 264, Article ID 118728, 2021.

[59] S. Wen, S. Li, L. Li, and Q. Fan, “circACTR2: a novel mechanism regulating high glucose-induced fibrosis in renal tubular cells via pyroptosis,” Biological and Pharmaceutical Bulletin, vol. 43, no. 3, pp. 558–564, 2020.

[60] Q. Xuan, Y. Ouyang, Y. Wang et al., “Multiplatform metabolomics reveals novel serum metabolite biomarkers in diabetic retinopathy subjects,” Advanced Science, vol. 7, no. 22, Article ID 2001714, 2020.

[61] D. A. Antonetti, P. S. Silva, and A. W. Stitt, “Current un-
derstanding of the molecular and cellular pathology of di-
abetic retinopathy,” Nature Reviews Endocrinology, vol. 17, no. 4, pp. 195–206, 2021.

[62] B. Liu, C. Cong, Y. Ma, X. Ma, H. Zhang, and J. Wang, “Potential value of IncRNAs as a biomarker for proliferative diabetic retinopathy,” Eye, vol. 36, no. 3, pp. 575–584, 2022.

[63] Z. Wu, B. Liu, Y. Ma, H. Chen, J. Wu, and J. Wang, “Discovery and validation of hsa_circ_0001953 as a potential biomarker for proliferative diabetic retinopathy in human blood,” Acta Ophthalmologica, vol. 99, no. 3, pp. 306–313, 2021.

[64] L. Huang, J. You, Y. Yao, and M. Xie, “High glucose induces pyroptosis of retinal microglia through NLRP3 inflamma-
some signaling,” Arquivos Brasileiros de Oftalmologia, vol. 84, no. 1, pp. 67–73, 2021.

[65] Y. Zhang, Z. Song, X. Li et al., “Long noncoding RNA KCNQ1OT1 induces pyroptosis in diabetic corneal endothelial keratopathy,” American Journal of Physiology - Cell Physiology, vol. 318, no. 2, pp. C346–C359, 2020.

[66] Y. Yin, F. Chen, W. Wang, H. Wang, and X. Zhang, “Resolvin D1 inhibits inflammatory response in STZ-induced diabetic retinopathy rats: possible involvement of NLRP3 inflamma-
some and NF-κB signaling pathway,” Molecular Vision, vol. 23, pp. 242–250, 2017.

[67] J. A. Vincent and S. Mohr, “Inhibition of caspase-1/in-
terleukin-1β signaling prevents degeneration of retinal capillaries in diabetes and galactosemia,” Diabetes, vol. 56, no. 1, pp. 224–230, 2007.

[68] J. Hao, H. Zhang, J. Yu, X. Chen, and L. Yang, “Methylene blue attenuates diabetic retinopathy by inhibiting NLRP3 inflammasome activation in STZ-induced diabetic rats,” Ocular Immunology and Inflammation, vol. 27, no. 5, pp. 836–843, 2019.

[69] W. Chen, M. Zhao, S. Zhao et al., “Activation of the TXNIP/ NLRP3 inflammasome pathway contributes to inflammation in diabetic retinopathy: a novel inhibitory effect of minocy-
cline,” Inflammation Research, vol. 66, no. 2, pp. 157–166, 2017.

[70] C. Gu, D. Draga, C. Zhou et al., “miR-590-3p inhibits pyroptosis in diabetic retinopathy by targeting NLRP1 and inactivating the NOX4 signaling pathway,” Investigative
Evidence-Based Complementary and Alternative Medicine

Ophthalmology & Visual Science, vol. 60, no. 13, pp. 4215–4223, 2019.

X. Zha, X. Xi, X. Fan, M. Ma, Y. Zhang, and Y. Yang, “Overexpression of METTL3 attenuates high-glucose induced RPE cell pyroptosis by regulating miR-25-3p/PTEN/Akt signaling cascade through DGCR8,” Aging, vol. 12, no. 9, pp. 8137–8150, 2020.

G. H. Liang, Y. N. Luo, R. Z. Wei et al., “CircZNF532 knockdown protects retinal pigment epithelial cells against high glucose-induced apoptosis and pyroptosis by regulating the miR-20b-5p/STAT3 axis,” Journal of diabetes investigation, vol. 13, no. 5, pp. 781–795, 2022.

K. Yang, J. Liu, X. Zhang et al., “H3 relaxin alleviates migration, apoptosis and pyroptosis through P2X7R-mediated nucleotide binding oligomerization domain-like receptor protein 3 inflammation activation in retinopathy induced by hyperglycemia,” Frontiers in Pharmacology, vol. 11, Article ID 603689, 2020.

Authors/Task Force Members, P. J. Grant, C. Berne et al., “ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD),” European Heart Journal, vol. 34, no. 39, pp. 3035–3087, 2013.

G. Jia, M. A. Hill, and J. R. Sowers, “Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity,” Circulation Research, vol. 122, no. 4, pp. 624–638, 2018.

M. Kunirc, T. Ticinovic Kurir, J. A. Borovac, and J. Bozic, “Role of novel biomarkers in diabetic cardiomyopathy,” World Journal of Diabetes, vol. 12, no. 6, pp. 685–705, 2021.

G. Murtaza, H. U. H. Virk, M. Khalid et al., “Diabetic cardiomyopathy - a comprehensive updated review,” Progress in Cardiovascular Diseases, vol. 62, no. 4, pp. 315–326, 2019.

B. Luo, B. Li, W. Wang et al., “NLRP3 gene silencing ameliorates diabetic cardiomyopathy in a type 2 diabetes rat model,” PLoS One, vol. 9, no. 8, Article ID e104771, 2014.

S. Kar, H. R. Shahshahan, B. T. Hackfort et al., “Exercise training promotes cardiac hydrogen sulfide biosynthesis and mitigates pyroptosis to prevent high-fat diet-induced diabetic cardiomyopathy,” Antioxidants, vol. 8, no. 12, p. 638, 2019.

F. Yang, Y. Qin, J. Lv et al., “Silencing long non-coding RNA KCnq1ot1 alleviates pyroptosis and fibrosis in diabetic cardiomyopathy,” Cell Death & Disease, vol. 9, no. 10, p. 1000, 2018.

X. Li, N. Du, Q. Zhang et al., “MicroRNA-30d regulates cardiomyocyte pyroptosis by directly targeting foxo3α in diabetic cardiomyopathy,” Cell Death & Disease, vol. 5, no. 10, Article ID e1479, 2014.

F. Yang, Y. Qin, Y. Wang et al., “LncRNA KCNQ1OT1 mediates pyroptosis in diabetic cardiomyopathy,” Cellular Physiology and Biochemistry, vol. 50, no. 4, pp. 1230–1244, 2018.

A. Wu, W. Sun, and F. Mou, “IncRNA-MALAT1 promotes high glucose-induced H9C2 cardiomyocyte pyroptosis by downregulating miR-141-3p expression,” Molecular Medicine Reports, vol. 23, no. 4, p. 259, 2021.

F. Yang, A. Li, Y. Qin et al., “A novel circular RNA mediates pyroptosis of diabetic cardiomyopathy by functioning as a competing endogenous RNA,” Molecular Therapy - Nucleic Acids, vol. 17, pp. 636–643, 2019.

X. Wang, J. Pan, H. Liu et al., “AIM2 gene silencing attenuates diabetic cardiomyopathy in type 2 diabetic rat model,” Life Sciences, vol. 221, pp. 249–258, 2019.

P. Jeyabal, R. A. Thandavarayan, D. Joladarashi et al., “MicroRNA-9 inhibits hyperglycemia-induced pyroptosis in human ventricular cardiomyocytes by targeting ELAVL1,” Biochemical and Biophysical Research Communications, vol. 471, no. 4, pp. 423–429, 2016.

Y. Xu, H. Fang, Q. Xu, C. Xu, L. Yang, and C. Huang, “LncRNA GAS5 inhibits NLRP3 inflammasome activation-mediated pyroptosis in diabetic cardiomyopathy by targeting miR-34b-3p/AHR,” Cell Cycle, vol. 19, no. 22, pp. 3054–3065, 2020.

W. Xiao, D. Zheng, X. Chen et al., “Long non-coding RNA MIAT is involved in the regulation of pyroptosis in diabetic cardiomyopathy via targeting miR-214-3p,” iScience, vol. 24, no. 12, Article ID 103518, 2021.

L. Fu, J. Zhang, Z. Lin, Y. Li, and G. Qin, “CircularRNA circ_0071269 knockdown protects against from diabetic cardiomyopathy injury by microRNA-145/gasdermin A axis,” Bioengineered, vol. 13, no. 2, pp. 2398–2411, 2022.

R. Cao, D. Fang, J. Wang et al., “ALDH2 overexpression alleviates high glucose-induced cardiotoxicity by inhibiting NLRP3 inflammasome activation,” Journal of Diabetes Research, vol. 2019, pp. 4857921–4858011, 2019.

F. Yang, Y. Qin, Y. Wang et al., “Mettformin inhibits the NLRP3 inflammasome via AMPK/mTOR-dependent effects in diabetic cardiomyopathy,” International Journal of Biological Sciences, vol. 15, no. 5, pp. 1010–1019, 2019.

H. Wei, R. Bu, Q. Yang et al., “Exendin-4 protects against hyperglycemia-induced cardiomyocyte pyroptosis via the AMPK-TXNT pathway,” Journal of Diabetes Research, vol. 2019, Article ID 8905917, 13 pages, 2019.

X. F. Qu, B. Z. Zhai, W. L. Hu et al., “Pyroloquinoline quinone ameliorates diabetic cardiomyopathy by inhibiting the pyroptosis signaling pathway in C57BL/6 mice and AC16 cells,” European Journal of Nutrition, vol. 61, no. 4, pp. 1823–1836, 2022.

R. K. Liang, Y. Y. Zhao, M. L. Shi et al., “Skimmia protects diabetic cardiomyopathy in streptozotocin-induced diabetic rats,” The Kaohsiung Journal of Medical Sciences, vol. 37, no. 2, pp. 136–144, 2021.

M. Xue, T. Li, Y. Wang et al., “Empagliflozin prevents cardiomyopathy via sGCG-cGMP-PKG pathway in type 2 diabetes mice,” Clinical Science, vol. 133, no. 15, pp. 1705–1720, 2019.

S. Zhao, X. Li, J. Wang, and H. Wang, “The role of the effects of autophagy on NLRP3 inflammasome in inflammatory nervous system diseases,” Frontiers in Cell and Developmental Biology, vol. 9, Article ID 657478, 2021.

M. F. McCarty, S. B. Iloki Assanga, L. Lewis Luj ´an, N. D. Chávez, J. H. O’Keefe, and J. J. DiNicolantonio, “Nutraceutical strategies for suppressing NLRP3 inflammasome activation: pertinence to the management of COVID-19 and beyond,” Nutrients, vol. 13, no. 1, p. 47, 2020.