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REVIEW

NLRP3 Inflammasome Targeting Offers a Novel Therapeutic Paradigm for Sepsis-Induced Myocardial Injury

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Abstract: Cardiac or myocardial dysfunction induced by sepsis, known as sepsis-induced cardiomyopathy or sepsis-induced myocardial injury (SIMI), is a common complication of sepsis and is associated with poor outcomes. However, the pathogenesis and molecular mechanisms underlying SIMI remain poorly understood, requiring further investigations. Emerging evidence has shown that NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasomes contribute to SIMI. Compounds that inhibit NLRP3-associated pyroptosis may exert therapeutic effects against SIMI. In this review, we first outlined the principal elements of the NLRP3 signaling cascade and summarized the recent studies highlighting how NLRP3 activation contributes to the pathogenesis of SIMI. We outlined selective small-molecule modulators that function as NLRP3 inhibitors and delineated their mechanisms of action to attenuate SIMI. Finally, we discuss the major limitations of the current therapeutic paradigm and propose possible strategies to overcome them. This review highlights the pharmacological inhibition of SIMI as a promising therapeutic strategy.

Keywords: sepsis, sepsis-induced myocardial injury, NLRP3, pyroptosis, bioactive compounds

Introduction

Sepsis is a highly heterogeneous syndrome commonly diagnosed in critically ill patients. It is a complex disorder associated with acute organ dysfunction caused by a dysregulated host response to infection.[1,2] The high global incidence of sepsis annually causes approximately 31.5 million deaths.[3] Sepsis-induced myocardial injury (SIMI), or sepsis-induced cardiomyopathy, is an increasingly recognized and emerging form of transient cardiac dysfunction in patients with sepsis.[4,5] Epidemiological studies have revealed that the prevalence of SIMI ranges from 10% to 70%.[6–8]

Despite advances in the understanding of the pathophysiology of sepsis and SIMI, no SIMI-targeted therapy has been approved.[9] Therefore, uncovering the specific molecular mechanisms underlying SIMI to improve patient outcomes is essential. Mechanistic insights have revealed several pathophysiological mechanisms that are potentially involved in SIMI, including mitochondrial dysfunction, downregulation of adrenergic pathways, release of circulating myocardial depressant substances, reactive oxygen species (ROS), and nitric oxide (NO), coronary microvascular perturbation, calcium handling abnormalities, and downregulation of genes encoding mitochondrial and sarcomeric proteins.[7] A dysregulated host response to an infection triggers SIMI.[5,7] This dysregulation involves many pathways of the septic inflammatory response driven by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[7]

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These DAMPs and PAMPs activate pattern-recognition receptors, including Toll-like receptors (TLRs) expressing on cardiomyocytes.[10] Circulating DAMPs, PAMPs, and cytokines activate cardiomyocytes, cardiac fibroblasts (CFs), and endothelial cells to generate inflammatory agents that further enhance the production of inducible nitric oxide synthase, causing myocardial suppression.[11] The nucleotide-binding oligomerization domain-containing protein (NOD)-like receptor (NLR) family, particularly NOD-, carboxy-terminal leucine-rich repeat (LRR)-, and pyrin domain-containing protein 3 (NLRP3), that recognizes PAMPs and DAMPs in the cytoplasm, has attracted increasing attention. NLRP3 generates a complex known as the inflammasome, which activates intracellular signaling pathways to release proinflammatory cytokines, such as interleukin-1β (IL-1β) and interleukin-18 (IL-18).[12] In the past decade, there has been growing interest in elucidating the role of NLRP3 in SIMI (Figure 1). Given the vital role of NLRP3 signaling in the pathogenesis of SIMI, drug discovery targeting the NLRP3 pathway has gained significant attention in the past few years.[8] NLRP3 inhibitors are new and attractive targets for treating SIMI.

In this review, we outline the principal elements of the NLRP3 signaling cascade and summarize the mechanism underlying the contribution of NLRP3 to SIMI. We focused on emerging therapeutic agents that can inhibit the activation of the NLRP3 inflammasome and NLRP3-associated pyroptosis and delineated their beneficial pharmacological effects in SIMI treatment. The present review highlights that pharmacological inhibition of NLRP3 offers a novel and attractive therapeutic strategy against SIMI.

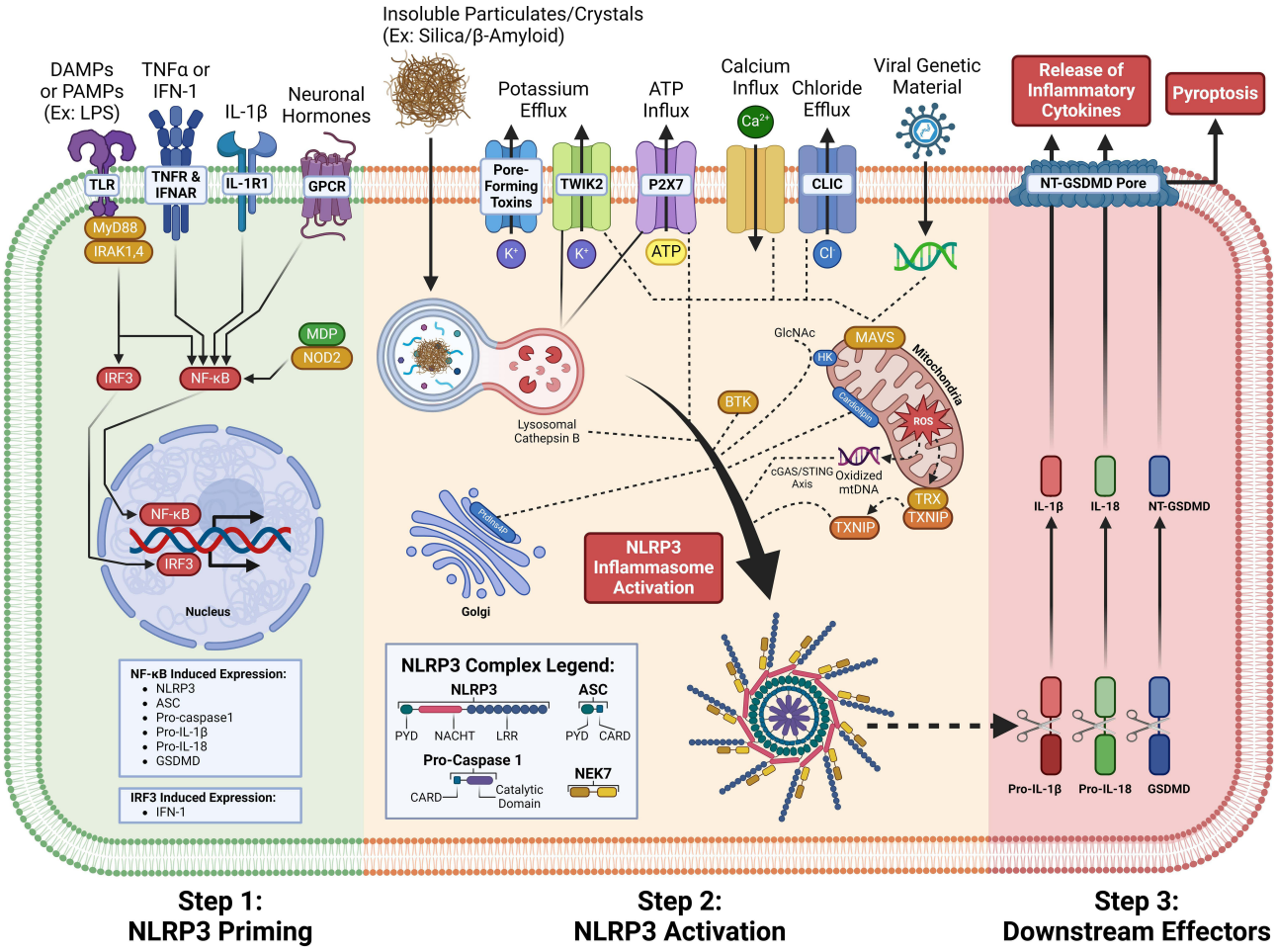

Figure 1 NLRP3 priming, activation, and downstream effectors NLRP3 activity is initiated by extracellular signaling derived from damage-associated molecular patterns (DAMPs)/pathogen-associated molecular patterns (PAMPs), cytokines, or neuronal hormones. Integrated signals promote the activity of the NF-kB and IRF3 transcription factors, promoting the expression of the NLRP3 protein components and substrates. Lysosomal degradation of insoluble particulates/crystals, potassium efflux, calcium influx, chloride efflux, viral infection, and mitochondrial ROS generation promote the assembly of the mature NLRP3 complex. Once mature and active, the NLRP3 complex cleaves pro-IL-1b, pro-IL-18, and GSDMD to initiate pyroptosis and the paracrine spread of pro-inflammatory cytokines.

Overview of NLRP3 Inflammasome and Pyroptosis

NLRP3 Inflammasome: An Overview

The NLRP3 inflammasome comprises NLRP3 (a sensor), an apoptosis-associated speck-like protein containing a carboxy-terminal caspase recruitment domain (CARD) (ASC, an adaptor; also known as PYCARD), and caspase 1 (an effector).[13] NLRP3 is the most well-characterized and extensively studied inflammasome sensor molecule that detects PAMPs and DAMPs.[14,15] Similarly, it is a tripartite protein of the NLR family that contains central NACHT (in NAIP, CIITA, HET-E, and TP1), LRR, and amino-terminal pyrin (PYD) domains.[13] The NACHT domain has an ATPase activity that is vital for NLRP3 self-association and function.[16] The LRR domain mediates autoinhibition by folding back into the NACHT domain. ASC possesses two protein interaction domains: CARD, that recruits caspase-1 through CARD-CARD interactions,[17–19] and an amino terminal PYD.[20] Full-length caspase 1 has an amino-terminal CARD, a small carboxy-terminal catalytic subunit domain (p10), and a large central catalytic domain (p20).

NLRP3 detects and senses a broad range of endogenous danger signals, environmental irritants, and microbial motifs, causing the formation and activation of the NLRP3 inflammasome. NLRP3 inflammasome assembly with pro-caspase 1 and ASC causes the proteolytic maturation of caspase 1.[14] Two distinct steps, priming and activation, initiate the assembly of the fully functional NLRP3 inflammasome[14] (Figure 1). The priming step is involved in the recognition of DAMPs or PAMPs via receptors such as TLRs or NOD2 and the detection of IL-1β and tumor necrosis factor (TNF), which activates nuclear factor-kappaB (NF-κB) and upregulates the expression of NLRP3, caspase 1, and IL-1β.[21–23] In the activation step, through homotypic PYD-PYD interactions, NLRP3 oligomerizes and recruits ASC, nucleating the formation of helical ASC filament.[20,24] Multiple ASC filaments coalesce into a single macromolecular complex, forming an aggregate assembly known as the "ASC speck" (also termed the "inflammasome speck"), which acts as a molecular platform for pro-caspase 1 activation.[20,24–26] The ASC and pro-caspase 1 combine via CARD-CARD interactions to form prion-like filaments. Pro-caspase 1 undergoes auto-proteolytic cleavage within this complex to produce mature caspase 1.[25] NLRP3 inflammasome assembly causes caspase 1-dependent release of the proinflammatory cytokines IL-1β and IL-18 and gasdermin D (GSDMD)-mediated pyroptotic cell death, ie, pyroptosis.

Pyroptosis

Pyroptosis is a GSDMD-dependent form of inflammatory, lytic cell death.[13,27,28] NLRP3 inflammasome activation exacerbates the inflammatory response and amplifies tissue injury by inducing the process and release of IL-1β and IL-18, triggering cell death via pyroptosis.[27] Caspase 1 is the primary effector of pyroptosis. Pyroptosis results from membrane permeability induced by the N-terminal fragment of GSDMD (GSDMD-NT), causing cell swelling and plasma membrane rupture via ninjurin.[29,30] GSDMD-NT has a high affinity for phosphatidylserine and phosphatidylinositol phosphates, which mostly exist on the intracellular face of the plasma membrane, decreasing injury to neighboring cell membranes.[31] Pyroptosis is attracting increasing attention in SIMI.

Activation of the NLRP3 Inflammasome in the Development of Septic Cardiomyopathy

Histologically, the primary cells within the heart are cardiomyocytes and non-myocytes, such as fibroblasts, endothelial cells, and macrophages, which have recently been the focus of immunocardiology and SIMI studies.[32] The process of NLRP3 inflammasome formation and activation in the heart is cell-type-specific during sepsis.[27] NLRP3 inflammasome activation provides a source of cytokines that exert paracrine and systemic effects on heart contractility during sepsis.[27,33,34] Experimental NLRP3 inflammasome activation was primarily observed in the fibroblasts, macrophages, and cardiomyocytes of the heart during sepsis (Figure 2).

Role of CFs

A previous study in 2014 was the first to reveal that NLRP3 inflammasome activation contributes to the pathogenesis of SIMI.[34] Activation of the NLRP3 inflammasome has been observed in CFs in SIMI.[34] Lipopolysaccharide (LPS) upregulates

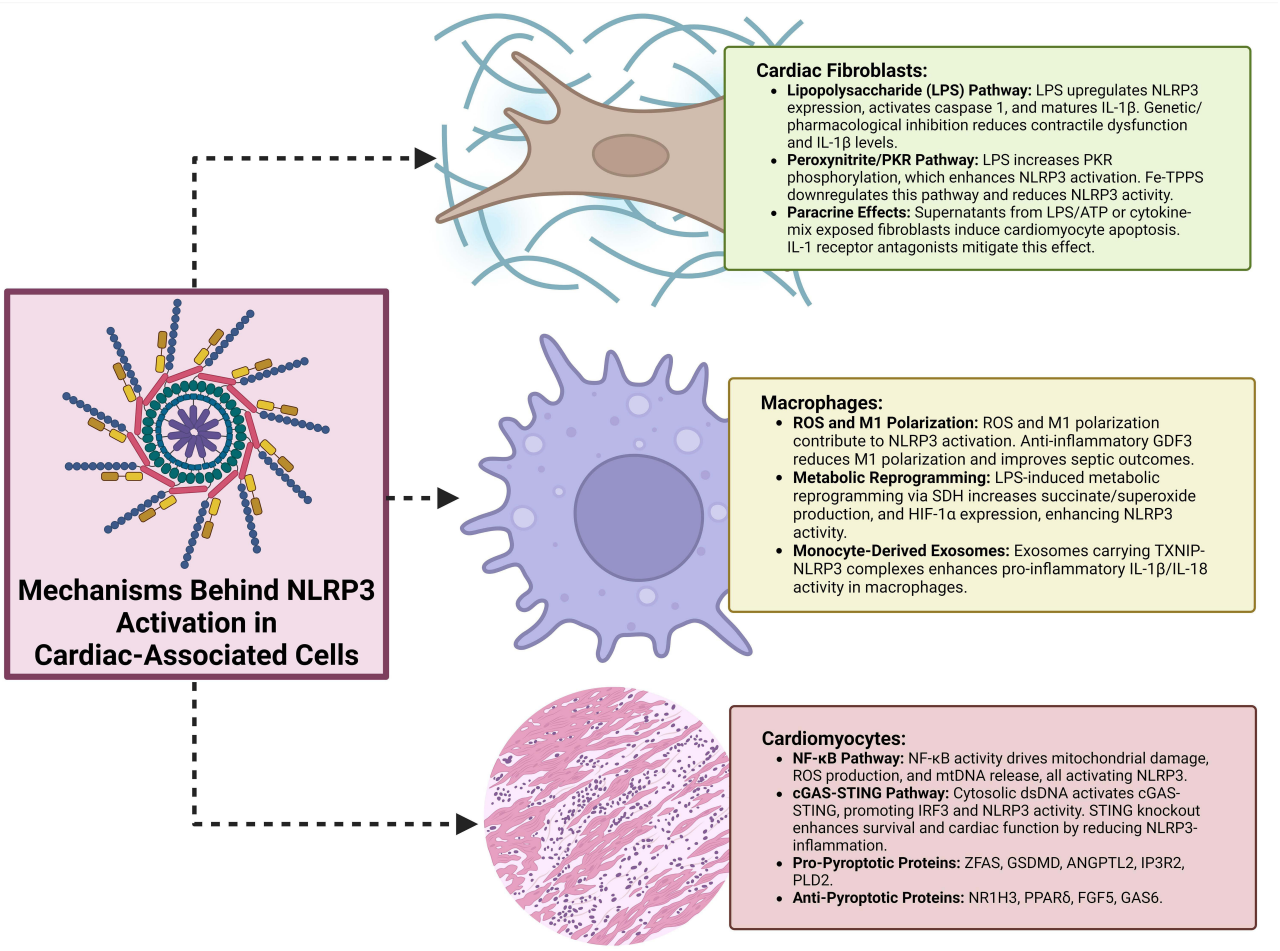

Figure 2 Mechanisms underlying NLRP3 activation in cardiac-associated cells In addition to cardiomyocytes, NLRP3 activation in cardiac fibroblasts and macrophages is crucial for the onset and progression of sepsis-induced myocardial injury (SIMI). Cardiac fibroblasts are primarily regulated by the lipopolysaccharide (LPS), peroxynitrite/PKR, and paracrine pathways. Macrophages are regulated by reactive oxygen species (ROS)/M1 polarization, metabolic reprogramming, and exosomal exposure. Finally, cardiomyocytes are regulated by nuclear factor-kappaB (NF-kB) pathway activity, cGAS-STING pathway activity, and the balance between pro/anti-pyroptotic protein expression.

NLRP3, activates caspase-1, and induces the maturation and release of IL-1β from CFs.[34] Genetic and pharmacological inhibition of NLRP3 suppresses NLRP3 inflammasome activation in CFs. NLRP3 inflammasome inhibition in CFs attenuates the ability of LPS-challenged CFs to affect cardiomyocyte function. Activation of the NLRP3 inflammasome contributes to myocardial contractile dysfunction in LPS-induced septic mice, while NLRP3 inhibition by glyburide alleviates myocardial contractile dysfunction and decreases myocardial and circulating IL-1β, boosting the survival rate of mice.[34] LPS activates the NLRP3 inflammasome, as evidenced by the upregulated expression of NLRP3, ASC, and caspase-1 in primary neonatal CFs.[35] Inhibition of protein kinase R (PKR) downregulates LPS-induced upregulation of NLRP3 and pro-IL-1β expression before LPS priming is performed. Inhibiting PKR after priming but before activation decreases caspase 1 activation and mature IL-1β secretion without altering protein NLRP3 or pro-IL-1β protein levels.[36] Fe-TPPS, a peroxynitrite decomposition catalyst, inhibits the priming and activation of the NLRP3 inflammasome. Similarly, Fe-TPPS prevents the LPS-induced phosphorylation of PKR (T451) in fibroblasts. These results suggest that LPS/ATP modulates the priming and activation of the NLRP3 inflammasome through the peroxynitrite/PKR pathway in CFs.[36] Challenging cardiomyocytes with supernatants of CFs with LPS/ATP or Cyto-mix (IL-18, IL-1β, and HMGB1) triggered apoptosis in cardiomyocytes, which was alleviated by IL-1 receptor antagonist or CORM-3.[37]

Role of Macrophages

Sepsis or endotoxemia induces NLRP3 inflammasome activation in macrophages, which causes the release of IL-1β, an essential mediator in the inflammatory response. ROS are involved in NLRP3 inflammasome activation. Inhibition of M1 phenotypic polarization and inflammation in macrophages attenuates SIMI.[38] Elevated levels of growth differentiation factor 3 (GDF3), a member of the transforming growth factor beta superfamily, were observed in the serum of patients with sepsis, and they were associated with sepsis severity and mortality.[39] Recombinant GDF3 protein (rGDF3) improves survival rates and enhances cardiac function by suppressing the M1 macrophage proinflammatory phenotype in septic mice.[39] rGDF3 reduces the production of proinflammatory cytokines in macrophages. Metabolic reprogramming is associated with NLRP3 inflammasome activation and altered glycolysis in activated macrophages, causing inflammatory responses in septic cardiomyopathy.[40] Succinate dehydrogenase (SDH) and succinate are involved in macrophage metabolic reprogramming. LPS facilitates SDH activity, accumulation of succinate, and production of superoxide anion to promote mitochondrial dysfunction and increases the expression of hypoxia-inducible factor-1α (HIF-1α) in macrophages, causing SIMI.[40] Macrophage depletion alleviates LPS-induced SIMI.[33] IL-30 ablation promotes proinflammatory effects by enhancing Ly6Chigh macrophage polarization and pyroptosis.[41] NLRP3 inhibition by MCC950 reverses IL-30 loss-induced cardiac dysfunction, macrophage polarization and pyroptosis,[41] suggesting that inhibition of proinflammatory macrophage polarization and pyroptosis can attenuate SIMI. The upregulated TXNIP-NLRP3 complex in monocyte-derived exosomes facilitates the trafficking of monocytes in circulation to local macrophages, where they enhance the cleavage of inactive IL-18 and IL-1β to aggravate cardiovascular inflammation.[42]

Role of Cardiomyocytes

The connection of NF-kB with the NLRP3 inflammasome causes a disproportionate inflammatory response in mouse myocardium during sepsis.[43] Receptor-mediated recognition of inflammatory signals converges on protein kinases, degrading the NF-kB inhibitor I-kappa-B-alpha (IkBa) via ubiquitination and enhancing NF-kB translocation to the nucleus, where it upregulates IkBa and NLRP3. NF-kB-dependent mediators and proinflammatory stimuli damage the mitochondria and facilitate ROS production, inducing mtDNA damage and opening mitochondrial permeability transition pores. The release of mtDNA and ROS into the cytoplasm triggers NLRP3 inflammasome activation, causing caspase-1-dependent IL-1β maturation.[43] NLRP3 inflammasome activation contributes to SIMI, while NLRP3 ablation protects against myocardial dysfunction in septic $NLRP3^{-/-}$ mice.[44] NLRP3 ablation inhibits NF-κB activation, which accounts for the reduction in the inflammatory response.[44]

Cyclic GMP-AMP (cGAMP) synthase (cGAS) and cyclic endoplasmic reticulum-associated adaptor stimulator of interferon (IFN) genes (STING) are crucial elements of the innate immune system.[45,46] Microbial DNA is a PAMP and the primary "molecular threat" needed to activate the DNA sensor cGAS. cGAS synthesizes the cyclic dinucleotide cGAMP, which binds to STING, allowing it to migrate from the ER to the Golgi and recruit TANK-binding kinase 1, which phosphorylates the transcription factor IFN regulatory factor 3 (IRF3). Phosphorylated IRF3 dimerizes and translocates to the nucleus to upregulate the expression of Type I IFN (IFN-I) and IFN-stimulated gene (ISG).[46–48] Increasing evidence has revealed that cGAS-STING overactivation and aberrant regulation trigger undesired outcomes, such as neuroinflammation and neurodegeneration, contributing to neurological disorders and accelerating disease progression.[45–47,49–52] Recent studies have indicated that the cGAS-STING pathway is involved in sepsis and sepsis-associated organ dysfunction, including SIMI.[53] A previous study has shown that the STING-IRF3 axis contributes to SIMI by activating NLRP3.[54] The LPS challenge promoted STING translocation to the perinuclear area, whereas IRF3 translocated to the nucleus in H9c2 and neonatal rat cardiomyocyte (NRCM) cells. Phosphorylated IRF3 upregulates NLRP3 expression.[54] Silencing STING increases the survival rate, attenuates cardiac function, apoptosis, and pyroptosis, and suppresses inflammatory cytokines in the myocardium and serum of mouse cardiomyocytes.[54] NLRP3 overexpression reverses the protective effects of STING knockdown against LPS in vitro in cardiomyocytes.[54] Dissociated TXNIP binds directly to NLRP3 to form a cytosolic inflammasome, causing cardiomyocyte injury. These findings suggest that STING loss attenuates LPS-induced septic cardiomyopathy in mice, highlighting that targeting cardiomyocyte STING is a promising therapeutic strategy for preventing SIMI. STING loss inhibits IRF3 phosphorylation and results in its nuclear translocation, which further halts NLRP3-mediated inflammation and pyroptosis in cardiomyocytes.[54]

Specific regulators modulate NLRP3 expression in cardiomyocytes during SIMI. Increased expression of zinc finger antisense 1 (ZFAS1) was observed in septic hearts. Silencing ZFAS1 decreased LPS-mediated pyroptosis and alleviated autophagy inhibition.[55] SP1 is an essential transcription factor that upregulates ZFAS1 expression. miR-590-3p functions as a downstream effector to reverse ZFAS1-mediated SIMI. Moreover, 5'AMP-activated protein kinase/mechanistic target of rapamycin kinase (AMPK/mTOR) signaling participates in miR-590-3p-regulated autophagy and pyroptosis in cardiomyocytes.[55] These results suggest that SP1-activated ZFAS1 aggravates SIMI by acting as a ceRNA for miR-590-3p to regulate AMPK/mTOR signaling, suppress autophagy, and induce pyroptosis in cardiomyocytes.[55] The decreased expression of liver X receptor α (NR1H3)-related molecules and increased NLRP3 levels were observed in septic mice. NR1H3 ablation aggravates SIMI by facilitating NLRP3-mediated inflammation, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress (ERS), and apoptosis.[56] Decreased nuclear translocation of peroxisome proliferator-activated receptor delta (PPARδ) causes heart metabolic dysregulation, oxidative stress, apoptosis and dysfunction, improving survival rate with a larger effect size in males than females.[57] Furthermore, decreased expression of fibroblast growth factor 5 (FGF5) has been observed in septic hearts. FGF5 overexpression alleviates SIMI in vivo and in vitro and decreases LPS-induced oxidative stress and pyroptosis.[58] Similarly, FGF5 overexpression reduces levels of NLRP3, IL-1β, caspase-1, IL-18, phosphorylated calmodulin kinase II (CaMKII), and p-NFκB. The CaMKII inhibitor KN93 also inhibits LPS-induced pyroptosis. These results reveal that FGF5 inhibits SIMI by suppressing CaMKII-mediated pyroptosis.[58] Increases in GSDMD-NT were observed in the heart tissue during SIMI. GSDMD knockout inhibits LPS-induced SIMI and enhances the survival rate in mice. GSDMD ablation prevents the increase of serum IL-1β and TNF-α contents and myocardial IL-1β and TNF-α mRNA levels. In addition, GSDMD ablation inhibits LPS-induced inflammatory cell infiltration into the myocardium and suppresses the activation of NF-κB and the maturation of the NLPR3 inflammasome.[59] GSDMD-NT enrichment in myocardial mitochondria resulted in mitochondrial dysfunction and ROS overproduction, further promoting NLRP3 inflammasome activation in LPS-induced septic mice. These results indicate that GSDMD participates in SIMI pathophysiology by facilitating ROS-dependent NLRP3 inflammasome activation.[59] The upregulated expression of angiopoietin-like protein 2 (ANGPTL2) has been observed in LPS-induced hearts and cardiomyocytes. ANGPTL2 overexpression aggravated LPS-induced SIMI while silencing ANGPTL2 attenuated LPS-associated SIMI. A mechanical study revealed that ANGPTL2 activates the NLRP3 inflammasome by inhibiting DUSP1, and silencing NLRP3 reverses the detrimental role of ANGPTL2-mediated SIMI.[60] DUSP1 overexpression inhibits SIMI- and ANGPTL2-mediated NLRP3 activation. These results reveal that ANGPTL2 facilitates SIMI by activating NLRP3-mediated inflammation in a DUSP1-dependent manner.[60] Decreased expression of growth arrest-specific gene 6 (GAS6) has been observed in the cardiomyocytes of septic mice.[61] GAS6 overexpression improves cardiac dysfunction and alleviates mitochondrial injury, ERS, oxidative stress, and apoptosis in septic mice.[61] Ablation of GAS6 increased NLRP3 levels, which reconciled with GAS6 overexpression. These results suggest that GAS6 attenuates SIMI by inhibiting the NLRP3 inflammasome.[61] LPS upregulates NLRP3 and promotes GSDMD-mediated pyroptosis in rat hearts. LPS increases intracellular Ca^{2+} release and inositol 1,4,5-trisphosphate receptor 2 (IP3R2) expression in ATP-induced NRCMs.[62] IP3R inhibition reverses intracellular Ca^{2+} release and suppresses pyroptosis by inhibiting the NLRP3/Caspase-1/GSDMD pathway.[62] The interplay between IP3R2-mediated Ca^{2+} release and ERS contributes to cardiomyocyte pyroptosis. These results indicate that IP3R2-mediated Ca^{2+} release facilitates pyroptosis via the activation of the NLRP3-Caspase-1-GSDMD pathway in LPS-induced cardiomyocytes.[62] Elevated phospholipase D2 (PLD2) levels were observed in the myocardial tissues of septic mice. PLD2 ablation inhibits SIMI and enhances the survival of septic mice. Silencing PLD2 inhibited pyroptosis in LPS-induced H9C2 cardiomyocytes, whereas PLD2 overexpression increased NLRP3 expression in cardiomyocytes.[63] This indicates that PLD2 promotes SIMI by enhancing pyroptosis via the NLRP3/caspase 1/GSDMD pathway in cardiomyocytes.[63]

Pharmacological Inhibition of NLRP3 as a Therapeutic Target for Septic Cardiomyopathy

Inhibiting NLRP3 inflammasome activation is an emerging therapeutic strategy to combat SIMI. Several compounds have shown therapeutic potential against SIMI by targeting the NLRP3 inflammasome (Table 1 and Figure 3).

Table 1 Emerging Compounds Targeting NLRP3 to Inhibit SIMI

Compounds	Type	Experimental model	Effects	Ref
Glyburide	Oral antidiabetic drug	LPS/mice	↑Survival rate;↓myocardial contractile dysfunction; ↓ IL-1β myocardium and circulation; ↓Activation of the NLRP3 inflammasome in CFs; ↓ability of LPS-challenged CFs to impact cardiomyocyte function.	[34]
MCC950	NLRP3 inhibitor	CLP/rats	↓Levels of serum cTnI and LDH; ↓disordered myocardial tissue structure; ↓cell edema; ↑cardiac function; ↓expressions of TNF-α, IL-6 and IL-8.	[64]
MCC950	NLRP3 inhibitor	LPS/H9c2 cells	↓Inflammation and pyroptosis.	[64]
Artemisinin	Antimalarial agents	Burn sepsis/Male BALB/c mice	↓Mortality rate;↓serum inflammatory cytokines;↓levels of adhesion molecules and neutrophil infiltration in heart;↓NLRP3 and caspase 1;↓mRNA expression of IL-1β and IL-18 in Raw 264.7 cells that were stimulated with burn sepsis serum.	[65]
Nifuroxazide	Oral antibiotic	LPS/male SD rats	↑Heart histopathological characteristics and architecture;↓ inflammatory-infiltration; ↓biomarkers of cellular injury in serum;↓CK-MB, LDH, and ALP;↓oxidative stress; ↓TLR4/the inflammasome NLPR3/IL-1β.	[66]
Melatonin	Plant hormone	CLP/C57BL/6J mice	↑Sirtuin1-dependent NF-κB deacetylation in septic mice; ↓NF-κB activity; ↓NF-κB-mediated proinflammatory response; ↑redox balance and mitochondrial homeostasis;↓NLRP3 inflammasome.	[43]
Melatonin	Plant hormone	CLP/WT C57BL/6 and NLRP3-KO mice	↑Restoration of the normal cardiac muscle fibers; ↓P65 in the nucleus;↓TNFα and iNOS;↓ protein level of caspase-1,NLRP3, IL-1β and pro-IL-1β;↓ mRNA level of NLRP3.	[44]
Melatonin	Plant hormone	LPS/hiPSC-CMs	↓Cell injuries;↓LDH release;↑cell viability;↑induction of autophagy; ↓pyroptosis; ↓NLRP3; ↓GSDMD-NT; ↓cleaved caspase-1; ↓production of the cleaved IL-1β and cleaved IL-18 cytokines.	[67]
Melatonin	Plant hormone	CLP/C57BL/6J	↑Nrf2;↓NLRP3 inflammasome activation;↑myocardial homeostasis.	[68]
Carvacrol	Aromatic monoterpenoids	LPS/Balb/C mice	↑Survival rate;↓histopathological alterations; ↑ echocardiographic parameters; ↓ reduction in fraction shortening and ejection fraction;↑ myocardial antioxidants; ↓pro-inflammatory cytokine contents; ↓ protein levels of NLRP3, caspase 1, ASC, IL-1β, IL-18, and the GSDMD; ↑beclin 1 and p62.	[69]
Carvacrol	Aromatic monoterpenoids	LPS/H9c2 cells	↓ROS generation; ↓pyroptosis; ↓NLRP3 inflammasome.	[69]
Chicoric acid	Natural plant polyphenol	LPS/Male C57BL/6 mice	↓Succinate dehydrogenase activity in macrophages; ↓succinate accumulation; ↓superoxide anion production; ↓mitochondrial dysfunction; ↓HIF-1α in macrophage; ↓glycolysis;↑activated macrophages NAD^+/NADH ratio;↑dissociation of KAT2A from α-tubulin; ↓α-tubulin acetylation; ↓NLRP3 inflammasome;↑cardiac mitochondrial structure and function disruption.	[40]
Estradiol	Estrogen	LPS/female C57BL/6 mice	↑Cardiac function;↑cardiac electrical activity;↓cardiac metabolism;↑PPARδ nuclear translocation; ↓oxidative stress and apoptosis in females.	[57]
Vaccarin	Flavonoid glycoside	LPS/H9C2 cells	↓Oxidative stress, apoptosis, inflammation, mitochondrial disorder in cardiomyocytes.	[70]
Vaccarin	Flavonoid glycoside	LPS/C57BL/6 J mice	↓Myocardial injury;↑cardiac function parameters;↑cardiac structure; ↓inflammation /oxidative response;↑NLRP3 palmitoylation to inactivate NLRP3 inflammasome by acting on zDHHC12. In support, the NLRP3 agonist ATP and the 2-BP prevented the effects of VAC.	[70]
Emodin	Natural anthraquinone derivative	LPS/C57BL/6 mice	↑Survival rate;↓myocardial injury;↓cardiac dysfunction; ↓ inflammatory cytokines; ↓cardiac inflammation; ↓NLRP3;↓GSDMD.	[71]
Emodin	Natural anthraquinone derivative	LPS/cardiomyocytes	↓Cell injury;↓inflammation;↓activation of NLRP3 inflammasome.	[71]

(*Continued*)

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Table 1 (Continued).

Compounds	Type	Experimental model	Effects	Ref
Harmine	Natural β-carboline alkaloid		↑Survival rate;↓cardiac dysfunction;↓inflammation;↓apoptosis.	[38]
Harmine	Natural β-carboline alkaloid	LPS/RAW 264.7 cells	↓M1 phenotype markers iNOS and COX-2; ↓inflammatory cytokines(IL-1β,TNF-α, IL-6, iNOS, COX-2, PGE2 and TXB2)	[38]
Harmine	Natural β-carboline alkaloid	LPS/H9C2 cells	↓Macrophage-mediated inflammation and apoptosis; ↓NLRP3; ↓cleaved caspase 3 levels; ↓NF-κB activation.	[38]
Ruscogenin	Natural steroidal sapogenin	LPS/mice	↑Survival rate; ↑cardiac function; ↓myocardial pathological damage;↓myocardial injury; ↓NLRP3; ↓myocardial inflammation and pyroptosis.	[72]
Ruscogenin	Natural steroidal sapogenin	LPS/HL-1 cardiomyocytes	↓Cytotoxicity;↓inflammation and pyroptosis;↓NLRP3 upregulation.	[72]
Geniposide	Iridoid glycoside	LPS/C57BL/6 mice	↑Survival rate;↑cardiac function;↓myocardial inflammation;↓myocardial loss; ↓NLRP3 inflammasome activation;↓p47phox;↑ phosphorylation and activity of AMPKα; silencing AMPKα abolishs geniposide-mediated protection against NLRP3 inflammasome activation, ROS accumulation and loss of cardiomyocytes.	[73]
Syringaresinol	Natural polyphenolic compound	CLP/C57BL/6 male mice	↑Cardiac function; ↓myocardial injury;↑SIRT1;↓NLRP3 activation and proinflammatory cytokines release; ICI182780, PHTP and AZD9496 reverses the protective effect of syringaresinol against SIMI.	[74]
Thymoquinone	Natural polyphenolic compound	CLP/male BALB/c mice	↓Intestinal histological alterations;↓plasma cTnT levels;↑ATP;↓ p62, NLRP3, caspase-1, TNF-α, IL-18, IL-1β, IL-6, and MCP-1 expressions;↑beclin 1 and IL-10 level; ↓PI3K.	[75]
Shikonin	Natural naphthoquinone	LPS/C57BL/6J male mice	↑Survival rate;↑cardiac function;↓inflammatory cytokines release;↓macrophage infiltration; ↓cleaved caspase-1;↓NLRP3; ↓caspase-1 activity;↑SIRT1 expression; SIRT1 inhibitor blocks SHI-mediated upregulation of SIRT1 expression and downregulation of cleaved caspase-1,NLRP3, and caspase-1 activity.	[76]
Shikonin	Natural naphthoquinone	LPS/H9C2 cells	↓LDH and cTn;↓cell inflammation;↓apoptosis;↑ SIRT1 expression;↓cleaved caspase-1;↓NLRP3;↓caspase-1 activity	[76]
Carbachol	Nonselective muscarinic receptor agonist	CLP/C57BL/6 male mice	↑Survival rate;↓ activity of CK-MB;↓LVIDs;↑LVEF and LVFS;↓apoptosis level of myocardial cells;↓inflammatory factors (TNF-α, IL-1ß and IL-6); ↓Caspase-3; ↑Bcl-2/Bax;↓expressions of phosphorylated -PI3K, p-AKT, NLRP3, and Caspase-1.	[77]
YL-109	CHIP agonist		↓Mortality;↓cardiac dysfunction;↓proinflammatory response;↓NLRP3 expression; ↓pyroptosis;↓phosphorylated ERK levels and NF-κB activation;↑CHIP expression; ↓ activation of c-Jun and c-Fos; CHIP ablation reverses YL-109-mediated protective effects against SIMI, inflammation and pyroptosis.	[78]
YL-109	CHIP agonist	LPS/ HL-1 cells	↓Cytokine release;↓pyroptosis; CHIP overexpression enhances the degradation of phosphorylated ERK and decreases expression of NF-κB-mediated NLRP3.	[78]
PSSM1443	Small molecule disrupt the TXNIP-NLRP3 interaction	LPS/C57BL/6 mice	↓Activation of caspase-1;↓inflammation;↓cleavage of pro-IL-18 and pro-IL-1β.	[42]
IL-1RA	Interleukin 1 receptor antagonist	CLP/mice	↑IL-1β decreased contractility and relaxation of adult rat ventricular cardiomyocytes.	[79]
T0901317	Liver X Receptor agonist	CLP/male C57BL/6 or Balb/c mice	↓Systemic infection;↑cardiac dysfunction;↓NLRP3 activity.	[56]
JQ1	BRD4 inhibitor	CLP/C57BL/6 J male	↑Survival rate;↓cardiomypathological injury;↑cardiac function;↓CD45 infiltration; ↓release of CK-MB, LDH, IL-1, IL-18;↑SOD viability; ↓MDA;↑SIRT1; ↓NLRP3, caspase-1p20, and GSDMD.	[80]

JQ1	BRD4 inhibitor	LPS/H9C2 cells	↓LDH release, infammation, and oxidative damage;↑ SIRT1 expression;↓ NLRP3 activation; SIRT1 inhibitor EX527 reveres the JQ1-mediated decrease in NLRP3, caspase-1p20, and GSDMD.	[80]
Baricitinib	JAK1/JAK2 inhibitor	CLP/C57BL/6 mice	↑Cardiac function;↓cardiac injury;↓multiple-organ failure;↓JAK2/STAT3 activation; ↓NLRP3 inflammasome activation;↓ NF- κB.	[81]
GYY4137	H_2S slow -releasing donor	CLP/male C57BL/6 mice	↓Myocardial injury; ↓ Macrophage infiltration;↓ activation of NLRP3 inflammasome in macrophages; ↓ inflammatory factors secretion;↓ ROS in cardiomyocytes.	[82]
$NaHSO_3/Na_2SO_3$	SO_2 donor	CLP/Male SDr rats	↑Cardiac functions;↑ levels of SO_2 in plasma and heart;↓apoptosis;↓ inflammatory response;↓expression of TLR4, NLRP3, and caspase-1.	[83]
$NaHSO_3/Na_2SO_3$	SO_2 donor	LPS/Primary NRCMs	↓Myocardial injury;↑ cell viability;↓LDH;↓apoptosis;↓expression of TLR4, NLRP3, and caspase-1.	[83]
CORM-3	CO-releasing molecule-3	LPS/C57BL/6 mice	↓Myocardial dysfunction;↓myocardial NLRP3 inflammasome activation.	[37]
CORM-3	CO-releasing molecule-3	LPS/primary cardiac fibroblasts	↓NLRP3 and pro-IL-1β expression; ↓activation of the NLRP3 inflammasome; ↓NLRP3 interactions with adaptor ASC;	[37]
CORM-3	CO-releasing molecule-3	Neonatal cardiomyocytes	CORM-3 or IL-1 receptor antagonist decreases CM apoptosis that challenged with supernatants of CF with LPS/ATP or Cyto-mix (IL-1β, IL-18, and HMGB1).	[37]
GW501516	PPARbeta/delta-specific agonist	LPS/GPER-$1^{-/-}$ mice	↓Oxidative stress; ↓NLRP3 expression in the heart.	[57]
HU308	Cannabinoid receptors 2 agonist	CLP/C57BL/6 mice	↓Pyroptosis; ↓NLRP3 and activating caspase-1 and GSDMD.	[84]
Cinnamyl alcohol		Escherichia coli /male C57BL/6J mice	↓Mortality; ↓inflammatory reaction in heart; ↓IL-1β and IL-18; ↓expression of ASC, NLRP3, and caspase-1 in heart.	[85]
Ketone esters		LPS/C57BL/6 N mice	↓ Profound systemic inflammation;↓ cardiac dysfunction;↓ inflammation in the heart.	[86]
rGDF3	Recombinant GDF3 protein	LPS/mice	↑Survival rate;↓macrophage infiltration; ↓systemic and cardiac inflammation with less pro-inflammatory macrophages (M1) and more anti-inflammatory macrophages (M2); ↑Smad2/Smad3 phosphorylation; ↓NLRP3 in macrophages.	[39]
Elabela	Small molecule hormone	CLP/C57BL/6J mice	↑Survival rate of septic mice;↑cardiac function;↓production of myocardial injury markers, oxidative stress and pyroptosis.	[87]
Elabela	Small molecule hormone	LPS/ AC16 human ventricular myocytes	↓Cell death;↓ROS production;↓pyroptosis, and smooth autophagy flow;↑degradation of autophagosomes.	[87]
Intermedin1-53	Novel paracrine /autocrine peptide	CLP/SD rat	↑Cardiac function;↑MABP;↓inflammation; ↓NLRP3, ASC, pro-IL-1β, caspase 1; ↓NF-kB nuclear translocation;↓apoptosis.	[88]
Intermedin1-53	Novel paracrine /autocrine peptide	LPS/Cardiac fibroblasts	↑Cell survival rates;↓ ASC, NLRP3, and caspase 1 protein levels;↓IL-1β production.	[88]
rhACE2	Recombinant human ACE2 peptide	LPS/male C57/B6 mice	↓Myocardial injury;↑cardiac function; ↑Ang 1–7 in serum; ↓Ang II; ↓ NLRP3 inflammasome activation; ↓ ↓ pyroptosis; inflammatory response;↓ activation of NF-κB and p38MAPK;↑AMPK-α1activation.	[89]
Tirzepatide	Glucagon-like peptide-1 receptor agonist	LPS/C57BL/6 mice	↓Cardiac dysfunction; ↓susceptibility ventricular arrhythmia↓inflammatory responses; ↓cardiac protein levels of TNF-α, IL-6, and IL-1B; ↓cardiomyocytes apoptosis ↓TLR4 /NF-kB/NLRP3.	[90]
Cortistatin	Neuroendocrine polypeptide	LPS/Male SDr rats	↓ASC pyroptosome formation induced by NLRP3; ↓IL-1β secretion; ↓caspase-1 activation; ↓proinflammatory pathways (NF-κB and pro-IL-1β).	[35]
Cortistatin	Neuroendocrine polypeptide	LPS/C57BL/6J mice	↓Myocardial injury;↓ROS levels; ↓Drp1-mediated mitochondrial fission; ↓NLRP3 inflammasome activation-mediated cardiomyocyte pyroptosis; ↑AMPK phosphorylation.	[91]

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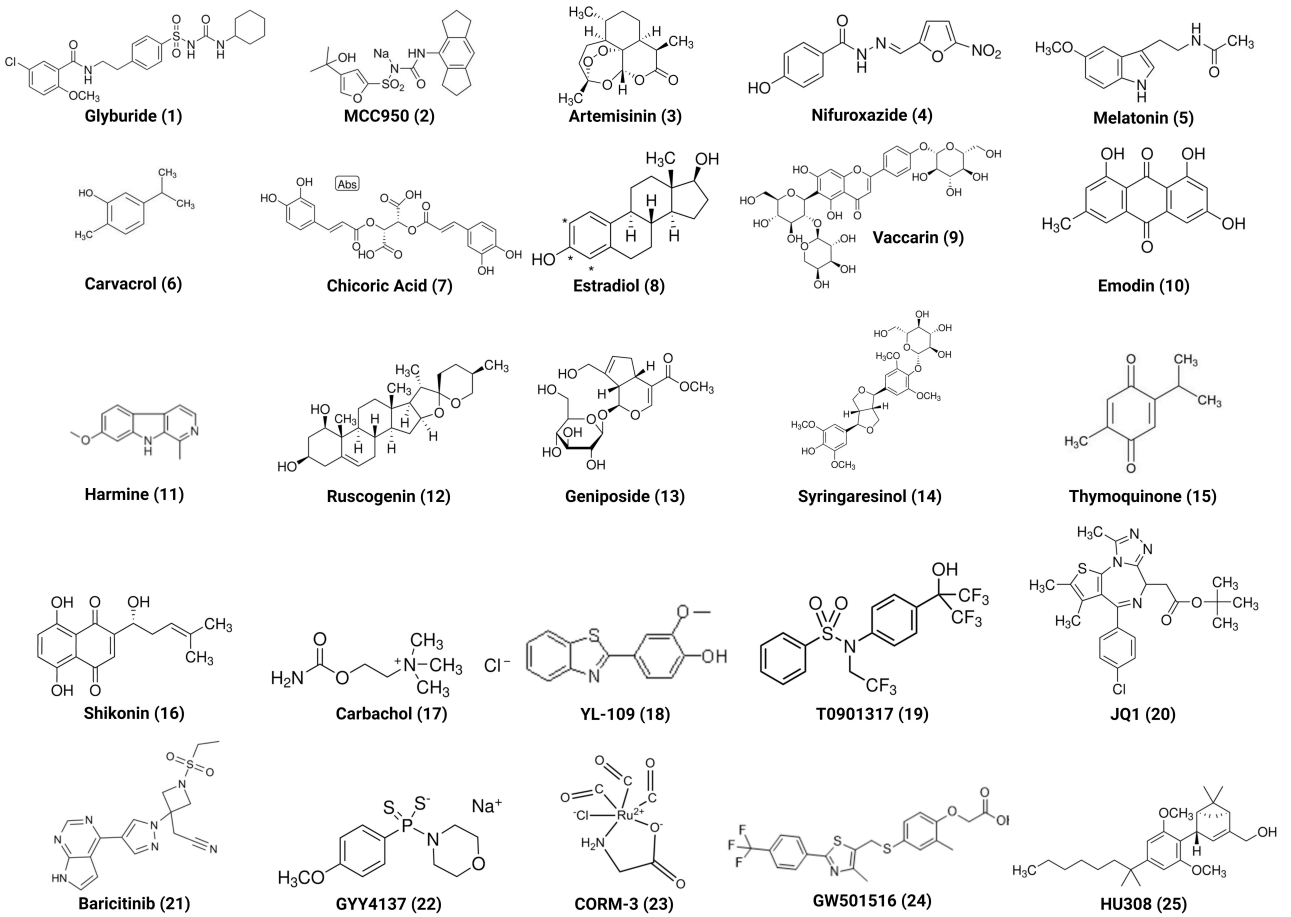

Figure 3 Chemical structures of small molecules targeting NLRP3 to treat SIMI.

Food and Drug Administration (FDA)-Approved Medications

The small-molecule drug glyburide is an FDA-approved antidiabetic medication that acts as an inflammasome antagonist. Pharmacological inhibition of NLRP3 by glyburide blocks NLRP3 inflammasome activation in CFs[34] (Figure 4). Furthermore, inhibition of the NLRP3 inflammasome in CFs attenuates the effect of LPS-treated CFs on cardiomyocyte function. NLRP3 inhibition by glyburide inhibits myocardial contractile dysfunction and decreases myocardial and circulating IL-1β, boosting the survival rate of mice.[34] Artemisinin is a traditional Chinese medicine and natural product with significant antimalarial, anti-inflammatory, and immunoregulatory effects.[92] Similarly, it decreases mortality rates, serum inflammatory cytokines, adhesion molecule levels, and neutrophil infiltration in the hearts of burn septic mice.[65] Artemisinin decreases protein levels of NLRP3/caspase 1 and downregulates mRNA expression of IL-1β and IL-18 in burn sepsis serum-stimulated Raw 264.7 cells. Moreover, 3,4-methylenedioxy-β-nitrostyrene inhibits NLRP3 inflammasome activation and its synthesis of inflammatory cytokine in burn wounds, enhancing the effects of artemisinin. These results suggest that artemisinin protects against SIMI by alleviating the inflammatory response and infiltration through the suppression of NLRP3 inflammasome activation.[65] Nifuroxazide is an FDA-approved antidiarrheal drug that significantly improves heart architecture and histopathological characteristics by inhibiting LPS-induced inflammatory infiltration.[66] Nifuroxazide decreases serum LDH, CK-MB, and ALP levels and reduces the heart oxidative status. In addition, it inhibits the TLR4/NLRP3 inflammasome/IL-1β pathway in the heart.[66]

Natural Compounds

Melatonin (N-acetyl-5-methoxytryptamine) is synthesized in the pineal glands of mammals, produced in many other cells, and has cardioprotective, antitumor, and neuroprotective activities. Emerging evidence has shown that melatonin

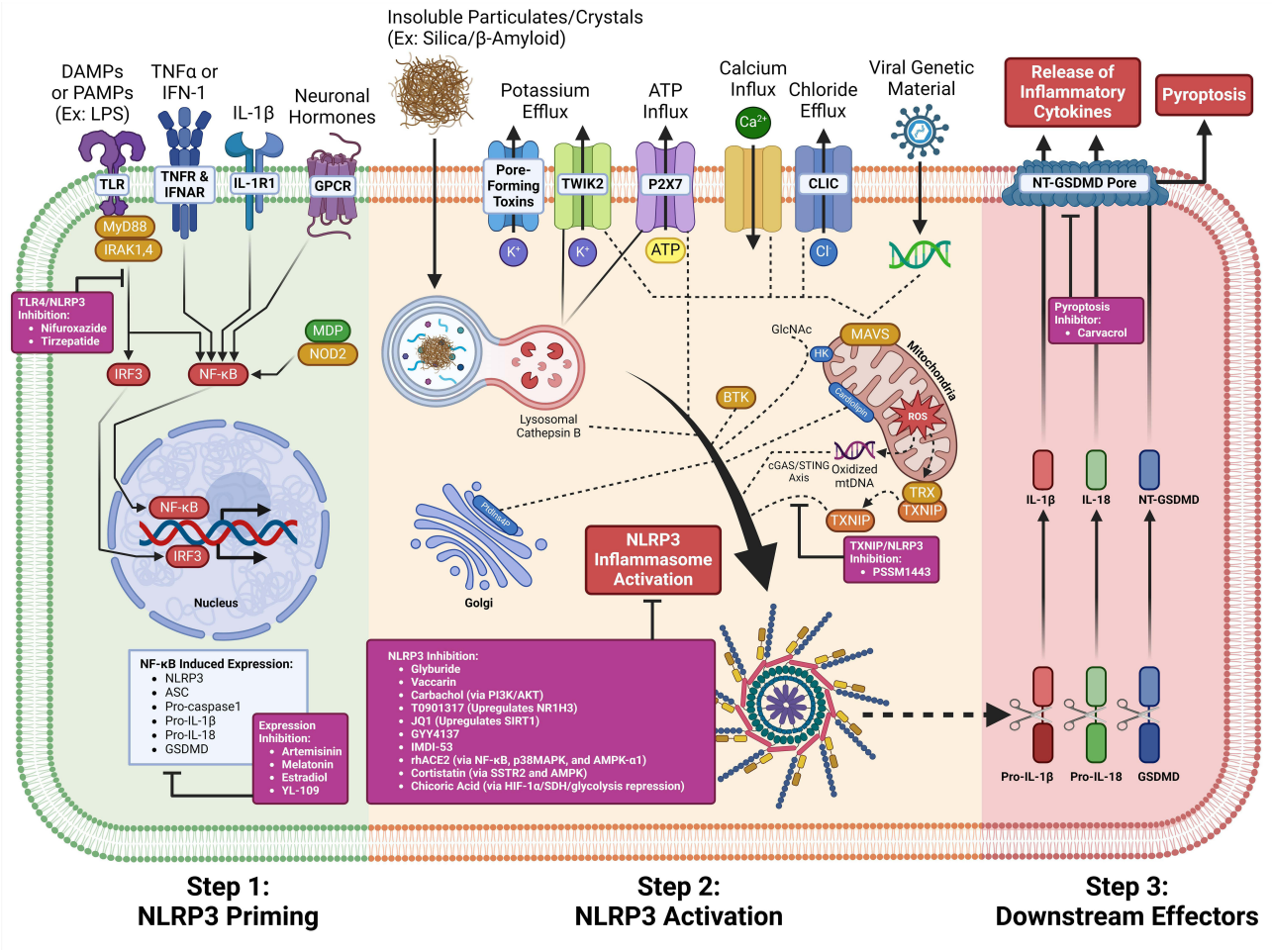

Figure 4 Pharmacology of NLRP3 antagonists against SIMI Multiple generic classes of NLRP3 inhibitors have been identified. Some compounds have been found to repress upstream toll-like receptor 4 (TLR4) signaling, repress the transcription of NLRP3-associated genes, inhibit NLRP3 complex assembly/maturation, and prevent downstream NLRP3-induced pyroptosis.

exerts a protective effect against SIMI via different pathways.[93] Garcia et al revealed for the first time that melatonin inhibits the NF-kB/NLRP3 pathway through the retinoid-related orphan receptor (ROR)-α to recover normal mitochondrial function and cellular redox status against SIMI.[43] Melatonin reduces NF-κB-mediated proinflammatory responses and boosts mitochondrial homeostasis and redox balance, inhibiting NLRP3 inflammasome activation. RORα ablation reverses melatonin-mediated NF-κB inhibition but not that of NLRP3, suggesting that RORα is necessary for initiating the innate immune response against inflammation.[43] Melatonin inhibits NF-κB activation through sirtuin1-dependent NF-κB deacetylation.[43] This observation was corroborated by a study from the same group, which reported that melatonin exerts myocardial protection by restoring the clock gene turnover required to activate SIRT1[44]. Similarly, melatonin protects the myocardium by inhibiting pyroptosis in LPS-induced human stem cell-derived cardiomyocytes (hiPSC-CMs).[67] Melatonin decreased hiPSC-CM injury, as evidenced by decreased LDH release, increased cell viability, and induction of autophagy. Moreover, melatonin alleviates cell pyroptosis, as evidenced by downregulated expression of NLRP3, cleaved caspase-1, and GSDMD-NT and decreased production of the cleaved IL-1β and IL-18. Furthermore, 3-MA (an autophagy inhibitor) and rapamycin (an autophagy activator) alleviates and accentuates melatonin-mediated anti-pyroptotic activity, respectively. These results suggest that melatonin exerts myocardial protection by inhibiting pyroptosis through autophagic stimulation.[67] Melatonin inhibits SIMI, which is further supported by the observation that it inhibits myocardial damage by facilitating Nrf2 activation to reduce mitochondrial oxidative damage and inhibits NLRP3 inflammasome activation, inhibiting apoptosis.[68]

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Carvacrol is a phenolic monoterpenoid found in the oils of aromatic plant species such as Origanum, thymus, and pepperwort.[94–96] This natural compound inhibits ROS generation and ablates NLRP3 inflammasome-mediated pyroptosis in LPS-induced H9c2 cells.[69] Similarly, it enhances the survival rate, improves echocardiographic parameters, and prevents ejection fraction reduction in LPS-induced BALB/c mice. Carvacrol restores myocardial antioxidant levels, reduces histopathological alterations, and reduces proinflammatory cytokine levels in the heart.[69] Mechanistic studies have revealed that carvacrol downregulates the protein levels of NLRP3, caspase 1, ASC, IL-18, IL-1β, and GSDMD, restoring autophagy-indicative proteins, p62 and beclin 1 in the heart. Our findings suggest that carvacrol inhibits SIMI by inhibiting the NLRP3 inflammasome and activating autophagy.[69]

Chicoric acid (molecular formula: $C_{22}H_{18}O_{12}$), the tartaric acid ester of two caffeic acids and a phenolic compound, is a caffeic acid derivative that can be isolated and purified from plant materials.[97,98] This natural compound attenuates SIMI by regulating the metabolic reprogramming of macrophages. Chicoric acid downregulates HIF-1α levels by suppressing SDH activity and inhibiting glycolysis in macrophages, inactivating the NLRP3 inflammasome and attenuating sepsis-induced myocardial damage.[40]

Increased estradiol levels agonize G protein-coupled estrogen receptor 1(GPER-1) to augment PPARδ nuclear translocation, attenuating cardiac metabolism and apoptosis through reduced oxidative stress and NLRP3 expression in LPS-induced female mice.[57] Activation of GPER-1 by G1 (a GPER-1 agonist) enhanced survival rates and improved cardiac function and electrical activity in LPS-challenged male mice.[57] G1 attenuated injury, reduced cardiac apoptosis, and enhanced metabolism by inhibiting NLRP3 in the hearts of male mice.[57]

Vaccarin is a flavonoid glycoside with cardio-protective benefits against cardiovascular remodeling and doxorubicin-induced cardiotoxicity.[99,100] This natural compound attenuated septic myocardial injury, as evidenced by preserved cardiac structure, increased cardiac function parameters, and decreased inflammation/oxidative response.[70] A mechanistic study has revealed that vaccarin inactivates the NLRP3 inflammasome by promoting zDHHC12-mediated palmitoylation. The acylation inhibitor 2-bromopalmitate and NLRP3 agonist ATP reversed the protective effects of vaccarin. These results reveal that vaccarin inhibits SIMI and oxidative stress by decreasing cardiac inflammation and increasing palmitoylation-induced NLRP3 inactivation, respectively.[70]

Small-Molecule Drugs

Carbachol, a muscarinic agonist, attenuates SIMI by reducing NLRP3 inflammasome inflammation through the suppression of the PI3K/AKT signaling pathway.[77] Similarly, 2-(4-hydroxy-3-methoxyphenyl)-benzothiazole (YL-109) decreases mortality and inhibits SIMI by attenuating the proinflammatory response of NLRP3-mediated pyroptosis in vivo. YL-109 inhibits pyroptosis in LPS-induced HL-1 cells. A mechanistic study has shown that YL-109 decreases levels of phosphorylated ERK and activates NF-κB by upregulating the expression of the carboxy terminus of Hsc70-interacting protein (CHIP), inhibiting c-Fos and c-Jun activation and NLRP3 expression. CHIP ablation reverses the protective effects of YL-109 against SIMI.[78] These results suggest that YL-109 attenuates SIMI by inhibiting NLRP3-mediated pyroptosis via CHIP/ERK/NF-κB pathways.[78] PSSM1443, a small molecule that disrupts TXNIP-NLRP3 interaction, attenuates SIMI by reducing inflammation through the suppression of caspase-1 activation and the cleavage of pro-IL-18 and pro-IL-1β.[42] The Liver X Receptor agonist T0901317 attenuates SIMI by inhibiting NLRP3 via NR1H3 upregulation.[56] JQ1 is a bromodomain-containing protein 4 inhibitor with cardio-protective benefits against cardiac fibrosis, cardiac hypertrophy, and doxorubicin-induced cardiotoxicity.[101–105] It enhances the survival rate and attenuates SIMI by inhibiting NLRP3 via SIRT1 upregulation. The SIRT1 inhibitor EX527 partially reversed the JQ1-mediated decrease in NLRP3, caspase-1p20, and GSDMD levels.[80] These results reveal that JQ1 attenuates SIMI by modulating the SIRT1/NLRP3 axis.[80] GYY4137 decreases macrophage infiltration in the heart tissue of septic mice. Furthermore, it inhibits the NLRP3 inflammasome in macrophages, decreases inflammatory cytokine secretion, and reduces ROS production in cardiomyocytes, exerting protective effects against SIMI.[82]

Peptide

Elabela is a small-molecule hormone that plays an essential role in heart development.[106] The mature elabela peptide contains 32 amino acids.[107,108] This hormone attenuates septic myocardial damage and improves the survival rate of mice

with sepsis in vivo. Furthermore, it enhances autophagy, and autophagosomes selectively degrade inflammatory bodies, resulting in a reduction in pyroptosis.[87] Intermedin$_{1\text{-}53}$ (IMD$_{1\text{-}53}$), a novel paracrine/autocrine peptide, exhibits strong cardio-protective effects through endogenous anti-inflammatory activity.[109–111] IMD$_{1\text{-}53}$ alleviates SIMI by inhibiting the NLRP3/caspase-1/IL-1β pathway in cecal-ligation-and-puncture-induced mice and LPS-induced CFs. Similarly, IMD$_{1\text{-}53}$ reduces inflammation and apoptosis, as evidenced by the downregulated expression of NLRP3, ASC, caspase 1, pro-IL -1β, and NF-kB protein nuclear translocation levels and decreased caspase 3 activity and Bax expression.[88] IMD1-53 protects against SIMI by inhibiting the NLRP3/caspase-1/IL-1β pathway. rhACE2 protects against SIMI by inhibiting NLRP3 inflammasome activation, inflammatory response, and pyroptosis in LPS-induced male C57/B6 mice.[89] In addition, it inhibits the activation of the NF-κB and p38 mitogen-activated protein kinase (MAPK) pathway and facilitates AMPK-α1 activation in heart tissues.[89] A MAS receptor antagonist that blocks Ang(1–7) action reverses the rhACE2-mediated protective effects against cardiac injury and dysfunction in LPS-induced male C57/B6 mice.[89] rhACE2 inhibits SIMI through NF-κB, p38MAPK, and the AMPK-α1/NLRP3 inflammasome axis dependent on converting Ang II to Ang 1–7. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, exerts cardio-protective effects against doxorubicin-induced cardiotoxicity.[112] It attenuates SIMI by inhibiting inflammation and apoptosis via inactivation of the TLR4/NF-kB/NLRP3 axis. Tirzepatide also lowers susceptibility to ventricular arrhythmia in LPS-treated mice.[90] Cortistatin, a neuroendocrine polypeptide belonging to the somatostatin family, is a novel peptide that exerts cardio-protective effects against SIMI.[113,114] A mechanistic study has revealed that cortistatin attenuates SIMI by inhibiting NLRP3 inflammasome activation, as evidenced by decreased ASC pyroptosome formation, caspase-1 and NF-κB activation, and IL-1β secretion.[35] This observation was confirmed by a recent study, which showed that cortistatin attenuates SIMI by binding to somatostatin receptor subtype 2, activating AMPK and inactivating dynamin-related protein 1 to inhibit mitochondrial fission and reduce ROS levels, suppressing NLRP3 inflammasome-induced pyroptosis and attenuating SIMI.[91]

Conclusions and Perspectives

Sepsis can trigger a life-threatening SIMI. Emerging evidence suggests that NLRP3 inflammasome activation and NLRP3-induced pyroptosis play pivotal roles in the pathogenesis of sepsis and SIMI, and previous studies have revealed that NLRP3 inflammasome and pyroptosis antagonism reduce sepsis and SIMI in vitro and in vivo. Several agents exert therapeutic effects against SIMI by inhibiting NLRP3 (Figure 4). In this review, we summarized the core mechanisms underlying NLRP3 inflammasome activation and its contribution to the pathogenesis of SIMI. We focused on emerging therapeutic compounds that can inhibit NLRP3 inflammasome activation and characterized their pharmacological effects on SIMI. This review suggests that the pharmacological inhibition of the NLRP3 inflammasome may be a potential therapeutic regimen against SIMI.

The role of NLRP3 in SIMI has exponentially increased. However, the physiological significance and detailed mechanisms of action of NLRP3 are not well understood and require further investigation. This review primarily focused on studies that elucidated the core mechanisms of NLRP3 priming or activation in SIMI; however, further investigations are warranted. First, epigenetic modifications by non-coding RNAs (ncRNAs) mediate NLRP3 and related pyroptosis by regulating various related factors in other diseases; however, ncRNA role in the regulation of NLRP3 during SIMI remains unclear. Second, emerging evidence suggests that some post-translational modifications, such as the deubiquitinase USP7, play vital roles in regulating NLRP3 in SIMI. Whether other ubiquitination/deubiquitination pathways are involved in regulating NLRP3 during SIMI remains unclear. In addition, how post-translational modifications, including lactylation, succinylation, acetylation, malonylation, and ISGylation, are involved in the regulation of NLRP3 during SIMI is unknown. Third, emerging evidence suggests that regulated cell death (RCD), including pyroptosis, autophagy, and ferroptosis, contributes to the pathogenesis of SIMI and the specific pathophysiological functions of RCD in SIMI; however, more investigations are needed to fully understand the mechanistic implications. Fourth, the cGAS-STING axis contributes to SIMI by activating NLRP3-mediated inflammation and pyroptosis in cardiomyocytes; however, the role of the cGAS-STING axis in other cell types, such as macrophages and CFs, remains unclear. Fifth, uncovering diverse NLRP3 regulators in SIMI is crucial. Other specific genes and proteins that regulate NLRP3 in SIMI remain unidentified and may produce additional upstream/downstream nodes for pharmacological intervention. Sixth, the clinical use of

NLRP3 inhibitors requires further investigation in SIMI and inflammatory diseases. According to these guidelines, the conventional treatment for sepsis remains the early administration of antibiotics and supportive care.[5] Further investigations are required before NLRP3 can be targeted for clinical applications. Pharmacologically targeting NLRP3 may become a potential component of the pharmacopeia for septic cardiomyopathy in the near future. Finally, with the progressive discovery of NLRP3 biology, Nrf2 plays a critical role in regulating NLRP3 activity, which raises the possibility of repurposing old or already approved drugs, such as Nrf2 activators, to treat SIMI. Despite these considerations, studies on the role of NLRP3 in SIMI remain in their early stages. The pharmacological targeting of NLRP3 provides a novel and promising therapeutic approach against SIMI.

Disclosure

The authors report no conflicts of interest in this work.

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