Advances in the mechanisms of the NLRP3 inflammasome in sepsis-induced cardiomyopathy and targeted therapeutic studies (Review)

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Abstract. Sepsis is a systemic inflammatory disorder characterized by multi-organ dysfunction following infection. Sepsis-induced cardiomyopathy (SIC) represents a prevalent complication that markedly contributes to in-hospital mortality. The NOD-like receptor protein 3 (NLRP3) inflammasome serves as an important regulator in SIC pathogenesis, directly impairing cardiac function through multiple mechanisms: i) Driving cytokine storms; ii) inducing cardiomyocyte pyroptosis and apoptosis; iii) disrupting mitochondrial homeostasis; and iv) suppressing autophagy. Molecularly-targeted NLRP3 inhibitors have been developed, such as MCC950, curcumin, indole-3-propionic acid and carvacrol, which have demonstrated cardioprotective effects in cellular and animal models of SIC. Further exploration of NLRP3 mechanisms and resulting therapeutic targets may yield novel strategies for SIC diagnosis and clinical management. The present review examined NLRP3-mediated pathways involving inflammation, programmed cell death and mitophagy in SIC pathogenesis, summarized pharmacological interventions targeting these pathways and highlighted previous advances in NLRP3 research to inform future therapeutic development and clinical translation.

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Abbreviations: AMPK, adenosine 5'-monophosphate-activated protein kinase; APPL-1, adaptor protein containing PH domain, PTB domain and leucine zipper motif 1; ASC, apoptosis-associated speck-like protein containing a CARD; ATP, adenosine triphosphate; BAX, BCL-2-associated X protein; BCL-2, B-cell lymphoma 2; Cyt *c*, cytochrome *c*; DAMPs, damage-associated molecular patterns; Drp1, dynamin-related protein 1; ER, endoplasmic reticulum; FAAH, fatty acid amide hydrolase; GPCR, G protein-coupled receptor; GSDMD, gasdermin D; LPS, lipopolysaccharide; MIOX, myo-inositol oxygenase; mtDNA, mitochondrial DNA; mtROS, mitochondrial reactive oxygen species; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor protein 3; PAMPs, pathogen-associated molecular patterns; PARP, poly(ADP-ribose) polymerase; PHB1, prohibitin 1; PINK1, PTEN-induced putative kinase 1; RIPK, receptor-interacting serine/threonine kinase; ROS, reactive oxygen species; SSTR2, somatostatin receptor 2; Tan I, tanshinone I; TLRs, Toll-like receptors; USF2, upstream stimulatory factor 2

Key words: sepsis-induced cardiomyopathy, NLRP3, mechanism, NLRP3 inhibitor

Contents

1. Introduction

Sepsis is a life-threatening systemic-inflammatory response syndrome triggered by viral, bacterial, fungal or immunogenic pathogens. This condition initiates a cascade of reactions culminating in multiorgan dysfunction syndrome. Current epidemiological data indicate sepsis as the leading cause of mortality in intensive care units worldwide, with an overall mortality rate of 25-30% in global cohorts (1-4). Severe sepsis

may induce organ-specific injuries affecting the kidneys, lungs, brain and heart (5-8). Notably, sepsis-induced cardiomyopathy (SIC) represents a frequent complication, occurring in 10-70% of sepsis or septic shock cases (9). A 2023 cohort study reported a 20% prevalence of SIC among septic patients, associating with markedly elevated short-term mortality (10). SIC is defined as an acute, reversible myocardial depression syndrome during early septic shock, characterized by infection-driven cardiac dysfunction. While typically resolving within 7-10 days, SIC may accelerate cardiovascular collapse (11). Diagnostic criteria remain non-standardized, but key features include: i) Left ventricular dilation with normal or reduced filling pressure; ii) impaired contractility; and iii) biventricular systolic/diastolic dysfunction manifesting as reduced ejection fraction (12). Progressive SIC induces myocardial impairment, as evidenced by biventricular dilation and decreased left ventricular ejection fraction (12,13). Notably, myocardial dysfunction affects 40% of septic patients, with myocardial dysfunction-associated mortality reaching 70% (14-16), establishing SIC as a notable threat to patient survival.

The precise pathogenesis of SIC remains incompletely elucidated. Current evidence implicates multifactorial mechanisms, including dysregulated inflammatory responses, programmed cell death (PCD) mechanisms, such as apoptosis and pyroptosis, mitochondrial structural or functional impairment, aberrant calcium-handling protein regulation, endothelial dysfunction and metabolic disturbances (17-19). During SIC progression, pathogenic microorganisms and endotoxins enter systemic circulation, directly activating immune cells. This triggers excessive cytokine production that amplifies inflammatory cascades and induces cardiomyocyte cell death. Concurrently, mitochondrial dysfunction generates an overload of reactive oxygen species (ROS) and pathological calcium efflux. These interconnected pathways converge through synergistic amplification, ultimately impairing myocardial contractility and exacerbating SIC pathogenesis (Fig. 1).

Previous years have witnessed an intensified research focus on SIC. Emerging evidence identifies the NOD-like receptor protein 3 (NLRP3) inflammasome as a notable innate immune sensor important for maintaining homeostasis, with its dysregulation implicated in the pathogenesis of diverse chronic inflammatory and metabolic disorders (20-24). During SIC development, the NLRP3 inflammasome is activated by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which triggers caspase-1-dependent cytokine release, pyroptosis, apoptotic protein accumulation and mitochondrial injury. These events collectively drive cardiomyocyte dysfunction and SIC progression (25). Notably, pharmacological inhibition or genetic downregulation of NLRP3 attenuates SIC-induced cardiac impairment and improves survival in experimental models (26). Zhu *et al* (27) demonstrated that the specific NLRP3 inhibitor 5-methoxyindole-3-carboxaldehyde suppresses inflammasome assembly by disrupting NLRP3-apoptosis-associated speck-like protein containing a CARD (ASC) interactions. Similarly, MCC950, a selective small-molecule inhibitor, binds to the NACHT domain of NLRP3, which prevents the activation of caspase-1 and the resulting maturation of IL-1β and IL-18, thereby mitigating inflammation and pyroptosis (28). Although MCC950 demonstrated notable preclinical efficacy, its clinical development for inflammatory diseases, such as rheumatoid arthritis, was halted during phase II trials due to off-target liver toxicity related to carbonic anhydrase inhibition (29). Nevertheless, MCC950 remains a prototypical and widely used research tool, and its chemical scaffold continues to inform the design of next-generation NLRP3 inhibitors with improved safety profiles (30). These findings establish NLRP3 as a central node in the SIC pathological network that coordinates multiple injury mechanisms, including inflammatory cascades, PCD and impaired mitophagy. Consequently, NLRP3 represents a promising therapeutic target for SIC intervention.

Due to the absence of comprehensive reviews addressing NLRP3 inflammasome signaling in SIC, the present review provided a systematic analysis of its pathogenic role. The present review elucidated NLRP3 inflammasome priming and activation mechanisms, discussing clinical and experimental evidence from previous studies. Notable emphasis was placed on delineating molecular pathways through which NLRP3 mediates myocardial injury in SIC, including inflammatory cascades, pyroptosis, apoptosis and dysregulated mitophagy. Furthermore, the present review catalogued chemical compounds and pharmacological agents targeting NLRP3-associated signaling networks. As such, the present review consolidated current understanding of the central role of NLRP3 in SIC pathogenesis and identified promising molecular targets for therapeutic intervention, thereby informing future research directions.

2. Biological characteristics of the NLRP3 inflammasome

Structure and function. NOD-like receptors, a subclass of pattern recognition receptors, recognize not only PAMPs but also DAMPs such as adenosine triphosphate (ATP) and mitochondrial ROS (mtROS) (31). Among the most extensively studied inflammasomes, the NLRP3 inflammasome comprises three core components: Pro-caspase-1, ASC and NLRP3 (32). The NLRP3 protein features three distinct domains: i) A C-terminal leucine-rich repeat domain; ii) an N-terminal pyrin domain (PYD); and iii) a central NACHT domain with ATPase activity (33). Mutations in the NACHT domain impair NLRP3 oligomerization, thereby reducing caspase-1 activation, IL-1β and IL-18 secretion and pyroptosis (34). ASC serves as an important adaptor protein that bridges the PYD of NLRP3 to the CARD of pro-caspase-1, facilitating inflammasome assembly (34).

Activation mechanism. The NLRP3 inflammasome serves as a core regulator of inflammatory pathways, requiring two distinct signals for canonical activation: i) A priming signal: Ligands of Toll-like receptors (TLRs) or cytokine receptors activate the myeloid differentiation primary response gene 88 (MyD88)/nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) pathway, inducing transcriptional upregulation of NLRP3 and the pro-inflammatory cytokines IL-1β and IL-18 (26); and ii) an activation signal: Diverse PAMPs, such as bacterial flagellin, lipopolysaccharide (LPS) and viral RNA, or DAMPs trigger oligomerization of ASC

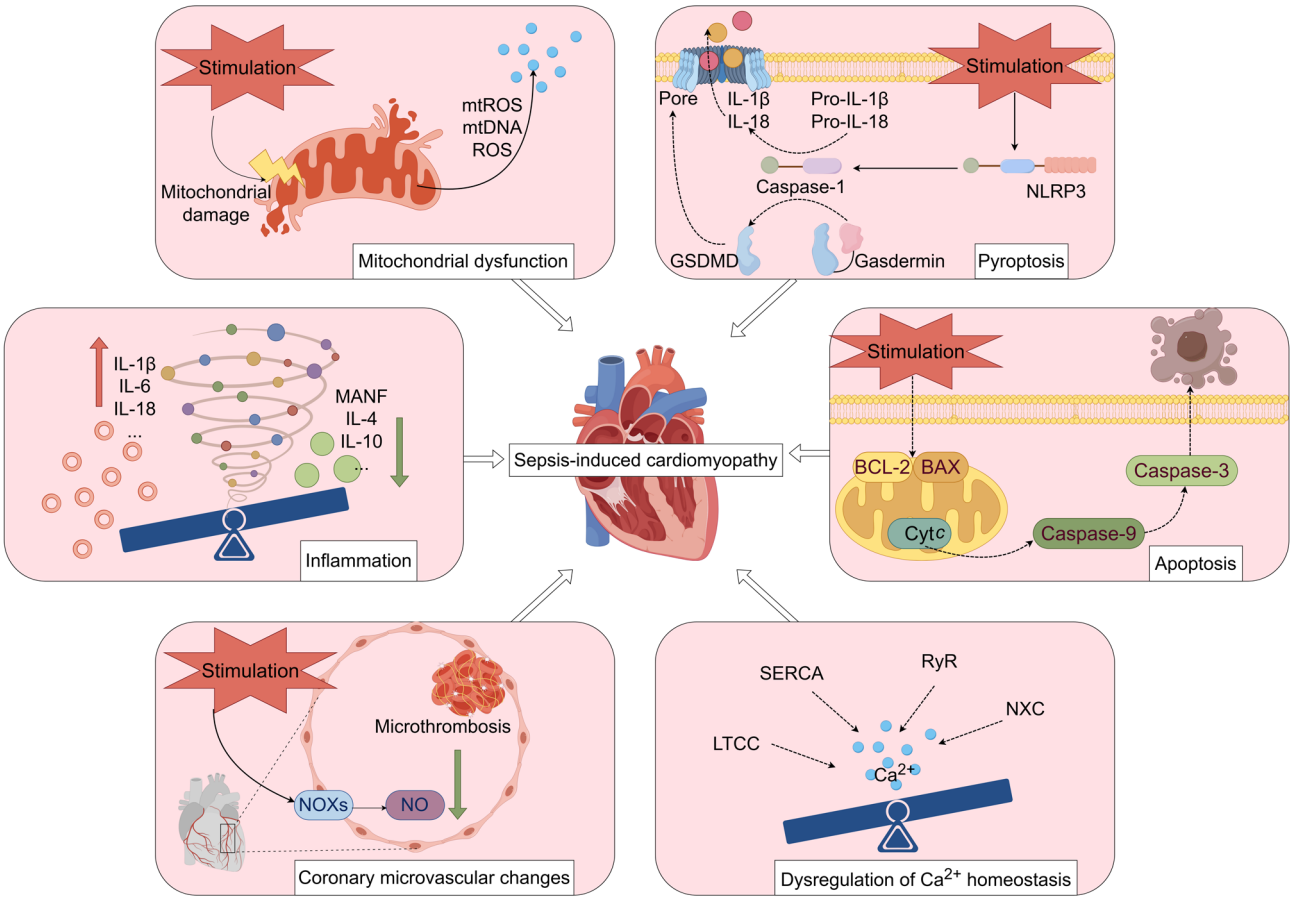

Figure 1. Mechanism of sepsis-induced cardiomyopathy. Sepsis-induced cardiomyopathy pathogenesis involves mitochondrial dysfunction, pyroptosis, apoptosis, dysregulation of Ca^{2+} homeostasis, coronary microvascular changes and inflammation. The present figure was generated using FigDraw. GSDMD, gasdermin D; ASC, apoptosis-associated speck-like protein containing a CARD; BAX, BCL-2-associated X protein; BCL-2, B-cell lymphoma 2; Cyt *c*, cytochrome c; LTCC, L-type Ca^{2+} channel; SERCA, sarcoplasmic reticulum calcium pump; RyR, ryanodine receptor; NCX, Na^{+}/Ca^{2+} exchanger; NOXs, nicotinamide adenine dinucleotide phosphate oxidases;; NO, nitric oxide; TNF-α, tumor necrosis factor-α; MANF, mesencephalic astrocyte-derived neurotrophic factor; ROS, reactive oxygen species; mtROS, mitochondrial ROS; mtDNA, mitochondrial DNA; IL-1β, interleukin-1β; NLRP3, NOD-like receptor protein 3.

and pro-caspase-1, culminating in NLRP3 inflammasome complex assembly (35).

During SIC, multiple pathways converge to activate the NLRP3 inflammasome through distinct mechanisms. Intracellular K^{+} depletion constitutes an important upstream event of NLRP3 inflammasome activation. ATP-mediated purinergic ligand-gated ion channel 7 receptor activation triggers K^{+} efflux, inducing NLRP3 assembly (36). LPS induces endoplasmic reticulum (ER) stress, promoting Ca^{2+} release via inositol 1,4,5-trisphosphate receptors and subsequent NLRP3 activation (37). SIC causes mitochondrial structural and functional impairment (38), increasing mtROS and mitochondrial DNA (mtDNA) release. These components facilitate NLRP3 oligomerization and exacerbate myocardial injury, with mitochondrial antiviral-signaling protein also contributing to inflammasome activation (39). Endocytosed crystalline or particulate matter, such as silica and cholesterol crystals, rupture lysosomes, releasing cathepsin B to promote NLRP3 oligomerization (40). Notably, crosstalk exists between NLRP3 priming and activation mechanisms. mtROS serves dual roles: As DAMPs activating TLR/MyD88/NF-κB signaling and as direct promoters of NLRP3 oligomerization (41). In addition to mtROS, ER stress and Ca^{2+} release constitute another crucial upstream event that orchestrates NLRP3 activation. Specifically, ER Ca^{2+} overload induces mitochondrial Ca^{2+} uptake; this increased mitochondrial Ca^{2+} load in turn amplifies mtROS production, thereby establishing a sustained pathological feedback loop that exacerbates inflammasome activation (25).

Upon oligomerization and activation, the NLRP3 inflammasome recruits ASC via PYD-PYD interactions. The resulting complex facilitates pro-caspase-1 autocleavage, generating active caspase-1 that processes pro-IL-1β and pro-IL-18 into mature cytokines (42). Concurrently, activated caspase-1 cleaves gasdermin D (GSDMD), liberating the GSDMD N-terminal (GSDMD-NT) domain that subsequently translocates to the plasma membrane, forming pores that mediate the release of inflammatory mediators, including IL-1β and IL-18, and drive pyroptosis, a mode of lytic inflammatory cell death (43). In SIC, pyroptosis releases DAMPs, such as IL-1β, IL-18 and mtDNA, amplifying inflammation and NLRP3 activation through positive feedback. Notably, the inflammatory milieu and DAMPs (e.g., mtDNA) released during pyroptosis can also modulate other cell death and clearance pathways, including apoptosis and mitophagy (44). This cascade ultimately induces myocardial dysfunction and structural damage, representing a core pathogenic mechanism in SIC (45). Pharmacologically, fatty acid amide hydrolase (FAAH) inhibitors disrupt NLRP3-FAAH interactions,

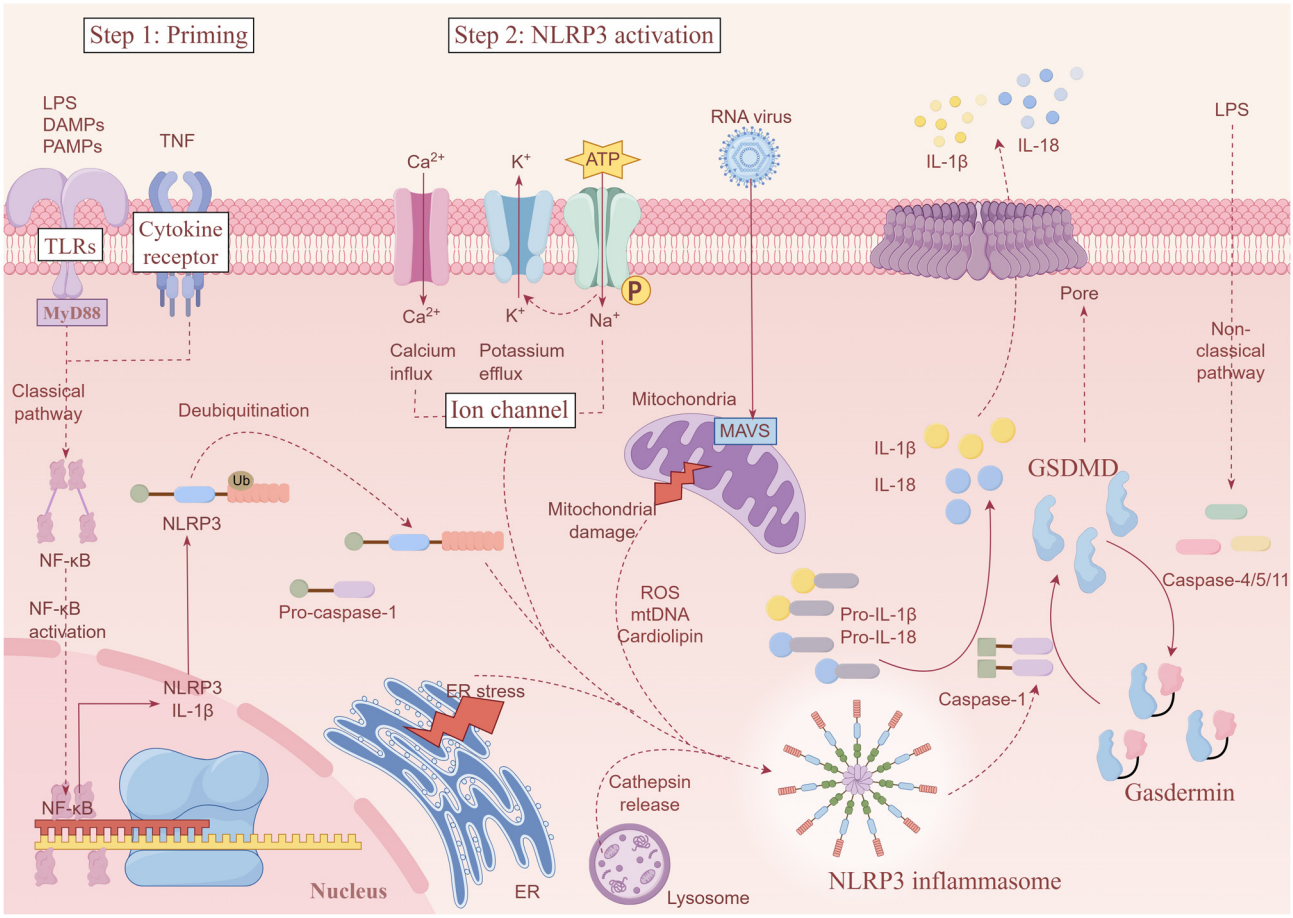

Figure 2. Mechanisms of activation for NLRP3 inflammasomes. The present figure was generated using FigDraw. DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; TLRs, Toll-like receptors; MyD88, myeloid differentiation primary response gene 88; ATP, adenosine triphosphate; MAVS, mitochondrial antiviral signaling protein; ER, endoplasmic reticulum; NLRP3, NOD-like receptor protein 3; Ub, ubiquitin; P, phosphate group; LPS, lipopolysaccharide; TNF, tumor necrosis factor; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; ROS, reactive oxygen species; mtDNA, mitochondrial DNA; IL-1β, interleukin-1β.

promoting NLRP3 degradation (46). This evidence indicates that targeting NLRP3 attenuates inflammatory responses by modulating interconnected pathways involving inflammation, pyroptosis, apoptosis and mitophagy. Nevertheless, the precise molecular targets governing these pathways require further elucidation (Fig. 2).

3. Core mechanisms of NLRP3 inflammasome-driven SIC pathogenesis

The central pathology of SIC involves a self-amplifying cascade initiated by NLRP3 inflammasome activation. Pathogen-derived DAMPs or PAMPs activate the TLR4/NF-κB signaling pathway, priming NLRP3 expression. This process triggers mitochondrial dysfunction and impairs mitophagy, leading to the release of mtROS and mtDNA that directly promote NLRP3 oligomerization. Concurrently, the mitochondrial permeability transition facilitates the release of cytochrome *c* (Cyt *c*) into the cytoplasm, which is a pivotal event that bridges mitochondrial damage with downstream programmed cell death (PCD) pathways (47). Regarding PCD convergence, these released mitochondrial components, such as Cyt c, not only initiate intrinsic apoptosis but also contribute to a complex interplay between apoptosis, pyroptosis, and inflammation (48). In this context, extrinsic apoptosis is initiated when TNF-α binds to TNF receptor (TNFR)1, activating caspase-8, while intrinsic apoptosis occurs as a result of Cyt *c* forming apoptosomes to activate caspase-9. Both pathways converge on caspase-3 of apoptosis-executing factors (e.g., endonucleases) and other proteins, culminating in apoptosis (49). In the pyroptosis-inflammation feedback loop, NLRP3-activated caspase-1 cleaves GSDMD, generating pore-forming GSDMD-NT fragments that induce pyroptosis in myocardial cells and can further exacerbate mitochondrial damage (50). This releases pro-inflammatory cytokines, such as IL-1β and IL-18, which disseminate systemically to amplify inflammation and generate secondary DAMPs, thereby reactivating the NLRP3 inflammasome.

The NLRP3 inflammasome exhibits distinct expression patterns and functional roles across different cardiac cell types, collectively contributing to the complex pathological network of SIC. In macrophages, early septic insults induce the expression of glucocorticoid-induced TNFR-related protein on their surface, which potentiates NLRP3 inflammasome activation and promotes pro-inflammatory macrophage polarization by modulating the post-translational modifications of the NLRP3 inflammasome, thereby amplifying the inflammatory cascade (51). In cardiomyocytes, NLRP3 activation

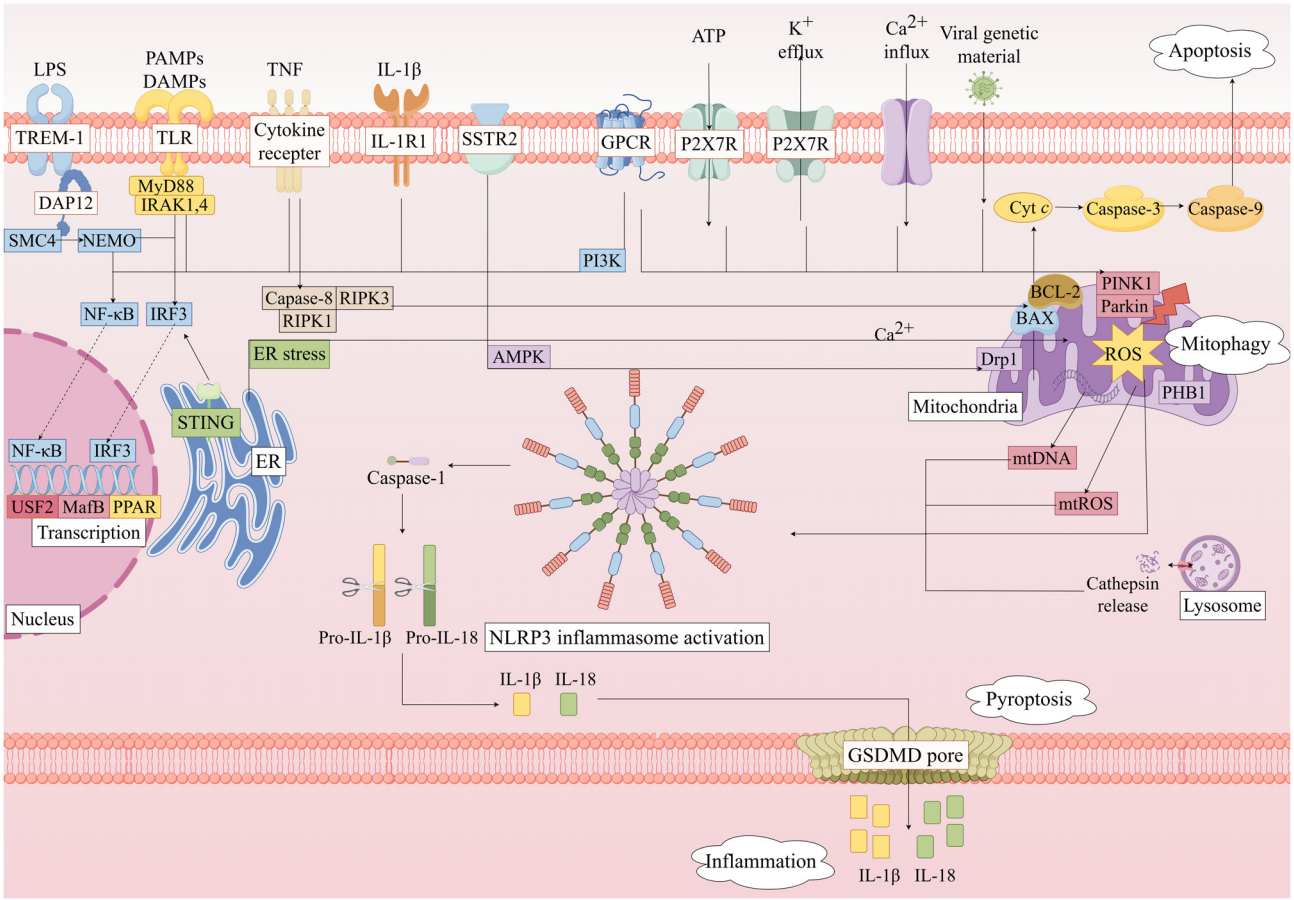

Figure 3. The regulatory mechanism of NLRP3 inflammasome in SIC. The figure was generated using FigDraw. LPS, lipopolysaccharide; TREM-1, triggering receptor expressed on myeloid cells-1; IL-1R1, IL-1 receptor 1; SSTR2, somatostatin receptor 2; GPCR, G protein-coupled receptor; DAP12, DNAX-activating protein of 12 kDa; IRAK1, IL-1 receptor-associated kinase 1; IRAK4, interleukin-1 receptor-associated kinase 4; NEMO, NF-κB essential modulator; PI3K, phosphatidylinositol 3-kinase; SMC4, structural maintenance of chromosome 4; IRF3, interferon regulatory factor 3; RIPK1, receptor-interacting serine/threonine kinase 1; RIPK3, receptor-interacting serine/threonine kinase 3; *STING*, stimulator of interferon genes; AMPK, adenosine 5'-monophosphate-activated protein kinase; Drp1, dynamin-related protein 1; PINK, PTEN-induced putative kinase 1; PHB1, prohibitin 1; USF2, upstream stimulatory factor 2; PARP, poly(ADP-ribose) polymerase; PPAR, peroxisome proliferator-activated receptor; MafB, v-maf musculoaponeurotic fibrosarcoma oncogene homolog B; P2X7R, purinergic ligand-gated ion channel 7 receptor; Cyt *c*, cytochrome *c*; BCL-2, B-cell lymphoma 2; BAX, BCL-2-associated X protein; ROS, reactive oxygen species; mtROS, mitochondrial ROS; mtDNA, mitochondrial DNA; ER, endoplasmic reticulum; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular patterns; TLRs, Toll-like receptors; MyD88, myeloid differentiation primary response gene 88; ATP, adenosine triphosphate; NLRP3, NOD-like receptor protein 3.

directly induces pyroptosis through GSDMD pore formation, compromising membrane integrity and leading to the release of intracellular contents. The released inflammatory mediators not only exacerbate autocrine dysregulation of calcium homeostasis but also recruit and activate macrophages, perpetuating a pro-inflammatory microenvironment and impairing cardiomyocyte contractile function, representing a primary mechanism of acute cardiac injury in SIC (52). Furthermore, cardiomyocytes can communicate directly with cardiac fibroblasts via membrane nanotubes, transmitting inflammasome activation signals that drive fibroblasts toward a pro-inflammatory and pro-fibrotic phenotype. This intercellular crosstalk results in excessive extracellular matrix production, exacerbating acute injury and laying the foundation for long-term myocardial fibrosis and diastolic dysfunction in survivors of sepsis (53). In summary, the NLRP3 inflammasome serves heterogeneous roles across different cardiac cell types, which collectively constitute the complex pathological network of SIC. These interconnected mechanisms form a notable cycle: Mitochondrial damage induces NLRP3 activation, which promotes inflammation, pyroptosis and apoptosis, resulting in secondary mitochondrial injury. Targeted disruption of any nodal point in this cycle represents a promising therapeutic strategy for SIC, as the overlapping pathways converge on NLRP3 inflammasome activation to sustain myocardial injury (Fig. 3).

Inflammatory storms and myocardial dysfunction. Dysregulated inflammation represents a notable pathophysiological process wherein pro-inflammatory cytokines activate immune cells and mediate tissue damage, while anti-inflammatory cytokines counteract these responses. SIC, an acute cardiac dysfunction syndrome stemming from systemic infection and inflammation, accelerates cardiovascular collapse by exacerbating microcirculatory dysfunction and hypoperfusion. Its pathogenesis involves complex interactions between the immune and cardiovascular systems, prominently featuring inflammatory activation (54). Excessive cytokine production triggers a cytokine storm that amplifies tissue injury and organ dysfunction (55). During SIC, PAMPs and DAMPs

activate the NLRP3 inflammasome via TLRs (56). This leads to caspase-1-mediated proteolytic maturation of pro-IL-1β and pro-IL-18. Mature IL-1β and IL-18 further activate downstream pathways, such as the NF-κB pathway, inducing secondary inflammatory cytokines, such as TNF-α, IL-6 and IL-1β, that establish a cytokine storm, ultimately causing cardiomyocyte dysfunction (57). Notably, NLRP3-knockout murine SIC models exhibit markedly reduced expression of IL-1β, IL-6, IL-18 and TNF-α, with concomitant improvement in cardiac function and attenuated myocardial injury (58). These findings suggest that combined targeting of NLRP3-derived IL-1β and IL-18 represents a novel therapeutic approach for SIC.

Upstream stimulatory factor 2 (USF2), a basic helix-loop-helix leucine zipper transcription factor, regulates NLRP3 expression in multiple disease contexts (59,60). A study reported by Dong *et al* (61) demonstrated that USF2 silencing attenuates NLRP3 inflammasome activation in experimental SIC models by targeting the microRNA (miR/miRNA)-206/Rho-related GTP-binding protein RhoB/Rho-associated protein kinase signaling axis, thereby reducing inflammatory responses and cardiac dysfunction. Conversely, in lupus nephritis, USF2 does not operate through this miRNA axis but rather directly binds to the NLRP3 promoter to drive its transcription and exacerbate podocyte injury (60). These findings underscore that the pathophysiological role of USF2 is not universal but is determined by specific cellular milieu.

The TLR4/MyD88/NF-κB pathway serves as the dominant upstream regulator of NLRP3 activation. During SIC, LPS upregulates NLRP3, IL-18 and IL-1β expression through this pathway, exacerbating myocardial inflammation. Notably, NF-κB inhibition with BAY 11-7082, a selective IκBα phosphorylation blocker, suppresses SIC-induced inflammation in cellular models (62). Myo-inositol oxygenase (MIOX), a key enzyme in inositol catabolism, functions as both a biomarker and therapeutic target in renal diseases (63,64). Notably, MIOX enhances NLRP3 inflammasome activity by inhibiting its degradation, aggravating infection-induced cardiac inflammation and dysfunction in SIC models (65).

Synergistic crosstalk between pyroptosis and apoptosis. PCD represents a conserved mechanism for eliminating damaged cells. Major PCD modalities include apoptosis, autophagy, ferroptosis, necroptosis and pyroptosis (66). Apoptosis, as a predominant PCD form, contributes notably to cellular injury during sepsis. SIC-induced mitochondrial dysfunction alters membrane permeability, triggering the activation of pro-apoptotic B-cell lymphoma 2 (BCL-2) family proteins, such as BCL-2-associated X protein (BAX), while suppressing anti-apoptotic members, such as BCL-2. This facilitates Cyt *c* release and caspase-3 activation (67). Similarly, TNF-α binding to TNFR1 activates caspase-8, which cleaves and activates the executioner protein caspase-3. Nuclear translocation of caspase-3 initiates substrate proteolysis, DNA fragmentation and apoptotic execution (68). Myocardial apoptosis severity associates with cardiac damage in sepsis. SIC models demonstrate impaired cardiac function coincident with the elevated expression of apoptosis-related proteins, including cleaved caspase-3 (69). The NLRP3 inflammasome indirectly regulates apoptosis via inflammatory signaling and cellular stress in SIC. Specifically, TNFR engagement activates NLRP3 through the receptor-interacting serine/threonine kinase (RIPK) 1/RIPK3 signaling axis (70), which promotes the release of pro-inflammatory cytokines, such as IL-1β and IL-18, and induces mitochondrial damage and ROS production. ROS trigger BAX oligomerization via compromising mitochondrial outer membrane integrity by impairing the anti-apoptotic function of BCL-2, which normally sequesters BAX (71). This mitochondrial membrane damage facilitates Cyt *c* release into the cytoplasm, where it forms apoptosomes that activate caspase-3 (72). Concurrently, NLRP3-driven ROS production also activates downstream caspase-8, which converges with the caspase-3 pathway to induce nuclear translocation of endonucleases, culminating in DNA fragmentation and apoptotic cell death (73). Several upstream regulators have been shown to modulate this process: Stimulator of interferon genes knockout attenuates cardiomyocyte injury by suppressing NLRP3 via an interferon regulatory factor 3-dependent pathway (74); poly(ADP-ribose) polymerase 1 (PARP1) overexpression decreases BCL-2 while elevating BAX and cleaved caspase-3, a cascade reversed by atractylenolide I targeting the PARP1/NLRP3 pathway (75); and oxysterols receptor LXR-α knockout exacerbates apoptosis by enhancing NLRP3 expression (76).

Pyroptosis represents a pro-inflammatory PCD distinct from apoptosis, mediated by GSDM family proteins that form transmembrane pores in the plasma membrane. These pores facilitate IL-18 and IL-1β release while disrupting ionic homeostasis, ultimately causing cellular swelling and lysis (77,78). The NLRP3 inflammasome exemplifies a 'double-edged sword' in the pathogenesis of SIC. As an important component of the innate immune system, NLRP3 inflammasome activation is necessary for host defense (79). Moderate pyroptosis, driven by NLRP3, facilitates the clearance of intracellular pathogens in SIC by eliminating their replicative niche and exposing them to extracellular immune surveillance, thereby preserving cardiac function in the early stages of sepsis (80). Conversely, excessive and uncontrolled NLRP3 activation triggers an excessive release of pro-inflammatory cytokines, including IL-1β and IL-18, and widespread pyroptotic cell death, which exacerbates myocardial injury and contributes to cardiac dysfunction (81). While inhibition of NLRP3 represents a promising strategy to mitigate septic cardiomyopathy, complete and long-term suppression may inadvertently compromise the ability of the patient to clear infections. Therefore, future therapeutic paradigms should not aim to abolish NLRP3 activity entirely, but to precisely modulate it, therefore suppressing its pathological overactivation while preserving its beneficial role in pathogen clearance.

Multiple pathways converge on NLRP3 to regulate pyroptosis: TLR4 activation initiates NLRP3 priming via the MyD88/NF-κB pathway, while pharmacological inhibition of NF-κB suppresses the resulting caspase-1 expression and pyroptosis (62,82). Protective factors such as heat shock protein 70 (83), apelin via adenosine 5'-monophosphate-activated protein kinase (AMPK) signaling (84) and cortistatin via somatostatin receptor 2 (SSTR2)/AMPK signaling (85) inhibit NLRP3 activation and downregulate pyroptosis-executing proteins such as GSDMD and caspase-1. Conversely, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit γ promotes NLRP3 assembly via G protein-coupled

receptor (GPCR)-induced NF-κB activation, exacerbating pyroptosis (86,87).

Mitochondrial homeostatic imbalance and autophagy inhibition. Mitochondria serve as important energy-producing organelles that regulate cellular functions and maintain homeostasis, being particularly abundant in cardiomyocytes and notably vulnerable during sepsis. Autophagy is a lysosomal degradation process that eliminates damaged macromolecules and organelles, sustaining intracellular homeostasis (88,89). Mitophagy specifically targets impaired mitochondria for autophagic clearance (90), operating primarily through parkin-dependent and -independent mechanisms. The PTEN-induced putative kinase 1 (PINK1)/parkin pathway represents the canonical mitophagy route: Upon mitochondrial damage or depolarization, PINK1 accumulates on the mitochondrial outer membrane and recruits Parkin to ubiquitinate damaged mitochondria, marking them for autophagosomal engulfment (91-94). Signal transducer and activator of transcription 3 (STAT3), a cytokine-responsive transcription factor, modulates this process; STAT3 inhibition in macrophages induces PINK1-dependent mitophagy (95), which clears dysfunctional mitochondria, restores mitochondrial membrane potential, suppresses mtROS release and inactivates the NLRP3 inflammasome (96).

During SIC, the pathogen-activated NLRP3 inflammasome inhibits mitophagy via caspase-1-mediated cleavage of autophagy-related proteins, such as beclin-1, leading to mitochondrial structural and functional damage (97). This results in a notable release of mtROS and mtDNA, which act as DAMPs in a positive feedback loop that activates the NLRP3 inflammasome, establishing a cycle of autophagy inhibition and exacerbated inflammation (98). Mitophagy, the selective clearance of damaged or dysfunctional mitochondria, has been shown to reduce mtROS levels, suppress NLRP3 inflammasome activation and consequently mitigate septic cardiomyopathy injury (99). A recent study indicated that inhibiting pyruvate dehydrogenase kinase suppresses NLRP3 inflammasome activation, reduces downstream caspase-1 cleavage and IL-1β secretion and diminishes ROS production by enhancing autophagy (100). Dual specificity phosphatase 1, a regulator of angiotensin II signaling (101), has been shown to enhance FUN14 domain-containing protein 1-dependent mitophagy, thereby reducing NLRP3 inflammasome formation and the generation of specific inflammatory cytokines, ultimately attenuating the inflammatory response (102-104). SSTR2, a GPCR, is an important functional receptor expressed in cardiomyocytes. The activity of dynamin-related protein 1 (Drp1), a GTPase primarily regulating mitophagy, is modulated by phosphorylation (105). During SIC, the neuropeptide cortistatin can activate SSTR2/Drp1-mediated mitophagy to reduce ROS production, thereby inhibiting NLRP3 inflammasome activation and pyroptosis, alleviating SIC-induced myocardial injury (85). Prohibitin 1 (PHB1), a key protein in the mitochondrial inner membrane, is involved in maintaining mitochondrial structure, regulating metabolism and inhibiting mtROS generation. Research demonstrates that PHB1 suppresses mtROS accumulation by enhancing mitophagy, consequently blocking NLRP3 inflammasome assembly; conversely, PHB1 deficiency exacerbates mitochondrial damage and inflammation (106). Additionally, autophagy can directly suppress inflammatory responses by clearing NLRP3 inflammasome components, such as ASC specks, or degrading active caspase-1 (107,108).

Mitophagy deficiency amplifies mitochondrial danger signals, including mtROS and mtDNA, which serve as important triggers and amplifiers for the NLRP3 inflammasome (109). The level of cardiomyocyte mitophagy is closely associated with the outcome and prognosis of septic cardiomyopathy; while damaged mitochondria acting as DAMPs induce NLRP3 inflammasome activation, the activated NLRP3 inflammasome conversely impairs autophagic capacity, establishing a detrimental positive feedback loop of inflammation and autophagy imbalance that exacerbates septic cardiomyopathic injury (110). Adaptor protein containing PH domain, PTB domain and leucine zipper motif 1 (APPL-1), a dynamic protein of the early endosome, translocates between cellular organelles under various stress conditions (111). A recent study indicated that APPL-1 deficiency suppresses mitophagy, consequently triggering excessive NLRP3 inflammasome activation (112). Additionally, v-maf musculoaponeurotic fibrosarcoma oncogene homolog B, a protein belonging to the transcription factor MAF subfamily that is responsible for binding specific DNA element motifs (113), has been shown to promote NLRP3 inflammasome-mediated mitochondrial damage upon its knockdown in SIC models, which also display consequent mtROS production and mtDNA release (114).

4. Interplay of molecular mechanisms

The pathological progression of SIC is driven by the NLRP3 inflammasome as a central hub, establishing self-amplifying injury through a triple amplification cascade: i) NLRP3 activation induces caspase-1-mediated maturation of IL-1β and IL-18, triggering inflammatory cascades (115); ii) concurrently, caspase-1 cleaves GSDMD to initiate pyroptosis, with resultant pore formation releasing DAMPs that further activate the TLR4/NLRP3 axis; and iii) pyroptosis and apoptosis pathways converge at the caspase-8/BH3-interacting domain death agonist (Bid)/truncated Bid node, where caspase-8 activation promotes BAX-mediated mitochondrial outer membrane permeabilization, resulting in mitochondrial Cyt *c* release and amplified apoptosis. Mitochondrial damage releases mtROS and mtDNA that directly activate NLRP3, while conversely, NLRP3 suppresses PINK1/parkin-mediated mitophagy via caspase-1 cleavage of beclin-1. The resulting mitophagy deficiency causes accumulation of damaged mitochondria and mtROS overproduction, further activating NLRP3 to establish a cycle of autophagy inhibition and inflammatory exacerbation (116). Key molecular targets mediating these interactions include: i) TNFR-associated factor 2, which bidirectionally regulates the NF-κB inflammatory pathway and the RIPK1-mediated apoptosis/survival switch in SIC; and ii) AMPK, an important cellular energy sensor that concurrently inhibits NLRP3 assembly and enhances PINK1/parkin-mediated mitophagy during SIC (117). Notably, mtROS released from damaged mitochondria in SIC cardiomyocytes serve as a common trigger that interconnect inflammatory activation, BAX oligomerization and autophagy suppression (118) (Fig. 4).

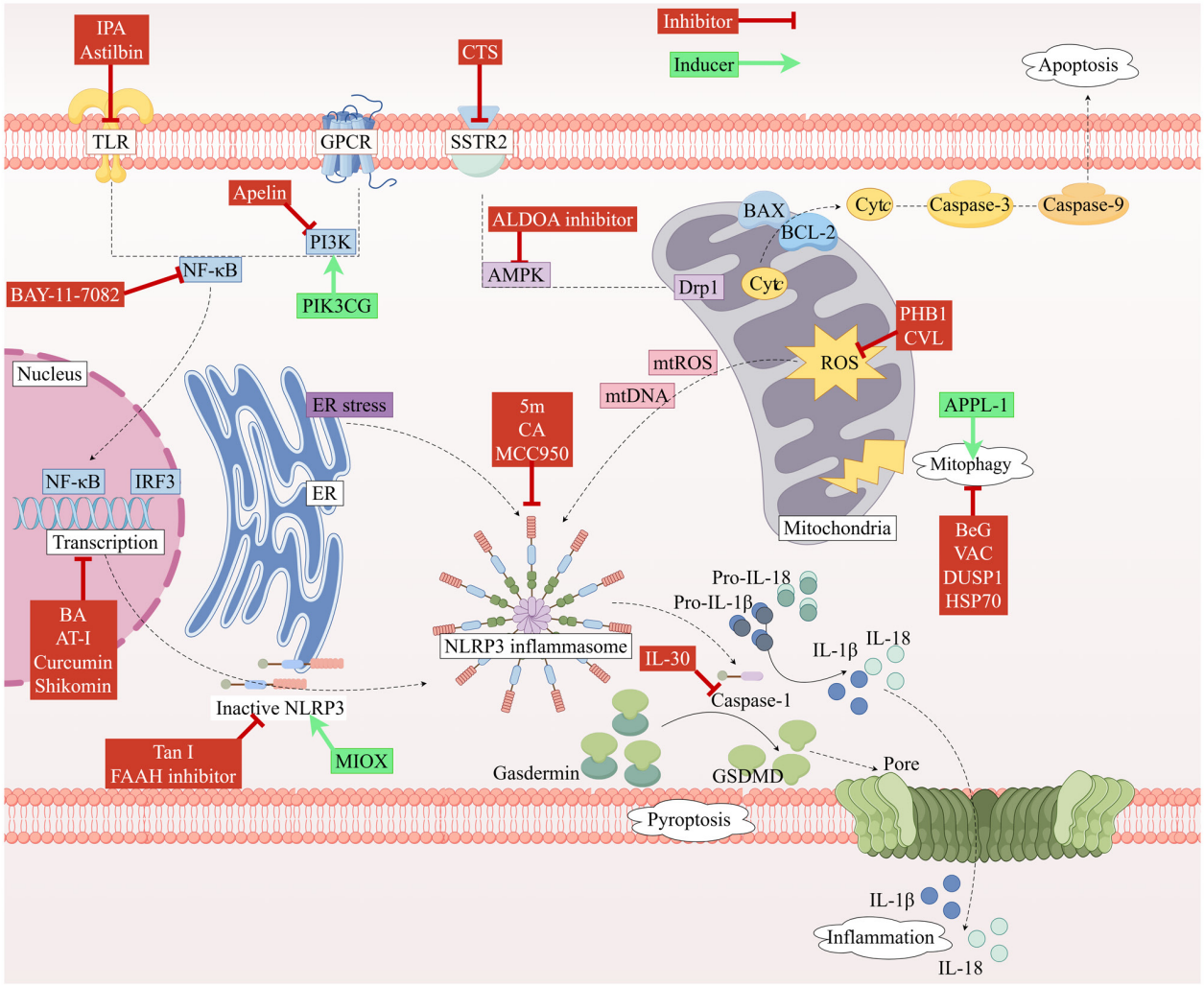

Figure 4. Inhibitors and promoters of the NLRP3 inflammasome and their mechanisms of action. The figure demonstrates promoters and inhibitors of the NLRP3 inflammasome and their specific modes of action, forming a complex regulatory network. Green boxes indicate inducers of the inflammasome, and red boxes indicate inhibitors. The figure was generated using FigDraw. CTS, cortistatin; IPA, indole-3-propionic acid; PIK3CG, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit γ; BA, brevilin A; AT-1, atractylenolide I; 5m, 5-methoxyindole-3-carboxaldehyde; CA, cinnamyl alcohol; Tan I, tanshinone I; FAAH inhibitors, fatty acid amide hydrolase inhibitors; MIOX, myo-inositol oxygenase; ALDOA, aldolase A; APPL-1, adaptor protein containing PH domain, PTB domain and leucine zipper motif 1; CVL, carvacrol; BeG, bergapten; VAC, vaccarin; DUSP1, dual specificity phosphatase 1; HSP70, heat shock protein 70; NLRP3, NOD-like receptor protein 3.

Therapeutic strategies targeting the NLRP3 inflammasome. As aforementioned, pharmacological agents and compounds targeting the NLRP3 inflammasome and its upstream or downstream pathways exhibit notable therapeutic potential for mitigating myocardial injury and treating SIC, potentially forming the foundation for future therapeutic strategies. The present section broadly categorizes the mechanisms of action of currently investigated compounds.

Direct inhibitors. Several pharmacological agents ameliorate SIC-induced myocardial dysfunction by directly inhibiting NLRP3 inflammasome assembly and activation. Tanshinone I (Tan I), an active constituent of *Salvia miltiorrhiza* with established therapeutic potential across multiple pathologies (119,120), suppresses inflammasome assembly and downstream caspase-1 activation in SIC model by targeting the NLRP3 PYD to disrupt its interaction with ASC; this mechanism positions Tan I and its derivatives as promising next-generation NLRP3-targeted therapeutics (121). Cinnamyl alcohol, a bioactive component of cinnamon demonstrating anti-inflammatory and antioxidant properties (122,123), reduces tissue inflammation and downregulates inflammatory cytokine expression via NLRP3 inflammasome inhibition, highlighting its therapeutic potential for sepsis (124). Genetic ablation of NLRP3 markedly attenuates IL-1β, IL-6, IL-18 and TNF-α expression while improving cardiac function and mitigating myocardial injury in SIC model (58). These findings indicate that combinatorial NLRP3 inflammasome inhibition represents a viable therapeutic strategy for SIC.

Upstream pathway inhibition. Several agents indirectly mitigate NLRP3 inflammasome-mediated myocardial injury and dysfunction in SIC by targeting upstream signaling pathways regulating its priming and activation. NF-κB, a central regulator of NLRP3 priming, facilitates inflammasome activation via the TLR4/MyD88/NF-κB pathway (125); a recent study demonstrated that the NF-κB antagonist BAY 11-7082 reduces pro-inflammatory cytokine expression, such as that of TNF-α, IL-6 and IL-1β, and suppresses pyroptosis (62). Shikonin, an anti-inflammatory phytochemical, exerts inhibitory effects on

NLRP3 inflammasome-mediated inflammation and pyroptosis via AMPK/NAD-dependent protein deacetylase sirtuin-1 pathway modulation when formulated as Zn^{2+}-shikonin nanoparticles (126). Astilbin, a protective flavonoid (127-131), markedly attenuates inflammatory marker concentrations and reduces TLR4/NF-κB pathway expression in septic cardiomyopathy model, indicating that its cardioprotective mechanism involves TLR4/NF-κB pathway inhibition to suppress NLRP3 inflammasome activation (132). Brevilin A, an anti-inflammatory sesquiterpene lactone derived from *Centipeda minima*, effectively suppresses NF-κB and NLRP3 protein expression in both cellular and animal models of septic cardiomyopathy, highlighting its promise as a natural therapeutic for SIC (133). Indole-3-propionic acid, an anti-inflammatory gut microbiota metabolite (134-137), inhibits NLRP3 and downstream caspase-1 expression via TLR4/MyD88/NF-κB pathway suppression in SIC models (62).

Downstream effector blockade. Specific pharmacological agents ameliorate SIC by inhibiting downstream signaling or effector proteins of the NLRP3 inflammasome. Curcumin, the primary active constituent of turmeric with demonstrated pleiotropic pharmacological activities (138), reduces NLRP3, ASC and caspase-1 expression in septic animal models when delivered via arginine-glycine-aspartic acid-anchored liposomal encapsulation, identifying this as a novel therapeutic strategy for SIC (139). The translational promise of this strategy is underscored by a phase II randomized controlled trial, where intervention with nano-curcumin in a cohort of patients with severe sepsis not only confirmed its safety and feasibility as a therapeutic but also mechanistically demonstrated a marked downregulation of NF-κB and NLRP3 mRNA expression in patients following treatment, thereby providing robust support for its future application in targeted SIC therapy and prognostic assessments (140). Furthermore, IL-30 exhibits anti-inflammatory properties across multiple pathologies (141-143); a study by Zhao *et al* (144) demonstrated that IL-30 treatment effectively suppresses the expression of pyroptosis-associated proteins, including IL-1β, IL-18, NLRP3 and GSDMD, in SIC murine models.

Mitophagy inducers. Several pharmacological agents mitigate myocardial injury resulting from SIC by enhancing mitophagy to disrupt the cycle of NLRP3 inflammasome activation and mitophagy inhibition. Carvacrol, a monoterpenoid phenol with anti-inflammatory properties (145), reduces ROS generation and enhances autophagy to suppress NLRP3 inflammasome formation in SIC (146). Vaccarin, a bioactive flavonoid derived from *Vaccaria segetalis* seeds (147-149), attenuates inflammatory cytokine expression and modulates mitophagy to confer cardioprotection in SIC (150). Bergapten, a bioactive coumarin (151-153), inhibits NLRP3 inflammasome activation by promoting mitophagy, suggesting therapeutic potential for SIC (154). Additionally, the aldolase A inhibitor LYG-202 suppresses activation of the NLRP3 inflammasome and attenuates inflammation in SIC through AMPK/mitophagy pathway activation (155).

5. Clinical translation challenges and future directions

Despite the compelling therapeutic potential of targeting the NLRP3 inflammasome in SIC, its translation from promising preclinical data to clinical reality faces numerous challenges. A critical and expanded analysis of these hurdles, informed by lessons from broader NLRP3 inhibitor development, is important for guiding future research.

Notable hurdle of cell-type specificity. The majority of current research focuses on the specific inhibition of NLRP3 (156). While this approach effectively suppresses inflammation, it may simultaneously impair pathogen clearance by disrupting the innate immune functions of NLRP3 (157). In fact, selectively modulating the downstream effects of NLRP3 in different cell types based on their pathological roles during SIC represents a promising future therapeutic strategy. For example, macrophages, influenced by NLRP3 activation, contribute markedly to immune dysregulation in the late stages of SIC (158). In cardiomyocytes, excessive NLRP3-driven pyroptosis disrupts membrane integrity and directly damages myocardial tissue (159). Furthermore, sustained NLRP3-mediated endothelial cell activation is a central factor in microcirculatory dysfunction (160). Future research on NLRP3 inhibitors should aim to develop cell-specific targeted delivery systems, such as nanoparticle-based carriers, to achieve precise intervention in NLRP3 activity across different cell types in SIC. This strategy would maximize cardiac therapeutic efficacy while minimizing systemic immunosuppression.

Navigating the therapeutic window and SIC reversibility. A defining feature of SIC is its potential reversibility following sepsis control (161). This characteristic implies a narrow therapeutic window for NLRP3 inhibition. The hyperinflammatory phase of early sepsis, when NLRP3 is most active (162), likely represents the optimal period for effective intervention to mitigate myocardial injury and improve patient outcomes. By contrast, administration of inhibitors during the later immunoparalytic phase may exacerbate immune imbalance and increase the risk of secondary infections (163). However, most current cellular and animal models of NLRP3 inhibition employ prophylactic or early treatment regimens (164). Therefore, future clinical trials of NLRP3 inhibitors must carefully define appropriate monitoring indicators and rigorously evaluate the therapeutic window.

Integration with the standard of care for sepsis. Although several NLRP3 inhibitors have advanced to clinical trials, current guidelines and clinical experience emphasize that conventional therapies, including early antibiotic administration and supportive care, remain the cornerstone of sepsis management (165). NLRP3 inhibitors are not intended to replace but rather to complement the existing standard of care, such as antibiotics, fluid resuscitation and vasopressors. For instance, by mitigating endothelial injury and capillary leakage (166), NLRP3 inhibitors may enhance hemodynamic stability achieved through fluid resuscitation and vasoactive agents. However, potential antagonistic interactions must be carefully considered in future clinical use. Certain antibiotics can induce mitochondrial stress or alter immune cell function, which may indirectly influence NLRP3 inflammasome activation pathways (167). As early and appropriate antimicrobial therapy is important (168), NLRP3 inhibition

Table I. Compounds targeting NLRP3 to inhibit sepsis-induced cardiomyopathy.

First author, year	Compound	Type	Mechanism of action	Experimental model	Experimental findings	(Refs.)
Zheng *et al*, 2024	MCC950	Synthetic small-molecule inhibitor	Binds the NACHT domain of NLRP3, preventing caspase-1 activation and IL-1β/IL-18 maturation	BV2 cells, HUVECs, THP-1 cells, primary neurons and podocytes	Reduces NLRP3 inflammasome activation; suppresses pyroptosis; downregulates inflammatory cytokines IL-1β and IL-18.	(28)
				tMCAO mice, APP/PS1 mice, CLP mice, ApoE-/- mice and db/db mice	Downregulates NLRP3, ASC, caspase-1, IL-1β and IL-18; reduces infarct volume and neuro-inflammation in stroke models; suppresses amyloid plaque and tau pathology in alzheimer's disease models; reduces liver injury markers ALT and AST; reduces atherosclerosis plaque area; reduces blood glucose and complications in diabetes; and increases survival in sepsis.	
				Clinical trial	Upregulates serum liver enzymes ALT and AST, indicating hepatotoxicity in a phase II trial for rheumatoid arthritis.	
Zhu *et al*, 2023	URB597 and PF-04457845	FAAH inhibitors	Disrupts the NLRP3-FAAH interaction and induces the autophagic degradation of NLRP3	LPS/cells	Increases K48 ubiquitination; promotes selective autophagy of NLRP3; downregulates NLRP3, IL-1β, GSDMD and caspase-1	(46)
				LPS/C57BL/6 mice	Downregulates IL-1β; decreases neutrophil infiltration; suppresses NLRP3 inflammasome activation	
				Clinical trial	Disrupted the NLRP3-FAAH interaction in patient PBMCs; suppressed IL-1β release	
Zhang *et al*, 2024	Indole-3-propionic acid	Anti-inflammatory gut microbiota metabolite	Inhibits NLRP3 and downstream caspase-1 expression via TLR4/MyD88/NF-κB pathway suppression	LPS/H9C2 cells	Downregulates the mRNA expression levels of IL-6 and TNF-α, MyD88, NF-κB and NLRP3	(62)
				LPS/C57BL/6J mice	Downregulates BNP and troponin T; downregulates inflammatory cytokines IL-1β, IL-6 and TNF-α; reduces macrophage infiltration; reduces expression of MyD88, caspase-1, NLRP3 and phosphorylation of NF-κB	
	BAY 11-7082	NF-κB antagonist	Inhibits the NLRP3 inflammasome by targeting its ATPase activity	LPS/BMDMs	Reduces caspase-1 activation and IL-1β; suppresses NLRP3 ATPase activity; inhibits ASC pyroptosome formation	
Zhou *et al*, 2023	Myo-inositol oxygenase	Nonheme iron oxygenase	Reduces the degradation of NLRP3	LPS/H9C2 cells	Upregulates IL-1β, IL-6, INF-γ and TNF-α	(65)
				CLP/db/db male mice	Decreases survival rate; upregulates inflammatory cytokines IL-1β, IL-6, INF-γ and TNF-α; promotes cardiac dysfunction; increases NLRP3 expression	

Table I. Continued.

First author, year	Compound	Type	Mechanism of action	Experimental model	Experimental findings	(Refs.)
Wang *et al*, 2024	Atractylenolide I	Sesquiterpene lactone compound	Modulation of the PARP1/NLRP3 signaling pathway	LPS/RAW 264.7 cells	Suppresses M1 polarization; downregulates Cox2, iNOS and CD11b; downregulates PARP1, NLRP3, ASC, IL-1β and IL-18;	(75)
				LPS/H9C2 cells	Reduces ROS; decreases expression of p-NF-κB, Nox2 and Nox4; suppresses apoptosis; downregulates BAX, cleaved-caspase3 and cleaved-caspase9; upregulates BCL-2	
Song *et al*, 2022	Heat shock protein 70	Heat shock protein	Attenuates mitochondrial dysfunction and inhibits NLRP3 inflammasome-mediated pyroptosis via the caspase-1/GSDMD pathway	LPS/H9C2 cells	Increases cell viability; reduces PI staining; downregulates DRP1; increases JC-1 aggregate formation; reduces mtROS production; reduces TNF-α and IL-1β levels; downregulates NLRP3, caspase-1 and GSDMD, GSDMD-N; HSP70 binds NLRP3	(83)
				LPS/C57BL/6 mice	Increases survival rate; increases ejection fraction; downregulates cTnT, TNF-α and IL-1β; reduces myocardial damage; suppresses mitochondrial vacuolization; and downregulates NLRP3, caspase-1, GSDMD and GSDMD-N	
Duan *et al*, 2024	Cortistatin	Neuroendocrine polypeptide	Inhibits the activation of the NLRP3 inflammasome and pyroptosis by activating SSTR2/AMPK/Drp1 signaling	LPS/H9C2 cells	Downregulates NLRP3, Drp1, GSDMD-NT, cleavage of caspase-1 and cleavage of IL-1β; upregulates expression of AMPK	(85)
			Inhibits the activation of the NLRP3 inflammasome and pyroptosis by activating SSTR2/AMPK/Drp1 signaling	LPS/C57BL/6J mice	Increases survival rate; reduces cardiac dysfunction; downregulates inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, and suppresses NLRP3 inflammasome activation	
Lu *et al*, 2023	AS-604850	PIK3CG inhibitor	Regulates PIK3CG/NLRP3/GSDMD signaling	CLP/BALB/c male mice	Inhibits cardiac dysfunction; decreases CK-MB, LDH, AST, BUN and red blood cell levels; increases levels of ALB, white blood cells, lymphocytes, monocytes, intermediate cells, eosinophils, granulocytes and platelets; downregulates PIK3CG and NLRP3	(86)

Table I. Continued.

First author, year	Compound	Type	Mechanism of action	Experimental model	Experimental findings	(Refs.)
Liu *et al*, 2023	Melatonin	Amine hormone	Inhibits the PIK3CG-related signaling pathway	LPS/HL-1 cells	Increases cell viability; reduces intracellular ROS; downregulates Akt, IL-6, TNF-α, Myc and Pdk1 mRNA expressions; reduces the levels of p-AKT/AKT, MYC, PDK1, NLRP3 and IL-6	(87)
				CLP/BALB/c male mice	Increases survival rate; inhibits cardiac dysfunction; downregulates IL-1β, IL-18, caspase-1, IL-6, TNF-α and NOX2; reduces PIK3CG expression	
Tan *et al*, 2022	Dual specificity phosphatase 1	Enzyme	Enhances FUNDC1-dependent mitophagy, reducing NLRP3 inflammasome formation	LPS/HL-1 cells	Increases FUNDC1 expression; promotes mitophagic activity; upregulates Atg5, beclin-1 and LC3II; downregulates p62; restores mitochondrial membrane potential; suppresses mtROS production	(102)
				LPS/C57BL/6J mice	Reduces cardiac dysfunction; downregulates inflammatory cytokines such as IL-6, TNF-α and MCP1; reduces neutrophil infiltration; suppresses cardiomyocyte apoptosis; promotes mitochondrial respiration; increases ATP synthesis; promotes cell viability	
Zhao *et al*, 2023	Tanshinone I	Active constituent of *Salvia miltiorrhiza*	Targets the NLRP3 PYD to disrupt its interaction with ASC	LPS/BMDMs LPS/C57BL/6 mice	Downregulates caspase-1, IL-1β and LDH Increases survival rate; downregulates IL-1β	(121)
Zou *et al*, 2022	Cinnamyl alcohol	Bioactive component of cinnamon	Downregulates inflammatory cytokine expression via NLRP3 inflammasome inhibition	LPS/C57BL/6 male mice	Increases survival rate; reduces tissues injury, for example in the liver, heart, lungs and kidneys; downregulates ASC, NLRP3 and caspase-1; inhibits expression of IL-1β, IL-18	(124)
Guo *et al*, 2023	Zn-Shik-PEG nanoparticles	Metal-polyphenol coordination NPs	Inhibits NLRP3 inflammasome via the AMPK/SIRT1 pathway	LPS/RAW264.7 cells	Reduces ROS production; upregulates Nrf2 and HO-1; increases expression of p-AMPK and SIRT1; downregulates NLRP3, ASC, cleaved caspase-1, IL-1β and IL-18; reduces levels of TNF-α and IL-6; suppresses apoptosis (as measured by TUNEL assay)	(126)
				LPS/C57BL/6 mice	Increases survival rate; reduces levels of TNF-α, IL-6; reduces BUN, creatinine ALT and AST; upregulates Nrf2 and HO-1; reduces apoptosis (as determined by TUNEL assay)	

Table I. Continued.

First author, year	Compound	Type	Mechanism of action	Experimental model	Experimental findings	(Refs.)
Fang *et al*, 2024	Astilbin	Protective flavonoid	Activates the NRF2/HO-1 pathway; inhibits the TLR4/NF-κB pathway; and reduces oxidative stress, inflammation and apoptosis	LPS/H9C2 cells	Increases cell viability; reduces CK-MB and LDH; suppresses ROS and MDA production; increases SOD levels; downregulates TNF-α, IL-6 and IL-1β; suppresses TLR4 and p-NF-κB; downregulates BAX; upregulates BCL-2	(132)
				LPS/C57BL/6 male mice	Reduces CK-MB and LDH; inhibits cardiac dysfunction; reduces ROS and MDA levels; increases SOD levels; downregulates TNF-α, IL-6 and IL-1β; inhibits TLR4 and p-NF-κB activity; downregulates BAX; and upregulates BCL-2	
Liu *et al*, 2023	Brevilin A	Anti-inflammatory sesquiterpene	Inhibits NF-κB/NLRP3 pathway-mediated inflammation activation	LPS/NRCMs	Increases cell viability; decreases cTnT and CK-MB; downregulates NLRP3, ASC, caspase-1 and NF-κB	(133)
				CLP/male Sprague-Dawley rats	Increases survival rate; inhibits cardiac dysfunction; downregulates NLRP3, ASC, caspase-1 and NF-κB; suppresses cTnT and CK-MB	
Shi *et al*, 2023	Curcumin	Primary active constituent of turmeric	Targeted delivery to macrophages via RGD-modified liposomes inhibits pyroptosis	LPS/RAW264.7 cells	Downregulates caspase-1, caspase-3, NLRP3, IL-1β and GSDMD; and suppresses pyroptosis	(139)
				LPS/ICR male mice	Downregulates TNF-α and IL-6; and reduces inflammatory cell accumulation	
Karimi *et al*, 2022	Curcumin	Primary active constituent of turmeric	Targeted delivery to macrophages via RGD-modified liposomes inhibits pyroptosis	Clinical trial	Suppresses NLRP3 inflammasome activation; downregulates NF-κB and IFN-γ mRNA expression; upregulates FOXP3; downregulates IL-17, IL-22 and HMGB1; reduces SOFA and MODS scores	(140)
Zhao *et al*, 2023	Interleukin-30	Anti-inflammatory properties	Inhibits NLRP3 inflammasome activation and therefore suppresses resulting pyroptosis	LPS/BMDMs	Downregulates NLRP3, caspase-1, IL-1β and IL-18	(144)
				CLP/C57BL/6 mice	Downregulates NLRP3, cleaved caspase-1, IL-1β and IL-18; and reduces cardiac dysfunction	
				Clinical trial	Positive association with SOFA score and CK-MB; and acts as a predictor of 28-day mortality	
Joshi *et al*, 2023	Carvacrol	Monoterpene phenol	Inhibits the NLRP3/caspase-1/GSDMD signaling pathway	LPS/H9C2 cells	Inhibits ROS production; downregulates NLRP3, ASC, GSDMD, IL-18, IL-1β and caspase-1; upregulates beclin-1	(146)
				LPS/BALB/c male mice	Increases survival rate; inhibits cardiac dysfunction; reduces CK-MB and LDH; downregulates NLRP3, ASC, GSDMD, IL-18, IL-1β and caspase-1; upregulates beclin-1	

Table I. Continued.

First author, year	Compound	Type	Mechanism of action	Experimental model	Experimental findings	(Refs.)
Zhu *et al*, 2024	Vaccarin	Bioactive flavonoid glycoside	Attenuates inflammatory cytokine expression and modulates mitophagy to confer cardioprotection	LPS/H9C2 cells	Increases cell viability; inhibits ROS production; downregulates NLRP3, ASC, cleaved caspase-1 and GSDMD-N; upregulates PINK1 and parkin; promotes mitophagy	(150)
				LPS/C57BL/6J mice	Increases survival rate; inhibits cardiac dysfunction; reduces CK-MB and LDH; reduces expression of IL-1β and IL-18; downregulates NLRP3, ASC, cleaved caspase-1 and GSDMD-N	
Luo *et al*, 2023	Bergapten	Bioactive coumarin	Inhibits NLRP3 inflammasome activation by promoting mitophagy and inhibiting pyroptosis	LPS/BMDMs	Decreases NLRP3 inflammasome activation; downregulates IL-1β and ASC speck; suppresses pyroptosis; reduces mtROS; promotes mitochondrial homeostasis	(154)
				LPS/C57BL/6J mice	Increases survival rate; reduces overt infiltration of inflammatory cells; downregulates IL-1β, GSDMD-N and caspase-1	
Bai *et al*, 2022	LYG-202	ALDOA inhibitor	Suppresses the activity of the NLRP3 inflammasome by activating the AMPK/mitophagy signaling pathway	LPS/J774A.1 cells	Downregulates IL-1β, cleaved-caspase-1 and mtROS; promotes mitophagy	(155)
				LPS/D-Gal/C57BL/6J mice	Reduces recruitment of neutrophils and monocytes; downregulates IL-1β and pro-caspase-1	
Zhu *et al*, 2025	5-methoxyindole-3-carboxaldehyde	NLRP3 inhibitor	Binds to the NACHT domain of the NLRP3 protein and blocks the interaction of NLRP3 and ASC	LPS/PMs LPS/C57BL/6 male mice	Downregulates caspase-1 and pro-IL-1β Downregulates inflammatory cytokines, such as IL-1β, IL-6 and TNF-α, as well as NLRP3	(27)

NLRP3, NOD-like receptor protein 3; ALDOA, aldolase A; FAAH, fatty acid amide hydrolase; FUNDC1, FUN14 domain-containing protein 1; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK-MB, creatine kinase myocardial band; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; ALB, albumin; LPS, lipopolysaccharide; cTnT, cardiac troponin T; CLP, cecal ligation and puncture; SSTR2, somatostatin receptor 2; AMPK, adenosine 5'-monophosphate-activated protein kinase; Drp1, dynamin-related protein 1; H9C2 cells, H9c2(2-1) rat cardiomyoblast cell line; C57BL/6J mice, C57BL/6J inbred mouse strain; GSDMD-NT, gasdermin D N-terminal domain; IL-1β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor α; mRNA, messenger ribonucleic acid; TLR4, toll-like receptor 4; MyD88, myeloid differentiation primary response gene 88; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; BMDMs, bone marrow-derived macrophages; ASC, apoptosis-associated speck-like protein containing a CARD; PIK3CG, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma; HL-1 cells, HL-1 murine cardiac muscle cell line; NOX2, NADPH oxidase 2; Akt, AKT serine/threonine kinase; Myc, MYC proto-oncogene; Pdk1, pyruvate dehydrogenase kinase 1; NRCMs, neonatal rat cardiomyocytes; PARP1, poly (ADP-ribose) polymerase 1; RAW 264.7 cells, RAW 264.7 mouse macrophage cell line; Cox2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; CD11b, cluster of differentiation molecule 11B; PMs, peritoneal macrophages; NACHT, NAIP, CIITA, HET-E and TP1 (domain of NLRP3); PYD, pyrin domain; INF-γ, interferon γ; ROS, reactive oxygen species; MCP1, monocyte chemoattractant protein-1; PI, propidium iodide; JC-1, 5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolylcarbocyanine iodide; HSP70, heat shock protein 70; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase-1; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling; SOD, superoxide dismutase; BAX, BCL-2-associated X protein; BCL-2, B-cell lymphoma 2; MDA, malondialdehyde; RGD, arginine-glycine-aspartic acid (peptide sequence); ICR male mice, institute of cancer research male mouse strain; FOXP3, forkhead box P3; HMGB1, high mobility group box 1; SOFA, sequential organ failure assessment; MODS, multiple organ dysfunction syndrome.

must not interfere with antimicrobial efficacy or the ability of septic patients to clear bacteria. Furthermore, patients with sepsis frequently experience acute renal or hepatic dysfunction (169), which can markedly alter the pharmacokinetics and safety profile of any adjunctive treatment, including NLRP3 inhibitors. Therefore, integrating NLRP3 inhibitors into septic care remains challenging and requires rigorous evaluation in relevant disease-state models. This includes determining the optimal timing of inhibitor administration relative to antibiotics, understanding the impact of NLRP3 inhibitors on hemodynamic management and conducting detailed pharmacokinetic studies in septic patients exhibiting varying degrees of organ failure to ensure both the safety and synergistic efficacy of these inhibitors.

Learning from the broader NLRP3 inhibitor clinical landscape. Valuable lessons can be drawn from the clinical development of NLRP3-targeting agents in other inflammatory diseases, offering notable insights for SIC clinical trial design and risk management (170). Primarily, the clinical development of pioneering compounds such as MCC950 and GDC-2394 was halted due to hepatotoxicity, with MCC950-associated liver injury linked to its off-target inhibition of carbonic anhydrase 2 (171). This underscores the necessity for thorough hepatic safety profiling of any SIC therapeutic candidate. Secondly, while the anti-IL-1β monoclonal antibody canakinumab has demonstrated cardiovascular benefits in the Canakinumab Anti-Inflammatory Thrombosis Outcome Study trial, it concurrently increased the incidence of fatal infections and hematological toxicities, highlighting the inherent immunosuppressive risks associated with broad anti-cytokine therapy in patient populations, such as patients with SIC (172). Finally, although glyburide supported the potential of NLRP3 inhibition in preclinical models, its clinical utility was notably constrained by dose-limiting hypoglycemia and other off-target effects, serving as a cautionary tale that the therapeutic benefit of drug repurposing must be carefully weighed against its inherent polypharmacology (173). Collectively, these experiences mandate that future SIC clinical trial designs prioritize hepatic safety, cautiously evaluate the consequences of immunosuppression and rigorously select therapeutic agents with high specificity. The compounds reported to target the NLRP3 inflammasome for the treatment of SIC are summarized in Table I (27).

Future perspectives and strategic directions. Future investigations should prioritize: i) Cell-specific NLRP3 functions using conditional knockout/knock-in models; ii) interorganellar communication mechanisms between NLRP3 and ER/golgi networks; iii) rational optimization of natural compound-derived inhibitors through structure-activity relationship studies; and iv) clinical translation initiatives. These initiatives may include: i) Advanced SIC models with improved clinical relevance; ii) preclinical development of principal compounds, such as MCC950; iii) predictive biomarker discovery; iv) novel drug delivery systems, such as nanoparticle encapsulation; and v) combination therapies with antibiotics, mitochondrial protectants or anti-apoptotic agents.

6. Conclusions

The NLRP3 inflammasome has emerged as a central molecular hub in SIC pathogenesis. By driving cytokine storms, inducing cardiomyocyte pyroptosis and apoptosis, disrupting mitochondrial homeostasis and suppressing protective autophagy, the NLRP3 inflammasome establishes a self-perpetuating cycle of inflammation and PCD that culminates in myocardial dysfunction. Pharmacological targeting of NLRP3 signaling pathways represents a promising therapeutic strategy for SIC. Therefore, further elucidating the multifaceted roles of NLRP3 in SIC will accelerate the development of mechanistically-grounded therapeutic interventions.

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Authors' contributions

The original draft of the manuscript and the figures were produced by YC. ZZ and GZ were responsible for reviewing and editing the manuscript and supervision of the study. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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