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NLRP3 Inflammasome Activation in Diabetes: A Molecular Nexus between Inflammation and Cardiac Dysfunction

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ABSTRACT

Diabetes mellitus (DM) is a major global health concern closely associated with cardiovascular diseases, particularly diabetic cardiomyopathy (DCM), which can develop independently of hypertension or coronary artery disease. Chronic hyperglycemia in DM promotes oxidative stress and inflammation, driving myocardial dysfunction and fibrosis. The NLRP3 inflammasome, a cytosolic multiprotein complex, is a central mediator linking metabolic stress to innate immunity. In both type 1 and type 2 DM, it senses injurious stimuli including mitochondrial reactive oxygen species (ROS), ATP, and advanced glycation end-products (AGEs) activating caspase-1 and triggering the release of pro-inflammatory cytokines IL-1β and IL-18, thereby promoting inflammation and pyroptotic cell death.

This review focuses on NLRP3 inflammasome activation in the diabetic heart, emphasizing upstream regulators such as thioredoxin-interacting protein (TXNIP) and NF-κB and downstream consequences including cardiomyocyte death, fibrosis, and contractile maladaptation. Therapeutic approaches targeting NLRP3 range from conventional drugs, including metformin and SGLT2 inhibitors, to specific inhibitors such as MCC950 and colchicine, highlighting their cardioprotective potential. Emerging evidence on microRNA-mediated regulation, exosomal signalling, and inter-organ communication further elucidates how systemic inflammation contributes to heart failure in diabetic patients.

Despite progress, significant gaps remain regarding the cell-type specificity, temporal dynamics, and epigenetic control of NLRP3 activation in the diabetic myocardium, limiting translation of preclinical findings into effective therapies. Understanding these mechanisms may enable precise, targeted interventions to mitigate inflammation-driven cardiac injury in DM.

KEYWORDS Cardiac fibrosis, caspase-1, diabetic cardiomyopathy (DCM), hyperglycemia, IL-1β, IL-18, NLRP3 inflammasome, oxidative stress, pyroptosis, TXNIP

INTRODUCTION

Diabetes mellitus (DM) is a prevalent metabolic disorder, currently affecting over 350 million people worldwide, with nearly one billion more at risk due to prediabetes. In 2017, about 451 million people age 18 to 99 years old had diabetes, a number projected to exceed 693 million by 2045. Each year, diabetes causes around 20 million deaths globally, with medical costs estimated at $850 billion. Type 2 diabetes mellitus (T2DM), the most common form, is rising at an alarming rate in both developed and developing countries, driven by sedentary lifestyles, unhealthy diets, obesity, and genetic susceptibility (1). Chronic hyperglycemia (HG), a defining feature of DM, initiates a cascade of biochemical processes including activation of the polyol and hexosamine pathways, protein kinase C signaling, and the formation of advanced glycation end-products (AGEs) that collectively induce oxidative stress. This oxidative stress significantly contributes to complications such as diabetic neuropathy and angiopathy, impairing the function of multiple organs, including nerves, blood vessels, kidneys, liver, retina, and notably the heart (2). Sustained HG and insulin resistance in chronic diabetes leads to profound metabolic disruptions, oxidative stress, and low-grade systemic inflammation, creating a pathological environment that accelerates organ damage.

Among the serious complications of chronic diabetes, diabetic cardiomyopathy (DCM) has emerged as a critical concern. It is characterized by structural and functional alterations of the myocardium, excluding coronary artery disease or hypertension (3). The prevalence of diabetes shows a strong correlation with a similar emergence of heart failure (HF), which may be observed in patients with diabetes but who lack other typical risk factors of cardiovascular diseases. Depicted in the literature more than forty years ago, DCM is an example of diabetic-specific cardiac dysfunction, the clinical significance of which is increasingly being recognized (4). Findings of epidemiologic data in the Framingham Heart Study demonstrate an inordinate increase in the risks of HF (roughly 2-fold in men and 5-fold in women) despite accounting for all possible confounding factors (5). These results underscore the importance of resolving the molecular associations between diabetes and cardiac dysfunction.

The role of inflammation is increasingly being implicated in the pathogenesis of type 1 diabetes and type 2 diabetes. Autoimmune β-cell destruction in T1DM is associated with NLRP3-mediated production of IL-1β due to mtDNA. Inflammation is involved in the development of T2DM, leading to insulin resistance and metabolic disorders. Due to chronic metabolic stress, particularly in the context of excessive nutrition and obesity, a low-grade systemic inflammation is generated, disrupting the balance of metabolic and immune homeostasis. These systems combine physiologically through the components of common signaling networks and transcriptional regulators. But when faced with prolonged metabolic oversupply, e.g., obesity or chronic HG, there is a breakdown in this integration. The subsequent proinflammatory condition causes impairment of insulin signalling, as well as fostering end-organ injury, especially in cardiac tissue (6-8). Therefore, the interaction between an immune response and a metabolic reaction is an essential area in the development of diabetic complications.

The NLRP3 inflammasome has been identified as a key molecular sensor bridging metabolic stress and innate immune activation in diabetes. Inflammasomes are multiprotein complexes in myeloid cells that detect DAMPs such as free fatty acids, uric acid, and extracellular ATP, all of which are elevated in diabetes. Activation of NLRP3 triggers caspase-1, leading to the release of IL-1β and IL-18, which contributes to insulin resistance and inflammation (9-11), increasing NLRP3, ASC, and caspase-1 activity, as well as cytokines, in the monocytes of untreated T2DM patients upon exposure to metabolic danger signals. Silencing NLRP3 or ASC via RNA interference has been shown to abolish this response, confirming the inflammasome's central role in mediating metabolic inflammation (11). These insights provide a compelling rationale for targeting NLRP3 inflammasome pathways as a therapeutic strategy in mitigating the metabolic and cardiovascular complications of diabetes.

METHOD

This narrative review was designed to provide a comprehensive overview of the role of NLRP3 inflammasome activation in DCM and its potential therapeutic targets. The primary focus was on

studies exploring the link between HG-induced oxidative stress, inflammation, and cardiac remodelling in diabetes.

A literature search was conducted using PubMed, Scopus, and Web of Science to identify relevant studies published between 2003 and 2025. Search terms included "NLRP3 inflammasome," "diabetic cardiomyopathy," "oxidative stress," "TXNIP," "IL-1β," "IL-18," "pyroptosis," "cardiac fibrosis," and related keywords. Additional studies were identified through citation tracking of key reviews and primary research articles.

The review considered experimental studies in human, animal, and in vitro models, with emphasis on molecular mechanisms, upstream and downstream regulators of NLRP3, and interventions targeting inflammasome-mediated cardiac injury. Studies focusing on therapeutic modulation, including pharmacological agents such as MCC950, colchicine, metformin, and SGLT2 inhibitors (SGLT2i), were also included.

Selected literature was synthesized descriptively to highlight mechanistic insights, emerging evidence on microRNA and exosomal signalling, and translational perspectives. Quality and relevance of the studies were considered in narrative synthesis, with particular attention to consistency and novelty of findings.

The NLRP3 inflammasome: structure and function

The NLRP3 inflammasome is a tripartite complex composed of the sensor NLRP3 (cryopyrin), the adaptor ASC, and the effector caspase-1. It mediates innate immune responses to cellular stress by processing pro-inflammatory cytokines IL-1β and IL-18, and by inducing pyroptosis via gasdermin D cleavage (12-15).

Structurally, NLRP3 is a NOD-like receptor containing an N-terminal pyrin domain (PYD), a central NACHT domain with subdomains (FISNA, NBD, HD1, WHD, HD2), and a C-terminal leucine-rich repeat (LRR) that maintains the protein in an autoinhibited state (12, 16-19). Upon detection of danger signals such as ATP release, mitochondrial dysfunction, or ionic flux ATP binding to the NACHT domain promotes oligomerization of NLRP3. This conformational change aligns PYD domains, enabling recruitment of ASC through PYD-PYD interactions (13, 20). ASC then recruits pro-caspase-1 via CARD-CARD binding, forming filamentous assemblies that amplify inflammasome activation (21). Activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature cytokines and activates gasdermin D, leading to pore formation and pyroptotic cell death (14, 15).

Recent cryo-electron microscopy studies have revealed the three-dimensional architecture of the NLRP3-NEK7 complex, showing an earring-like configuration that stabilizes NLRP3 oligomers and enables downstream signalling (22, 19). The structural interaction between NLRP3 and NEK7 not only ensures inflammasome assembly but also provides a mechanistic basis for tissue-specific responses to metabolic stress. For example, in cardiomyocytes and endothelial cells, NEK7-mediated NLRP3 activation under hyperglycemic conditions enhances IL-1β signalling and mitochondrial ROS generation, promoting myocardial inflammation and remodelling.

Thus, dysregulated NLRP3 activation serves as a molecular bridge linking cellular metabolic stress to chronic inflammation in cardiometabolic disorders such as type 2 diabetes, obesity, atherosclerosis, and DCM (23, 24). This emphasizes the significance of understanding NLRP3 structure-function relationships to inform therapeutic targeting. The structural and functional details of the NLRP3 inflammasome components, formerly presented in Table 1, are now provided in the supplementary materials.

Canonical NLRP3 inflammasome activation pathway

The canonical pathway relies on a two-signal model (Figure 1).

I. Priming signal (signal 1): transcriptional up-regulation (NF-κB)

The priming signal ensures the necessary components for the inflammasome are synthesized and ready in the cytoplasm.

• Triggers: pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) activate cell-surface receptors (e.g., TLRs, cytokine receptors). In the context of the figure, this signal is strongly driven by high glucose/HG and the resulting cellular stress.

• NF-κB activation: the canonical signaling cascade involves the activation of the IKK complex, which frees the transcription factor NF-κB from its inhibitor (IκB).

Table 1. The NLRP3 inflammasome: structure and function

Component	Domain structure	Key structural features	Function in inflammasome assembly
NLRP3 (sensor)	- N-terminal PYD (pyrin domain) - Central NACHT domain (includes FISNA, NBD, HD1, WHD, HD2) - C-terminal LRR domain	- PYD: 6-helix bundle; mediates PYD-PYD interactions - NACHT: ATPase activity; oligomerizes upon ATP binding - LRR: 12 repeats; maintains stability and protein-protein interactions	Detects danger signals and oligomerizes; recruits ASC via PYD-PYD interaction; initiates inflammasome formation
ASC (adaptor)	- N-terminal PYD - C-terminal CARD (Caspase recruitment domain)	- Forms prion-like ASC filaments - PYD: interacts with NLRP3 - CARD: interacts with caspase-1	Bridges NLRP3 and caspase-1; transmits oligomerization signal; scaffolds for caspase-1 recruitment
Caspase-1 (effector)	- N-terminal CARD - Catalytic subunits: p20 and p10	- CARD interacts with ASC's CARD - Undergoes dimerization and self-cleavage (activation)	Becomes proteolytically active; cleaves pro-IL-1β/IL-18; cleaves GSDMD to trigger pyroptosis

PYD, pyrin domain; NACHT, NAIP, CIITA, HET-E, and TP1 domain; FISNA, fish-specific NACHT associated domain; NBD, nucleotide-binding domain; HD1/HD2, helical domains 1 and 2; WHD, winged helix domain; LRR, leucine-rich repeat; CARD, caspase recruitment domain; ASC, apoptosis-associated speck-like protein containing a CARD; IL-1β/IL-18, interleukin-1 beta/interleukin-18; GSDMD, gasdermin D.

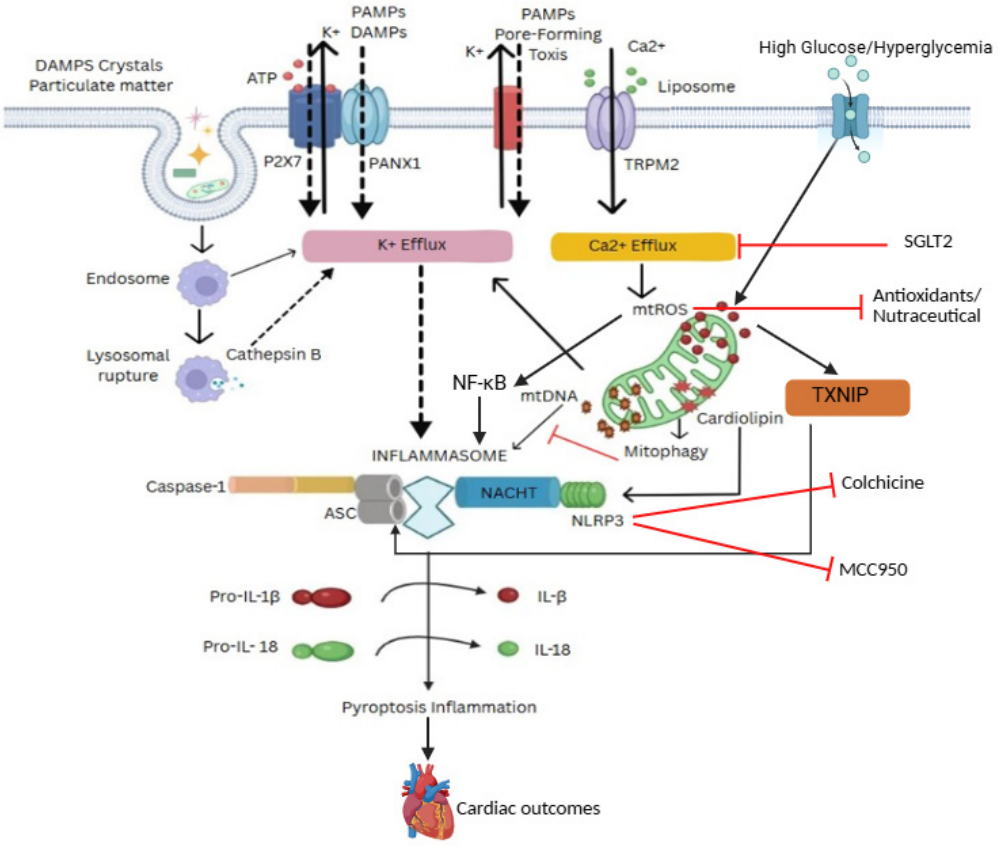


Figure 1. Mechanisms of stress-induced cardiac inflammation and emerging therapeutic targets
This schematic illustration depicts the activation pathway of the NLRP3 inflammasome, highlighting upstream signals such as DAMPs, PAMPs, and cellular stressors (e.g., high glucose/hyperglycemia) that lead to ion flux (K^+ and Ca^{2+}), mitochondrial dysfunction, and lysosomal damage. These signals culminate in the activation of the NLRP3 inflammasome complex, composed of NLRP3, ASC, and caspase-1, resulting in the maturation of pro-inflammatory cytokines IL-1β and IL-18 and inducing pyroptosis. Several pharmacological inhibitors (e.g., MCC950, colchicine) and modulators (e.g., antioxidants, SGLT2 inhibitors, TXNIP suppression) are indicated as potential therapeutic strategies targeting various points of the inflammasome activation pathway to mitigate adverse cardiac outcomes.

• Gene expression: NF-κB translocates to the nucleus (as indicated by the arrow pointing toward the nucleus/genes) and promotes the expression of:

1. The inflammasome sensor protein: NLRP3.

2. The inactive inflammatory precursor cytokines: Pro-IL-1β and Pro-IL-18.

II. Activation signal (signal 2): inflammasome assembly

The activation signal is triggered by the detection of acute danger and causes the NLRP3 protein to change conformation and assemble the complex. The figure shows four main pathways that provide this signal:

A. Ion flux disturbances (K^+ efflux and Ca^{2+} influx)

• Potassium (K^+) efflux: this is the most common activation signal.

o DAMPs (ATP): ATP released from damaged cells binds to the P2X7 receptor, opening a large pore (often via PANX1), causing a dramatic loss of intracellular K^+ (K^+ efflux).

o Pore-forming toxins also directly create pores, leading to K^+ efflux.

o The drop in intracellular K^+ concentration is the ultimate trigger for NLRP3 activation.

• Calcium (Ca^{2+}) influx: stimuli can activate the TRPM2 channel, leading to an influx of Ca^{2+} that contributes to mtROS generation, thereby linking to the activation signal.

B. Lysosomal damage

• Particulate matter: triggers like DAMPs (crystals, particulate matter) are internalized by the cell.

• Lysosomal rupture: these crystals can destabilize and rupture the Endosome/Lysosome, releasing lysosomal contents (like the enzyme Cathepsin B) into the cytosol, which acts as an NLRP3 activator.

C. Metabolic stress (the diabetic trigger)

• mtROS generation: HG causes mitochondrial stress, leading to the generation of mitochondrial reactive oxygen species (mtROS).

• TXNIP pathway: mtROS causes the release of thioredoxin-interacting protein (TXNIP) from the thioredoxin complex. TXNIP then directly binds to and activates NLRP3.

• mtDNA release: severe mitochondrial damage, indicated by changes to the lipid cardiolipin, can cause the release of mitochondrial DNA (mtDNA) into the cytosol, which acts as an NLRP3 ligand.

• Mitophagy: the cell attempts a protective measure called mitophagy (selective degradation of damaged mitochondria) to remove the source of mtROS/mtDNA and dampen NLRP3 activation.

III. Inflammasome assembly and effector functions

• Complex formation: signal 2 causes NLRP3 to oligomerize (assemble) with the adaptor protein ASC and the inactive pro-enzyme Pro-caspase-1. The assembly is mediated by the NACHT domain of NLRP3.

• Caspase-1 activation: within the complex, pro-caspase-1 autocatalytically cleaves itself into active Caspase-1.

• Effector functions: active caspase-1 then performs two critical functions:

1. Cytokine maturation: cleaves pro-IL-1β and pro-IL-18 into their mature, secretable forms (IL-1β and IL-18).

2. Cell death: triggers pyroptosis, a highly inflammatory form of programmed cell death.

IV. Pathology and therapeutic intervention (the cardiac context)

• Cardiac outcomes: the released pro-inflammatory cytokines (IL-1β/IL-18) are major drivers of cardiac pathology in DCM, leading to adverse remodeling, fibrosis, hypertrophy, and ultimately contractile dysfunction (HF).

• Therapeutics: the figure correctly highlights several intervention points:

o SGLT2i: act upstream by reducing high glucose, thereby limiting mtROS and TXNIP activation.

o Antioxidants/nutraceuticals: target and scavenge mtROS production.

o MCC950: a specific inhibitor that directly targets the NLRP3 component, blocking its activation.

o Colchicine: targets microtubule polymerization, indirectly inhibiting NLRP3 assembly/trafficking.

Non-canonical caspase-11 activation leading to pyroptosis and IL-β/IL-18 processing

This pathway illustrates how gram-negative bacterial infection and metabolic stress converge on NLRP3 inflammasome activation, leading to

cardiomyocyte injury through inflammatory signalling and pyroptotic cell death (Figure 2).

I. Recognition of gram-negative bacteria

• Internalization: Gram-negative bacteria are internalized within cellular vacuoles.

• Vacuolar lysis: guanylate-binding proteins (GBPs) facilitate vacuolar disruption, releasing bacterial components, particularly lipopolysaccharide (LPS), into the host cytoplasm.

II. Caspase-11 activation (non-canonical pathway)

• Cytosolic LPS recognition: cytoplasmic LPS binds directly to caspase-11 (caspase-4/5 in humans), inducing its activation.

• GSDMD cleavage and pore formation: activated caspase-11 cleaves gasdermin D (GSDMD), generating membrane pores. These pores allow K^+ efflux, which serves as the critical upstream signal for NLRP3 inflammasome activation.

• Crosstalk with canonical inflammasome: the K^+ efflux indirectly triggers NLRP3 activation, linking the non-canonical and canonical pathways. Caspase-8/FADD interactions may further modulate inflammasome activation in certain contexts.

III. Canonical NLRP3 inflammasome assembly

• NLRP3/ASC platform formation: upon activation, NLRP3 interacts with apoptosis-associated speck-like protein containing (ASC) a CARD and recruits pro- caspase-1.

• Caspase-1 activation: pro-caspase-1 undergoes autocleavage on the NLRP3/ASC platform to generate active caspase-1.

• Cytokine maturation: active caspase-1 processes pro-IL-1β and pro-IL-18 into their mature, biologically active forms.

• Pyroptosis: caspase-1 also triggers pyroptotic cell death, releasing inflammatory cytokines and propagating inflammation.

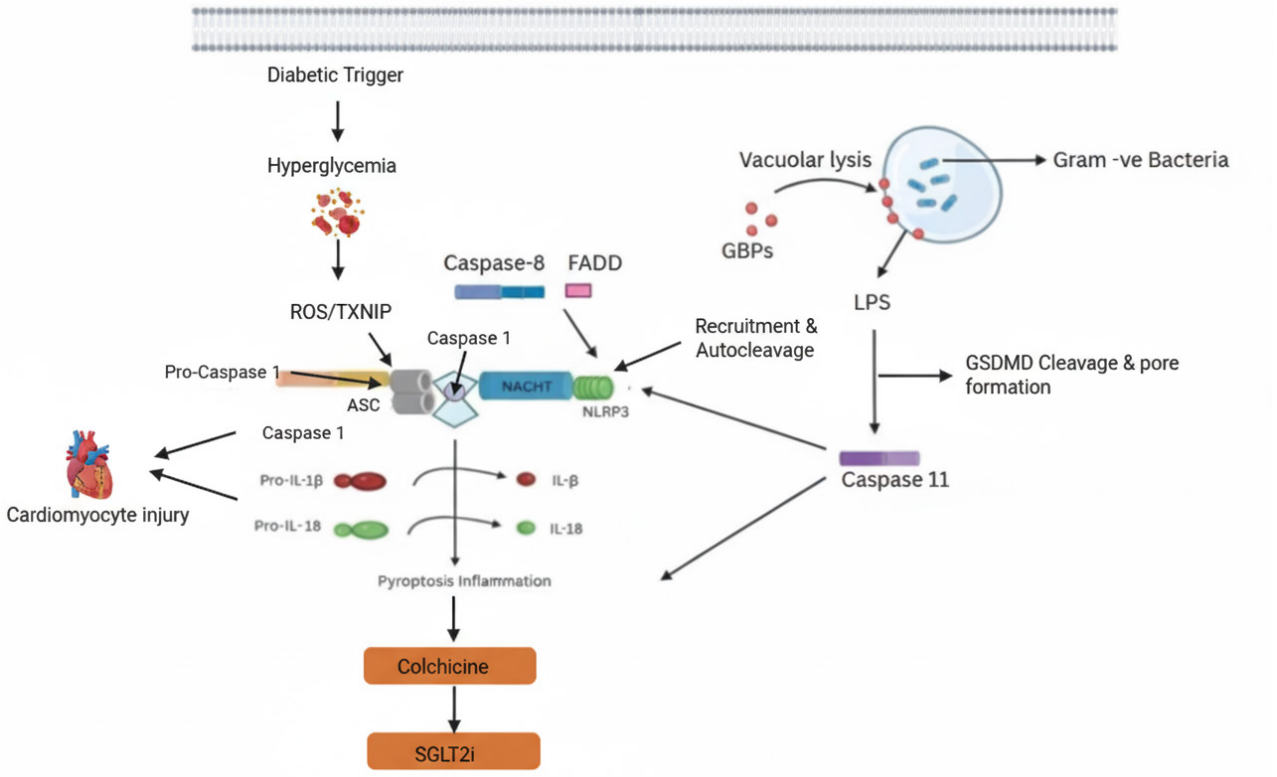


Figure 2. Canonical and non-canonical inflammasome pathways leading to cardiomyocyte injury
This diagram illustrates the non-canonical inflammasome pathway and its crosstalk with the canonical NLRP3 inflammasome, culminating in cardiomyocyte injury. Metabolic stress, such as hyperglycemia, induces ROS/TXNIP, which activates the NLRP3 inflammasome (canonical pathway). In the non-canonical pathway, Gram-negative bacteria release LPS, which is detected by Caspase-11. Caspase-11 cleaves Gasdermin D (GSDMD) to form membrane pores, causing K^+ efflux that activates NLRP3. Activated NLRP3/ASC recruits and autocleaves pro-Caspase-1 into active Caspase-1, which processes pro-IL-1β and pro-IL-18 into active cytokines, triggering pyroptotic inflammation and tissue injury. Clinically, this inflammatory cascade can be modulated by drugs such as Colchicine and SGLT2 inhibitors (SGLT2i).

IV. Parallel canonical activation by metabolic stress

• HG-induced ROS/TXNIP: metabolic stress, such as HG, generates reactive oxygen species (ROS) and TXNIP, which directly activate NLRP3, independent of bacterial infection. This represents a parallel canonical activation route relevant in diabetes-induced cardiac inflammation.

V. *Clinical relevance and therapeutic targets*

• Drug inhibitors: key therapeutics targeting this pathway include:

o Colchicine: NLRP3 inhibitor, reducing inflammasome activation and inflammation.

o SGLT2i: cardioprotective drugs shown to attenuate NLRP3-mediated injury.

The non-canonical inflammasome pathway begins with cytosolic LPS recognition by caspase-11, leading to GSDMD-mediated K^+ efflux, which activates NLRP3. The canonical pathway converges through caspase-1 activation, maturing IL-1β and IL-18, and inducing pyroptosis. Parallel metabolic stress can also trigger NLRP3 independently, and pharmacologic inhibitors offer potential therapeutic interventions.

Hyperglycemia and NLRP3 activation: molecular insights

In cardiomyocytes, HG-induced ROS promotes the release of pro-inflammatory mediators and triggers NLRP3 inflammasome activation. Genetic knockout or silencing of NLRP3, as well as pharmacological inhibition of ROS, preserves cardiomyocyte integrity and function, highlighting ROS as a key upstream mediator of HG-induced cardiac injury (25). Numerous studies indicate that HG-induced chronic inflammation and cardiomyocyte death drive the progression of DCM and may ultimately lead to HF (26). NLRP3 activation triggers pyroptosis, a form of inflammation-mediated cardiomyocyte death, leading to loss of contractile units, cardiac remodeling, and dysfunction. Importantly, silencing NLRP3 in diabetic models reduces caspase-1 and IL-1β expression, decreases cardiomyocyte death, alleviates inflammation and fibrosis, and improves cardiac function (27).

Persistent HG and dyslipidemia in diabetes promote a chronic inflammatory state largely regulated by NF-κB signaling. Elevated glucose levels enhance ROS production, AGE formation, and TLR4/MyD88 activation, all of which drive NF-κB activation. Once activated, NF-κB translocates to the nucleus and upregulates pro-inflammatory genes such as NLRP3, pro-IL-1β, and pro-IL-18, providing the essential "priming" step for inflammasome activation (28). Following priming, the NLRP3 inflammasome comprising NLRP3, ASC, and pro-caspase-1 is fully activated in response to secondary signals like mitochondrial ROS, lysosomal damage, or TXNIP interaction. This leads to caspase-1 activation, cleavage of pro-IL-1β and pro-IL-18 into active cytokines, and gasdermin D-mediated pyroptosis, further intensifying inflammation (29).

This pathogenic cascade is particularly evident in DCM, where cardiomyocytes and cardiac fibroblasts exhibit increased ROS production, driving TXNIP-mediated NLRP3 activation. Concurrently, TLR4/NF-κB signaling enhances priming and reinforces a feed-forward loop through IL-1β-mediated reactivation of NF-κB and JNK pathways, promoting myocardial inflammation, hypertrophy, apoptosis, and fibrosis (30). Inflammasome activation also accelerates cardiomyocyte pyroptosis, fibroblast activation, and extracellular matrix (ECM) remodeling, leading to impaired contractility and structural deterioration characteristic of DCM (31). Additionally, impaired angiogenesis in diabetic myocardial infarction is linked to NLRP3-induced dysfunction in endothelial progenitor cells via PI3K/Akt/mTOR pathway dysregulation (32). Chronic systemic and cardiac inflammation is a major contributor to DCM and the progression to HF, driving ECM remodeling, cardiac fibrosis, and contractile dysfunction (33).

NLRP3 gene silencing has been shown to reduce cardiomyocyte pyroptosis and myocardial fibrosis and to improve cardiac dysfunction in a type 2 diabetic rat model (34). Moreover, several antidiabetic drugs, including dapagliflozin, empagliflozin, liraglutide, exenatide, saxagliptin, pioglitazone, glyburide, and acarbose, have been reported to modulate NLRP3 signaling and confer favorable cardiac effects (35). Clinical studies provide translational support for this pathway: inhibition of IL-1β with canakinumab or NLRP3 with dapansutrile improves cardiac function and reduces HF risk in patients, underscoring the pathogenic relevance of HG-driven NLRP3 activation in the heart (36).

NLRP3 inflammasome of diabetic cardiomyopathy and HF

Fibroblast activation and fibrogenic pathways induced by HG depend largely on AGE-RAGE signalling, TGF-β/Smad pathway activation, oxidative stress, and cytokine-mediated immune cell recruitment, all of which contribute to cardiac fibrosis in diabetes. These mechanisms promote excessive accumulation and cross-linking of ECM proteins, resulting in myocardial stiffness and diastolic dysfunction, even in the absence of coronary artery disease. Histopathological studies in diabetic subjects have revealed interstitial and perivascular fibrosis associated with ECM remodelling and cross-linking processes that underlie this functional impairment (3, 31).

Beyond classical profibrotic mechanisms, accumulating evidence highlights the pivotal role of NLRP3 inflammasome activation in sustaining low-grade inflammation and metabolic stress in DCM. HG and insulin resistance chronically upregulate NLRP3 and its upstream activator TXNIP in cardiac tissue, leading to enhanced IL-1β production, myocardial fibrosis, and contractile dysfunction. Experimental studies in diabetic rat models have demonstrated that resveratrol (RSV) treatment improves both systolic and diastolic function, reduces fibrosis, and preserves mitochondrial and myofibrillar structure. These cardioprotective effects are largely mediated through inhibition of NLRP3 activation via suppression of TXNIP and MAPK signalling pathways (ERK1/2, JNK, and p38 MAPK. Notably, silencing NLRP3 using targeted miRNA restores cardiac architecture and function even without systemic metabolic improvement, confirming its central role in DCM pathogenesis. Furthermore, RSV fails to provide additional benefits in NLRP3-silenced animals, indicating that its therapeutic effects are dependent on NLRP3 inhibition (37).

Activation of NLRP3 also contributes to adverse cardiac remodelling through cleavage and maturation of pro-inflammatory cytokines such as IL-1β. Following myocardial injury, necrotic cardiomyocytes release IL-1α as an early alarmin, while inflammasome activation amplifies IL-1β secretion in cardiomyocytes and interstitial cells. IL-1 signalling recruits leukocytes, promotes ECM degradation, and delays reparative fibroblast responses, thereby exacerbating fibrosis and HF progression. Other IL-1 family cytokines, including IL-18 and IL-33, play additional roles, with IL-18 enhancing inflammation and IL-33 exerting cytoprotective effects. Clinical and preclinical studies support IL-1 inhibition as a promising therapeutic strategy for both ischemic and non-ischemic cardiomyopathies, including DCM (38).

Moreover, NLRP3 mediates myocardial apoptosis and contractile dysfunction in both diabetic and ischemic conditions. Cellular stress activates NLRP3 to trigger caspase-1-dependent processing of pro-IL-1β and pro-IL-18 into their active forms, promoting pyroptotic cell death. This exacerbates myocardial injury, reduces contractility, and contributes to ventricular dysfunction. In acute myocardial infarction (AMI) models, pharmacologic inhibition of NLRP3 markedly reduces myocardial damage and preserves systolic performance (39). Collectively, experimental and preclinical evidence demonstrates that inhibition of NLRP3 or its downstream cytokines suppresses inflammation, limits apoptosis, and preserves cardiac hemodynamics underscoring NLRP3 as a critical therapeutic target in arrhythmogenic and diabetic cardiomyopathies (40).

Therapeutic targeting of NLRP3 in diabetes-induced cardiac complications

Inflammasome activation, particularly involving NLRP3, is implicated in the pathogenesis of diabetic cardiomyopathy. Under diabetic and metabolically stressed conditions, NLRP3 activation can promote caspase-1-dependent maturation of IL-1β and IL-18 and pyroptotic cell death, contributing to myocardial inflammation and fibrosis. In an estrogen-deficient diabetic rat model, increased NLRP3 inflammasome activity was associated with cardiac pyroptosis, myocardial fibrosis, mast cell degranulation, and diastolic dysfunction. Treatment with the NLRP3 inhibitor MCC950 reduced pyroptosis-related markers, myocardial fibrosis, and mast cell degranulation and partially improved diastolic function, supporting a role for NLRP3-associated inflammation in cardiac remodeling under estrogen-deficient diabetic conditions (41).

Colchicine, a millennium-old drug has been a subject of interest, with respect to its cardiovascular properties, in the current line of anti-inflammatory therapy. Colchicine prevents the

assembly and activation of NLRP3 inflammasome, which limits the release of IL-1β/IL-18 and the further vascular inflammation. Clinical studies have demonstrated that low-dose colchicine (0.5 mg/d) provides cardiovascular protection in patients with stable angina and AMI and especially post-PCI, which indicates its possible use in a combination therapy in the treatment of diabetic cardiac complications (42).

In addition to colchicine, direct inhibition of the NLRP3 inflammasome has shown therapeutic potential in preclinical models. MCC950 (CRID3), a selective NLRP3 inhibitor, has been shown to reduce diabetes-associated atherosclerotic lesion development and improve plaque stability in diabetic mice (43). In an estrogen-deficient diabetic rat model, MCC950 reduced cardiac pyroptosis and myocardial fibrosis and partially improved diastolic function (41). Emerging inhibitors like dapansutrile and novel molecules such as INF200 and NP3-146 have also demonstrated cardiometabolic benefits, offering exciting avenues for drug development (36).

Beyond synthetic drugs, metabolic therapies such as metformin exhibit anti-inflammasome effects by reducing oxidative stress and inhibiting NF-κB-mediated priming of NLRP3 (44). Furthermore, lifestyle-linked interventions, including caloric restriction (CR), act via the AMPK/SIRT1 pathway to suppress NLRP3 activation. Due to adherence challenges with CR, CR-mimicking nutraceuticals like RSV, berberine, quercetin, and L-carnitine are gaining traction. Among these, RSV has shown significant efficacy in reducing NLRP3-mediated inflammation and cardiac remodeling (44).

Innovative molecular regulators, including microRNAs, long noncoding RNAs (lncRNAs), and exosomes, have emerged as critical modulators of NLRP3 inflammasome activity in cardiac tissues (45). Studies in ischemia/reperfusion (I/R) models have shown that lncRNA-H19 promotes NLRP3 activation by sponging miR-21, increasing PDCD4 expression and forming a competing endogenous RNA network (ceRNET), which drives caspase-1 activation, gasdermin D-mediated pyroptosis, and proinflammatory cytokine release. While these findings were originally demonstrated in retinal I/R models, similar regulatory mechanisms are increasingly implicated in cardiomyocyte dysfunction under diabetic stress, contributing to inflammation, pyroptotic cell death, and adverse cardiac remodeling. Moreover, exosomes derived from cardiac or immune cells can shuttle microRNAs and lncRNAs between cells, further modulating NLRP3 activity and amplifying inflammatory signaling. Taken together, these mechanisms provide important insights into the regulation of NLRP3 inflammasome activity in diabetic cardiovascular disease and may inform strategies to mitigate cardiac injury (46).

Challenges and research gaps

Although pharmacologic or genetic inhibition of NLRP3 has been shown to attenuate myocardial fibrosis, left ventricular dysfunction, and systemic inflammation in DCM, clinical translation remains limited. Preclinical studies, particularly in animal models treated with agents such as MCC950 or colchicine, demonstrate reduced IL-1β levels and improved cardiac remodelling. However, the long-term safety, optimal dosing, and overall efficacy of these interventions in diabetic patients are not yet well established (47, 48). Given NLRP3's role in innate immunity, systemic inhibition may impair host defence, highlighting the need for tissue-specific modulators and careful evaluation in clinical trials.

Current biomarkers for diabetes and cardiovascular disease, including HbA1c, troponins, and NT-proBNP, do not specifically reflect inflammasome activity. Although IL-1β, IL-18, and caspase-1 can indicate NLRP3 activation, their nonspecific nature limits clinical utility. Advanced tools such as exosome profiling, microRNA analysis, and single-cell RNA sequencing hold promise for improving the specificity and sensitivity of detecting inflammasome-mediated cardiac injury in diabetes, but these approaches require validation in large human cohorts (46, 49).

The pathogenesis of diabetes-associated cardiac dysfunction is multifactorial, involving metabolic stress, immune activation, and endothelial dysfunction. NLRP3 activation occurs not only in cardiac tissue but also in the pancreas, liver, adipose tissue, and kidneys, contributing to systemic inflammation and multi-organ damage. This widespread activation complicates the distinction between tissue-specific and systemic effects. Moreover, inter-organ communication

mediated by immune factors and extracellular vesicles may amplify inflammatory signals, with NLRP3 activation in organs such as adipose tissue or the gut potentially worsening cardiac pathology via paracrine or endocrine mechanisms. Addressing this complexity requires integrated approaches including spatial transcriptomics, metabolomic profiling, and inter-organ immune mapping to better delineate the role of inflammasome activation in the diabetic milieu (50, 51).

Overall, while preclinical findings highlight the therapeutic potential of targeting NLRP3, careful consideration of translational challenges, safety, and organ-specific effects is essential for future clinical application.

CONCLUSIONS

The NLRP3 inflammasome acts as a key link between metabolic disturbances in diabetes and cardiac dysfunction. Beyond its innate immune role, it integrates oxidative stress, mitochondrial damage, and inflammatory signals particularly via the ROS-TXNIP-NF-κB pathway. In diabetic hearts, NLRP3 activation promotes pyroptosis, fibrosis, and remodeling, leading to DCM and HF. Importantly, its involvement in cardiac injury occurs even without classic cardiovascular risk factors, underscoring its pathological significance.

Mechanistic studies consistently demonstrate that pharmacological and genetic inhibition of NLRP3 mitigates myocardial inflammation, improves cardiac function, and reduces fibrosis. These findings reposition the inflammasome from a passive inflammatory responder to an active driver of diabetic cardiac complications, underscoring its potential as a therapeutic target in both early and advanced disease stages.

Novelty of this review

This review advances the current understanding of NLRP3 inflammasome biology by emphasizing its role as a central molecular hub integrating HG, oxidative stress, and inflammatory signaling specifically in DCM. Unlike prior reviews that mainly describe canonical and non-canonical NLRP3 pathways, this synthesis highlights cell-type specific mechanisms, contrasting cardiomyocyte versus fibroblast inflammasome activity, and underscores the contribution of inter-organ communication, including adipose-heart and gut-heart crosstalk. Moreover, it incorporates emerging regulatory layers such as microRNAs, lncRNAs, and exosomal signaling, demonstrating how these molecular modulators amplify or restrain NLRP3-driven pyroptosis and fibrosis. By integrating mechanistic insights with translational potential, including pharmacologic inhibitors (MCC950, colchicine) and RNA-based strategies, this review provides a holistic perspective linking molecular, cellular, and systemic processes, offering a foundation for precision-targeted therapies in diabetes-induced cardiac dysfunction.

Future perspectives

To translate NLRP3-targeted interventions effectively, future research should:

1. Develop tissue- and cell-type specific inhibitors that selectively modulate cardiomyocyte, fibroblast, or endothelial NLRP3 activity to minimize systemic immune suppression.
2. Characterize temporal dynamics of inflammasome activation during diabetes progression using longitudinal in vivo models and single-cell transcriptomics.
3. Elucidate non-coding RNA networks and exosomal pathways that regulate NLRP3, including their role in inter-organ signaling (adipose-heart, gut-heart), providing novel targets for precision therapeutics.
4. Identify robust biomarkers of inflammasome activity using exosomal miRNA profiling, spatial transcriptomics, or metabolomics to enable early detection of cardiac injury in diabetic patients.
5. Integrate organ-level crosstalk studies to understand how systemic inflammation contributes to local myocardial pathology, potentially guiding combinatorial or multi-targeted therapies.
6. Conduct translational clinical trials to determine the safety, efficacy, and optimal dosing of NLRP3 modulators in diabetic populations, balancing anti-inflammatory benefits with preservation of host immunity.

By focusing on these directions, the field can move beyond descriptive mechanistic studies toward actionable interventions that mitigate inflammation-driven cardiac remodeling and improve outcomes in diabetic cardiomyopathy.

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CONFLICTS OF INTEREST

There was no conflict of interest in this manuscript.

AUTHOR CONTRIBUTIONS

R.K.S.: conceptualization, investigation, data curation, writing — original draft, writing — review & editing; B.K.: conceptualization, supervision, writing — review & editing; D.R.D.: supervision, writing — review & editing; A.S.: investigation, writing — review & editing; A.W.: validation, writing — review & editing; M.K.J.: investigation, data curation; N.J.V.: investigation, data curation; V.M.G.: investigation, data curation; S.S.: investigation, data curation; V.V.: investigation, data curation.

All authors have read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data used in this study are not publicly available due to concerns regarding participant confidentiality but are available from the corresponding author upon reasonable request.

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable

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