Journal of Inflammation Research

Dovepress
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REVIEW

Mechanisms and Targeted Therapeutic Strategies in Sepsis-Induced Myocardial Dysfunction: The Role of NLRP3 Inflammasome-Mediated Inflammation

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Abstract: Sepsis is a systemic inflammatory response syndrome triggered by infection, in which excessive immune responses can lead to multiple organ failure and shock. The heart, as one of the critical target organs in sepsis, is significantly impaired, which substantially increases the risk of mortality. Recent studies have increasingly highlighted the role of dysregulated inflammatory responses in the pathogenesis and progression of sepsis-induced myocardial dysfunction (SIMD). Among the key molecular mechanisms regulating various pathophysiological processes and modulating inflammation is the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3(NLRP3) inflammasome. This study aims to explore the role of the NLRP3 inflammasome in the pathogenesis of SIMD, with a focus on its involvement through pathways such as pyroptosis, oxidative stress, autophagy, mitochondrial damage, exosome release, and endoplasmic reticulum stress in the development of SIMD. Furthermore, the research seeks to uncover the potential key roles of the NLRP3 inflammasome in the underlying pathophysiological mechanisms of SIMD. Finally, the study will investigate NLRP3 inflammasome-based therapeutic strategies for targeting SIMD, providing theoretical support for the development of targeted management for SIMD.

Keywords: sepsis-induced myocardial dysfunction (SIMD), nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3(NLRP3) inflammasome, inflammation, mechanism

Introduction

Sepsis is widely recognized as a critical condition triggered by severe infections, and its definition has evolved from Sepsis 1.0 in 1991 to Sepsis 3.0 in 2016.[1,2] Sepsis is currently understood as a systemic inflammatory response to infection, where an excessive immune response can lead to multi-organ failure and shock. It remains one of the most common and life-threatening conditions in clinical practice. Due to its high mortality rate and the frequent occurrence of complex complications, sepsis imposes a significant economic and social burden worldwide.[2–4] According to data from 409 hospitals in the United States, approximately 1.7 million patients develop sepsis annually, with this number steadily rising.[5] A cross-sectional study conducted across 44 hospitals in China found that the 90-day mortality rate for hospitalized sepsis patients was around 35.5%.[6] The heart, which is rich in mitochondria, is one of the primary target organs affected by sepsis. Sepsis-induced myocardial dysfunction (SIMD) is a poor prognostic indicator in sepsis patients, characterized by adverse outcomes and an increased mortality rate.[7] Epidemiological studies suggest that myocardial injury or heart failure is commonly observed in sepsis patients, with an incidence ranging from 10% to 70%.[8–10]

Received: 27 February 2025
Accepted: 14 June 2025
Published: 5 July 2025

During sepsis, myocardial hypoxia, coupled with mitochondrial dysfunction and oxidative stress, leads to cardiac dysfunction and hemodynamic instability. This is primarily manifested by left ventricular dilation, normal or reduced filling pressures, decreased ventricular contractility, and right or left ventricular dysfunction, resulting in a diminished response to volume infusion.[11,12] Current treatment strategies for SIMD focus on two main approaches: one involves traditional symptomatic management such as fluid resuscitation and antimicrobial therapy, which often show limited efficacy. The other emerging approach includes advanced technologies like extracorporeal membrane oxygenation (ECMO) and remote ischemic conditioning (RIC), which offer potential benefits for cardiac and pulmonary support in sepsis patients. However, these advanced interventions are costly and increase the financial burden on patients. Furthermore, they are predominantly available in large, tertiary hospitals with specialized intensive care units, making their routine use impractical. Thus, exploring the molecular mechanisms underlying SIMD is critical to developing targeted therapies. Several factors contribute to the pathogenesis of SIMD, including the activation of inflammatory responses, dysregulation of calcium homeostasis, mitochondrial dysfunction, oxidative stress, and cell death.[13–16] Recent studies have shown that when the host encounters injury, infection, or viral invasion, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are activated. The body's pattern recognition receptors (PRRs) recognize specific pathogen structures, triggering the release of pro-inflammatory mediators and initiating an inflammatory cascade. A controlled inflammatory response can facilitate immune activation, enabling pathogen clearance and defending against external threats.[17] Nevertheless, when the inflammatory response becomes dysregulated, it can trigger immune dysfunction, contributing to sepsis and damage to target organs, including the heart.

NLRP3 (Nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3) is a well-established cytosolic pattern recognition receptor that plays a pivotal role in cellular responses to stress signals.[18] It is predominantly activated during host infections or inflammatory responses, leading to the assembly of the NLRP3 inflammasome, which subsequently induces apoptosis or pyroptosis.[18] As a crucial sensor of the innate immune system, NLRP3 detects various DAMPs and initiates inflammatory responses.[19] Recent studies have highlighted that NLRP3 modulates several pathophysiological processes, including pyroptosis, oxidative stress, autophagy, and mitochondrial dysfunction. Inhibition of NLRP3 has been shown to mitigate sepsis-induced myocardial injury and improve survival outcomes.[20] For example, Zhang et al demonstrated that in a cecal ligation and puncture (CLP) mouse model of sepsis and lipopolysaccharide (LPS)-stimulated cardiac fibroblasts, corticosteroid treatment effectively suppressed the formation of the NLRP3 inflammasome, caspase-1 activation, and IL-1β secretion, thereby offering protection against myocardial damage.[21] Likewise, Qiu et al showed that high-dose ulinastatin (UTI) attenuated NLRP3 inflammasome activation, resulting in myocardial protection and enhanced survival rates in septic rats.[22]

Recent research has increasingly underscored the critical role of aberrant NLRP3 inflammasome activation in driving a variety of inflammatory responses, including SIMD. The NLRP3 inflammasome is integral to a range of pathological processes such as pyroptosis, oxidative stress, autophagy, and mitochondrial dysfunction, and it is also involved in modulating the cardiac impairment associated with sepsis. Despite these advances, the current body of research remains dispersed, and a systematic review that consolidates these findings is lacking. Therefore, there is a pressing need for a comprehensive synthesis of the existing literature to enhance our understanding of SIMD. This review aims to provide a thorough analysis of the specific role of the NLRP3 inflammasome and the inflammatory pathways it orchestrates in the pathogenesis of septic myocardial dysfunction. We will focus on the NLRP3 inflammasome's involvement in various mechanistic pathways, including pyroptosis, oxidative stress, autophagy, mitochondrial injury, exosome secretion, and endoplasmic reticulum stress. Additionally, we will explore how these processes may contribute to the pathophysiological development of SIMD. Finally, the review will summarize the principal signaling pathways implicated in SIMD and briefly discuss current therapeutic strategies and their potential molecular targets for mitigating SIMD.

NLRP3 Inflammasome

Composition of NLRP3 Inflammasome

The NLRP3 inflammasome is a multi-protein complex composed of various intracellular components that recognize and respond to activation signals through cytosolic sensors.[23] These sensors include nucleotide-binding oligomerization

domain (NBD), nucleotide-binding oligomerization domain-like receptors (NLRs), adaptor proteins, and effector molecules.[23] The assembly of the inflammasome typically involves PRRs, apoptosis-associated speck-like protein (ASC), and caspase-1. PRRs involved in pathogen recognition are classified into two categories: membrane-bound PRRs, such as Toll-like receptors (TLRs) and C-type lectin receptors, and cytosolic PRRs, such as NLRs and retinoic acid-inducible gene I-like receptors (RIG-I-like receptors).[24] Some PRRs are capable of recognizing conserved microbial components or PAMPs, including peptidoglycan.[24] They can also detect DAMPs, which are released from cells or tissues undergoing injury, such as adenosine triphosphate (ATP).[24] Notably, not all of the aforementioned PRRs are involved in inflammasome formation. For instance, RIG-I-like receptors primarily detect viral RNA in the cytoplasm of infected cells, triggering the synthesis of type I interferons to initiate an antiviral response, but they are not directly related to inflammasome formation.[25] To date, five PRRs have been identified that are capable of forming inflammasomes: NLRP1, NLRP3, NLRC4, Pyrin, and AIM2.[26–29] These PRRs are considered to play important roles in pathological conditions, such as myocarditis.[26–29] The activated inflammasome detects DAMPs released from damaged cells and PAMPs derived from pathogens in the gut-liver axis. The assembly of these complexes induces the activation of caspase-1, which subsequently participates in the caspase-1-dependent pyroptotic pathway. Current research has demonstrated that the NLRP3 inflammasome plays a critical role in the inflammatory response in cardiomyocytes, immune cell activation, and myocardial injury.[29] Therefore, the NLRP3 inflammasome is regarded as a key player in the inflammatory response associated with SIMD.[30] Targeting the NLRP3 inflammasome for therapeutic intervention in SIMD holds great promise for the future.

The NLRP3 inflammasome is a large multimeric protein complex with an approximate molecular mass of 700,000 Da, composed of NLRP3, the adaptor protein ASC, and the effector protein caspase-1.[31] The assembly of the NLRP3 inflammasome requires interactions between the NLRP3 receptor, the adaptor protein ASC, and pro-caspase-1.[31]

NLRP3 is a member of the NLR (nucleotide-binding oligomerization domain-like receptor) family, which share a conserved structural framework. NLRP3 itself consists of three main structural domains. Leucine-rich repeat (LRR) domain at the C-terminus, which is primarily responsible for recognizing and binding PAMPs or DAMPs.[32] This domain engages with microbial or host-derived signals that trigger immune responses.[32] It is vital to note that the activation of the NLRP3 inflammasome does not always occur through direct interaction with PAMPs or DAMPs. It can also be triggered by secondary mechanisms, such as disruption of the mitochondrial membrane potential or potassium efflux.[33–35] Nucleotide-binding oligomerization domain (NACHT) in the central region, which facilitates self-oligomerization and is involved in mediating the formation of inflammasome complexes. This domain shares similarities with other proteins such as NAIP, CIITA, HET-E, and TP1. Caspase recruitment domain (CARD), pyrin domain (PYD), and baculovirus inhibitor of apoptosis protein repeat (BIR) domains at the N-terminus, which are involved in downstream protein-protein interactions. These domains facilitate the recruitment of other proteins necessary for inflammasome assembly and subsequent activation of caspase-1, leading to pyroptosis and inflammatory responses. Through the coordinated function of these domains, NLRP3 detects a wide range of PAMPs and DAMPs, triggering the assembly of the inflammasome complex and activating caspase-1, which plays a crucial role in the inflammatory response and cellular damage.

Under basal conditions, the NACHT domain of NLRP3 interacts with the LRR domain, thereby maintaining the protein in a self-inhibited conformation. The NACHT domain, which possesses ATPase activity, represents the central structural and functional unit of NLRs. Upon the detection of PAMPs or DAMPs, NLRP3 undergoes a conformational shift that disrupts its autoinhibition, resulting in the exposure of the NACHT domain and its subsequent oligomerization. This process enables NLRP3 to function as a scaffold for inflammasome assembly.[36] The N-terminal PYD of NLRP3 recruits the adaptor protein ASC, which also contains a PYD domain. The CARD of ASC then recruits pro-caspase-1, which contains a CARD domain, facilitating the assembly of the inflammasome complex.[36] In addition to these interactions, the domains of NLRP3 and its associated proteins are capable of engaging with other ligands, thereby activating downstream signaling pathways that regulate cellular responses and contribute to the inflammatory response.

ASC is recognized as a crucial adaptor protein closely involved in the formation of the NLRP3 inflammasome and its associated cell death mechanisms. Current studies on its structure and function reveal that ASC comprises two key domains: the PYD at the C-terminus and the CARD at the N-terminus.[37] Under conditions of cell damage or infection, activation of pattern recognition receptors, such as NLRP3, triggers the binding of its PYD domain to ASC, which in turn

facilitates the interaction between ASC's CARD domain and caspase-1, leading to the activation of caspase-1. Activated caspase-1 then cleaves pro-inflammatory cytokines, such as IL-1β and IL-18, thereby initiating their secretion and triggering an inflammatory response.[37] Furthermore, during ASC activation, visible intracellular aggregates known as ASC specks are formed. These specks are a result of ASC aggregation and indicate the process of inflammasome assembly. ASC specks are considered a marker of inflammasome activity, and their formation is essential for the detection and study of inflammasome activation.[38]

Caspase-1, alternatively referred to as interleukin-1β converting enzyme (ICE), functions as the effector protease within the NLRP3 inflammasome complex. Initially present as an inactive zymogen, caspase-1 is activated through interaction with upstream signals, leading to the formation of a highly conserved protease complex. Caspase-1 is involved in a variety of physiological processes, including signal transduction and transcriptional regulation.[39] Its primary role is to cleave precursor forms of interleukins (pro-IL-1β and pro-IL-18) into their mature, biologically active forms, IL-1β and IL-18.[39] These pro-inflammatory cytokines are critical for the regulation of innate immune responses and play key roles in the pathogenesis of numerous inflammatory and autoimmune disorders.[40,41]

Activation of the NLRP3 Inflammasome

The activation of the NLRP3 inflammasome facilitates the activation of pro-caspase-1 and the release of key inflammatory cytokines, which is crucial for the onset and progression of septic cardiomyopathy. The mechanism of NLRP3 inflammasome activation is complex, involving various inflammatory pathways and processes.[42] The prevailing hypothesis for NLRP3 inflammasome activation is the "two-signal model", which includes both the "priming" signal and the "activation" signal.[43,44] First, the "priming" signal provided by microbial or endogenous molecules is transduced via the TLR signaling pathway, leading to the activation of the NF-κB pathway. The transcriptional activity of NF-κB is tightly regulated by both intracellular and extracellular mechanisms. NF-κB remains inactive in the cytoplasm in complex with IκB.[45] Post-translational modifications or ubiquitination of IκB, in response to extracellular signaling, leads to its degradation, enabling NF-κB to translocate to the nucleus and become activated.[45] Bacterial components bind to TLRs and activate NF-κB transcriptional activity through the MyD88, IRAK, and TRAF6 signaling cascade.[46] As a result, the baseline expression of pro-IL-1β and NLRP3 proteins is significantly increased. Notably, the priming signal also induces post-translational modifications of NLRP3, such as deubiquitination and phosphorylation, to promote subsequent inflammasome activation.[47] For instance, NLRP3 can be considered a substrate of the BRISC complex containing the cytoplasmic BRCC3, which deubiquitinates NLRP3 and activates the inflammasome.[48] Once the priming signal is complete, various DAMPs and PAMPs trigger the assembly of the NLRP3 inflammasome through homologous interactions within its NACHT domain.

The activation signal in the second step can occur via three main pathways: the first involves extracellular ATP, which stimulates ion channels, promoting K+ efflux and the formation of membrane channels, directly facilitating the assembly and activation of the NLRP3 inflammasome.[33] The P2X7 receptor acts as a cation channel activated by ATP, allowing K^+ efflux.[49] K^+ efflux is widely recognized as a key mechanism in NLRP3 inflammasome activation.[50] The second pathway involves the internalization of extracellular crystals or specific particles, such as calcium or chloride ions, leading to lysosomal rupture and facilitating the aggregation and activation of the NLRP3 inflammasome.[34] The third pathway involves PAMPs and DAMPs, which, through ROS-dependent signaling, enhance intracellular ROS production and promote NLRP3 inflammasome assembly and activation.[35] Studies have shown that NLRP3 activators can initiate the production of mitochondrial ROS (mtROS), which further oxidize mtDNA. mtDNA, a potent inducer of IL-1β production, can co-localize with NLRP3 and promote inflammasome activation.[51–53]

In addition to the aforementioned factors, some non-degradable substances can activate the NLRP3 inflammasome through "frustrated phagocytosis". Many non-digestible particles are taken up by macrophages into intracellular phagolysosomes, leading to the release of stress-related substances and lysosomal proteases into the cytoplasm. For example, Cathepsin B, a representative lysosomal protease, can activate the NLRP3 inflammasome.[54,55]

The Role of NLRP3 Inflammasome in SIMD

Multiple studies have demonstrated that the activation of the NLRP3 inflammasome regulates myocardial inflammation in sepsis-induced myocardial injury through various intracellular pathways, including oxidative stress, pyroptosis, autophagy, mitochondrial dysfunction, exosome response, and endoplasmic reticulum (ER) stress. In the following sections, we will elaborate on the role of the NLRP3 inflammasome in septic cardiomyopathy from these perspectives.

Role of the NLRP3 Inflammasome in Pyroptosis-Mediated Pathogenesis of SIMD

Pyroptosis is a form of programmed cell death that functions as a defensive response to cellular injury or infection; however, when dysregulated, it can contribute to extensive tissue damage and the onset of sepsis. This process is largely mediated by members of the gasdermin (GSMD) protein family, which form pores in the plasma membrane, leading to the release of pro-inflammatory cytokines such as IL-1β and IL-18.[56] Key features of pyroptosis include the formation of membrane pores, cellular swelling, membrane rupture, and the subsequent release of inflammatory mediators and cellular contents into the extracellular space.[57,58] The excessive release of these cytokines plays a central role in driving the inflammatory cascade seen in sepsis. As such, pyroptosis is closely associated with both the systemic inflammatory response and the resultant organ dysfunction in sepsis, particularly in the context of SIMD. In a study by Kalbitz et al, it was observed that in a CLP-induced sepsis model, the expression levels of NLRP3 and IL-1β were markedly elevated in the left ventricular myocardium.[59] Notably, in mice with NLRP3 gene knockdown, both cardiovascular damage and plasma levels of IL-1β and IL-6 were significantly reduced compared to wild-type controls. These findings suggest that the NLRP3 inflammasome plays a critical role in the pathogenesis of SIMD by driving pyroptosis-mediated myocardial injury[59] (Figure 1).

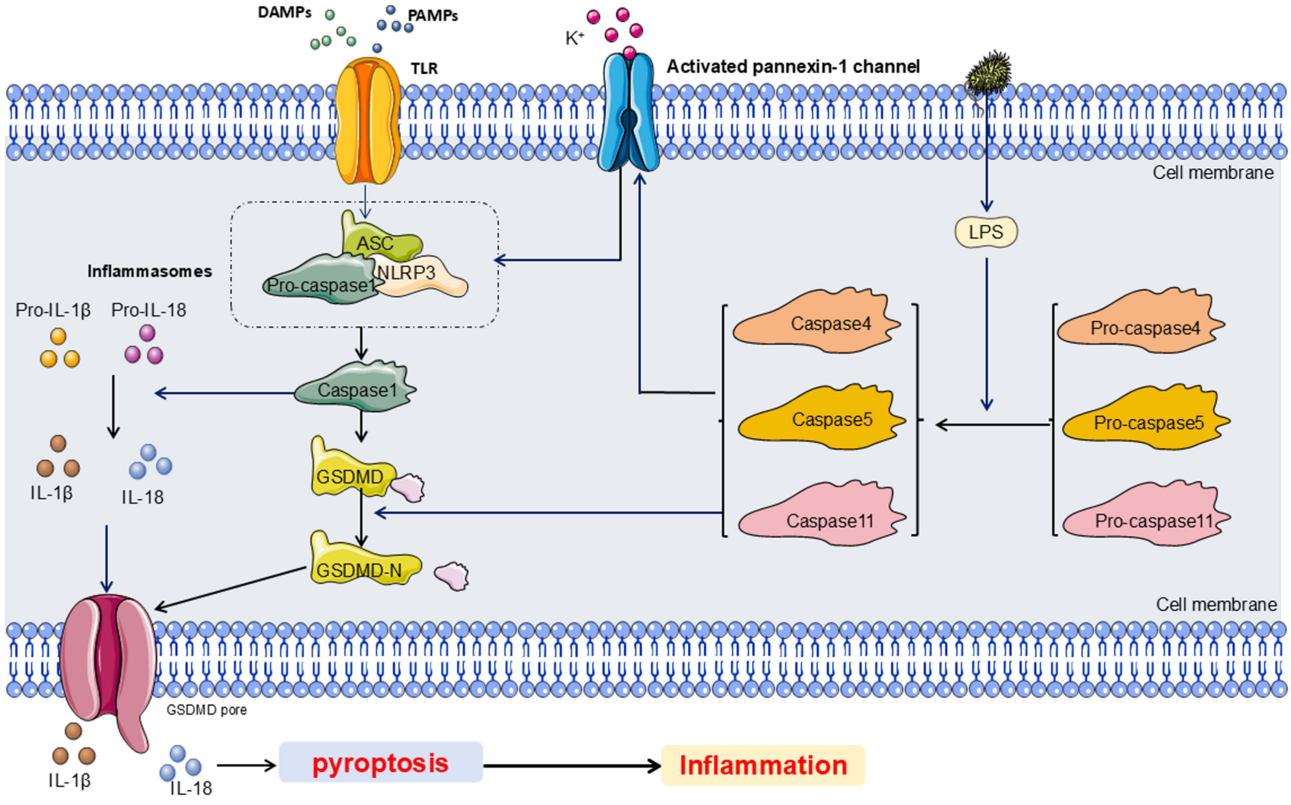

Figure 1 Role of the NLRP3 Inflammasome in Pyroptosis-Mediated Pathogenesis of SIMD. NLRP3 inflammasome-mediated pyroptosis can be classified into two distinct types based on the dependence on caspase-1. In caspase-1-dependent pyroptosis, the process is initiated by the assembly of the inflammasome. In contrast, caspase-1-independent pyroptosis is triggered by the interaction between caspase-4, caspase-5, or caspase-11 (depending on the species) and LPS.

https://doi.org/10.2147/JIR.S521655

Classic Pathways of Pyroptosis in SIMD

The prevailing view in the field of SIMD suggests that the classical pyroptosis pathway can be classified into two types based on whether or not it depends on caspase-1.[50] In the classical caspase-1-dependent pyroptosis pathway, when the body recognizes DAMPs and PAMPs in response to various endogenous and exogenous stimuli, the NLRP3 inflammasome is activated by these signals. The inflammasome then interacts with the adaptor protein ASC, leading to the activation of pro-caspase-1, which is subsequently cleaved into active caspase-1.[60] On one hand, active caspase-1 cleaves Gasdermin D (GSDMD), a protein belonging to the GSDM family, which is a key player in pyroptosis. The structure of GSDMD consists of a toxic N-terminal domain and a C-terminal inhibitory domain connected by a flexible linker. Upon cleavage of the C-terminal domain, the N-terminal domain of GSDMD is recruited to the cell membrane, where it interacts with lipids, forming intermediate structures known as pre-pores.[61] These pre-pores undergo conformational rearrangement, forming oligomeric arcs that further transition into ring-like structures, which ultimately form membrane pores.[61] This pore formation leads to the release of cellular contents and triggers pyroptosis.[61] Electron microscopy reveals that the inner diameter of the GSDMD-N pore is 10–15 nm, allowing the passage of pro-inflammatory cytokines such as IL-1β and IL-18, thereby enhancing the inflammatory response.[62,63] Additionally, the transcription of GSDMD is regulated by multiple molecules.[64] For example, in adipocytes, NF-κB can activate the transcription of GSDMD, while in endothelial or macrophage cells, activation of IRF1/2 can enhance GSDMD expression.[65–67] As a key effector molecule of the inflammasome, inhibiting the cleavage and oligomerization of GSDMD can block its role in pyroptosis, potentially providing a therapeutic strategy for disease treatment. On the other hand, activated caspase-1 cleaves and activates the precursor forms of IL-1β and IL-18. The mature cytokines are then released extracellularly, further amplifying the inflammatory response.

In the caspase-1-independent pyroptosis pathway, following LPS stimulation, caspase-4, caspase-5, and caspase-11 can directly bind to LPS and become activated, leading to the cleavage of GSDMD and the exposure of its N-terminal domain, initiating pyroptosis. Furthermore, the activation of caspase-4/5/11 also activates the Pannexin-1 channel and facilitates the release of K^+ ions, which in turn activates the NLRP3 inflammasome, leading to the activation of caspase-1 and further pyroptosis via the caspase-1-dependent pathway.[68] Notably, the NLRP3 inflammasome/caspase-1/IL-1β pathway is implicated in the development of SIMD due to excessive inflammation.[69,70] In a mouse model of SIMD, Busch et al observed that compared to wild-type septic mice, NLRP3 knockout mice exhibited lower serum levels of IL-1β, reduced cardiac and cardiomyocyte atrophy, improved cardiac diastolic and systolic functions, and increased survival rates.[71] Furthermore, Intermedin1-53 (IMD1-53) suppressed NLRP3 activity through the NLRP3/caspase-1/IL-1β pathway in septic cardiomyocytes, thereby alleviating SIMD.[72] In conclusion, targeting NLRP3 inflammasome-mediated pyroptosis to mitigate SIMD presents a promising new therapeutic target for the prevention and treatment of septic cardiomyopathy.

Classic Signaling Pathways of Pyroptosis in SIMD

Studies have shown that the ER/SIRT1/NLRP3/GSDMD signaling pathway, mediated by the NLRP3 inflammasome, is one of the classical pathways involved in SIMD, regulating pyroptosis and contributing to the pathogenesis of SIMD.[73] Inhibiting this signaling pathway effectively suppresses pyroptosis and alleviates the symptoms of SIMD.[73] Additionally, the STING-IRF3 pathway can activate the NLRP3 inflammasome, further participating in the progression of SIMD. In an endotoxemic model mimicking Gram (-) bacterial sepsis via LPS, Li et al found that after LPS treatment, STING undergoes perinuclear translocation, interacts with interferon regulatory factor 3 (IRF3), and phosphorylates IRF3.[74] The phosphorylated IRF3 is subsequently transported to the nucleus, where it increases NLRP3 expression and activates the NLRP3 inflammasome, triggering myocardial cell apoptosis and pyroptosis, ultimately leading to heart dysfunction. Knockout of the STING gene, inhibition of IRF3 phosphorylation, and blocking its nuclear translocation significantly reduced NLRP3-mediated myocardial inflammation and improved sepsis-induced myocardial injury.[74] Similarly, the SMC4/NEMO signaling pathway has been identified as a promoter of NLRP3 vesicle activation, inducing myocardial cell pyroptosis and contributing to SIMD development.[75]

Moreover, transcription factors play a crucial role in the activation of the NLRP3 inflammasome, influencing the onset and progression of sepsis-induced myocardial disease. NF-κB facilitates the activation and assembly of the NLRP3

inflammasome by upregulating the transcription of NLRP3 and pro-IL-1β.[76] The p65 subunit directly binds to the NLRP3 gene promoter, regulating LPS-induced NLRP3 expression in brain microvascular endothelial cells (BMECs).[77] Interestingly, the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) is negatively correlated with the activation of pyroptosis and the development of sepsis-induced myocardial dysfunction.[78,79] Based on these findings, some researchers propose that melatonin, by activating the Nrf2 pathway and inhibiting NLRP3 inflammasome formation, could alleviate sepsis-induced myocardial injury.[80]

In summary, when the NLRP3 inflammasome is activated by a range of danger signals, including hypoxia, PAMPs, DAMPs, and molecules associated with metabolic disturbances (such as ATP and K^+), the GSDMD pores open, and IL-1β and IL-18 are released into the bloodstream. This leads to widespread inflammatory responses and immune dysregulation, ultimately triggering sepsis and sepsis-induced myocardial injury. Therefore, targeting the inhibition of the NLRP3 inflammasome and its associated pyroptosis pathway may represent a potential therapeutic strategy for SIMD.

The Role of NLRP3 Inflammasome via Oxidative Stress in SIMD

ROS are by-products of oxygen metabolism and possess highly reactive properties. They primarily include peroxides, superoxides, hydroxyl radicals, and singlet oxygen.[81] ROS participate in various physiological processes such as differentiation, proliferation, necrosis, autophagy, and apoptosis by acting as signaling molecules or regulatory factors, often functioning as transcriptional activators.[82] In this context, maintaining appropriate cellular ROS levels is essential for redox homeostasis.[83] Furthermore, ROS serve as antimicrobial agents, capable of directly destroying microbial pathogens.[84] However, an excess of ROS can have detrimental effects. For instance, oxidative stress arises from an imbalance between ROS production and antioxidant defense mechanisms.[85] Studies have shown that during sepsis, stressors such as hypoxia led to an overproduction of ROS, which induces significant cellular apoptosis and organ dysfunction, contributing to sepsis and target organ damage.[86] Additionally, ROS are known to promote apoptosis, mitochondrial oxidation, and alterations in cellular signaling pathways. It is well-established that the onset of sepsis is associated with a range of dysregulated inflammatory responses, and ROS have been found to be closely linked to the NLRP3 inflammasome in inflammation. Therefore, the roles of ROS and the NLRP3 inflammasome in sepsis and related organ damage are of great interest. Research on the interaction between ROS and the NLRP3 inflammasome in the pathophysiological processes of septic cardiomyopathy primarily focuses on the following areas (Figure 2).

The Production of ROS Is Partially Dependent on the Activation of NLRP3 in SIMD

NLRP3 is a widely recognized cellular stress sensor, whose activation is closely associated with the generation of ROS and subsequent inflammasome activation.[87,88] Studies have shown that LPS triggers ROS production through the activation of TLR4, a key event in the initial activation of NLRP3.[89,90] The P2X7 receptor, a trimeric ATP-gated cation channel, facilitates increased membrane permeability, resulting in potassium (K^+) efflux. During sepsis and its associated renal and myocardial injuries, ATP stimulates NLRP3 inflammasome activation via P2X7 receptor-mediated feedback mechanisms, leading to the processing and release of IL-1β.[91,92] The production of ROS is often linked to K^+ efflux, suggesting that a decrease in intracellular K^+ concentrations may play a role in inducing ROS generation during NLRP3 inflammasome activation.[93] Therefore, it can be hypothesized that ROS production in sepsis-induced myocardial injury may be dependent on the synergistic activation of the P2X7 receptor and the NLRP3 inflammasome.[94] Based on this, targeting the activation of the NLRP3 inflammasome and inhibiting excessive ROS production and oxidative stress may offer a novel therapeutic strategy for sepsis-related cardiomyopathy.

ROS Promotes the Activation of the NLRP3 Inflammasome in SIMD

Recent studies have indicated that ROS are potential signals for the activation of the NLRP3 inflammasome. Two main hypotheses have been proposed regarding the role of ROS in promoting NLRP3 inflammasome activation. The first hypothesis involves thioredoxin-interacting protein (TXNIP). It has been demonstrated that ROS are sensed by a complex consisting of thioredoxin (TXN) and TXNIP.[94] The TXNIP-TRX system, along with NADPH and thioredoxin reductase (TRX-R), forms a redox system.[94] TRX exists in different isoforms, including TRX1 (12 kDa) in the cytoplasm

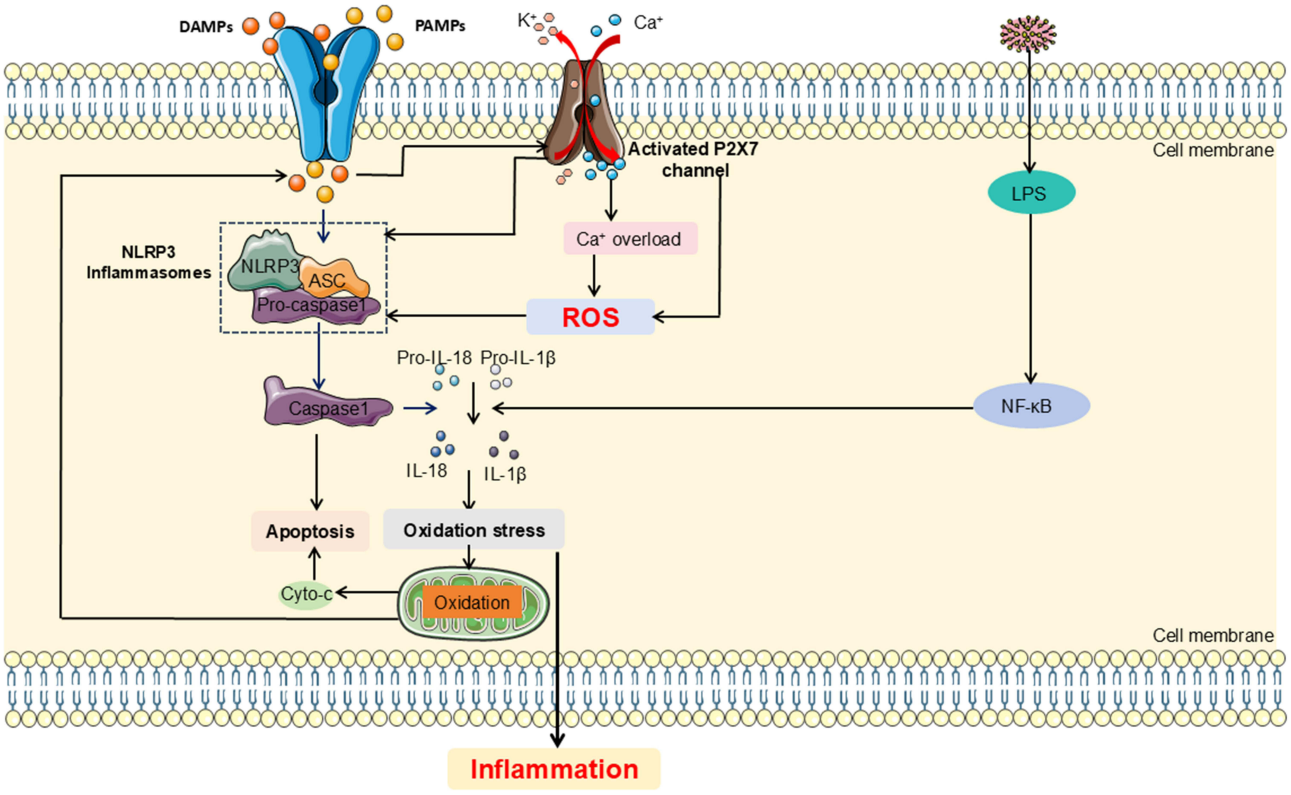

Figure 2 The Role of NLRP3 Inflammasome via Oxidative Stress in SIMD. Sepsis-induced oxidative stress promotes the generation of ROS through mitochondrial oxidation. The activation of P2X7 receptors by PAMPs and DAMPs triggers the influx of Ca^{2+} and the efflux of K^{+}. The resulting calcium overload and ROS disrupt mitochondrial integrity, leading to the release of cytochrome C into the cytoplasm. This process facilitates the assembly of NLRP3 inflammasomes and induces apoptosis. Additionally, LPS activates the NF-κB signaling pathway, which promotes the expression of pro-IL-1β and pro-IL-18. Subsequently, activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their active forms.

and TRX2 (15.5 kDa) in the mitochondria.[95] TRX functions to reduce oxidized proteins, leading to the oxidation of its two cysteine residues, and alternates between oxidized (inactive) and reduced (active) states.[96] Oxidized TRX is converted to its reduced form via NADPH-dependent TRX-R activity, which catalyzes the transfer of electrons from NADPH to oxidized TRX, thereby regulating the cellular redox balance.[97] The primary physiological function of the TRX system is to remove ROS and protect cells from oxidative damage while maintaining a reducing intracellular environment. TRX1 and TRX2 regulate ROS levels in the cytoplasm and mitochondria, respectively. However, TXNIP inhibits the antioxidant activity of TRX.[98] Under physiological conditions, TXNIP is localized to the nucleus, preventing its translocation to the cytoplasm. Under ROS-overproducing conditions, TXNIP upregulates its expression by inhibiting the phosphorylation of AMP-activated protein kinase (AMPK), which triggers the nuclear-to-cytoplasmic translocation of TXNIP, leading to endoplasmic reticulum and mitochondrial stress.[99] On one hand, the translocation of TXNIP from the nucleus to the cytoplasm promotes its interaction with TRX1, inhibiting TRX1 activity.[100] On the other hand, TXNIP translocated to the mitochondria, where it binds to TRX2 via disulfide bonds, inhibiting the reducing function of TRX2 and oxidizing it, forming the TXNIP/TRX2 complex.[96] TXNIP dissociates TRX2 from apoptosis signal-regulating kinase 1 (ASK1), triggering mitochondrial ROS generation and inducing ASK1 phosphorylation.[101] Phosphorylated ASK1 stimulates cytochrome c (Cyto c) release, leading to caspase 3 activation and mitochondrial apoptosis.[101] As mentioned earlier, NF-κB activation is considered the first step in NLRP3 inflammasome activation.[102] The second step involves the direct interaction between TXNIP and NLRP3, which is redox-state-dependent. The activation of pro-inflammatory pathways promotes the nuclear-to-mitochondrial translocation of TXNIP, where it forms a complex with TRX2. This process promotes mitochondrial ROS accumulation, oxidizing TRX2 and releasing TXNIP in the mitochondria.[101,103] TXNIP binds to the pyrin domain of NLRP3, followed by the recruitment of ASC's CARD domain, which interacts with the pro-caspase-1 precursor.[104] These interactions result in the formation of the NLRP3 inflammasome and the cleavage

of pro-caspase-1, leading to the activation of caspase-1 and triggering a widespread inflammatory response. Therefore, the association between TXNIP and NLRP3 is not a direct ROS-sensing mechanism but rather a secondary effect under oxidative stress conditions.[105] Li et al found that LPS stimulation promotes ROS generation, further inducing the translocation of NLRP3 from the nucleus. Isolated TXNIP can directly interact with NLRP3 and form the inflammasome, ultimately causing myocardial cell damage.[74] Yang et al discovered that knockdown of TXNIP expression inhibited NLRP3 inflammasome activation, accompanied by ROS production and increased activity of catalase and manganese superoxide dismutase (MnSOD), which alleviated SIMD.[106]

The second hypothesis is related to mtROS and mtDNA. Mitochondria are the primary sites for ROS production and are also the key cellular organelles targeted by ROS. NLRP3 activation factors can initiate the generation of mtROS, which can further oxidize mtDNA.[107,108] Ultimately, mtDNA acts as a potent inducer of IL-1β production and can co-localize with NLRP3, promoting the activation of the NLRP3 inflammasome and triggering septic shock and target organ damage.[51,53,109,110] Shimada et al observed the co-localization of mtDNA and NLRP3 through microscopy, confirming their interaction.[53] Qin et al found that Suhuang antitussive capsule (Suhuang) inhibits the inflammatory response and target organ damage of sepsis by maintaining mitochondrial homeostasis and suppressing ROS production and NLRP3 inflammasome activation.[111]

ROS-Mediated Activation of the NLRP3 Inflammasome May Trigger Apoptosis in SIMD

Previous studies have indicated that excessive ROS can induce apoptosis through both endogenous and exogenous pathways. In the exogenous pathway, Fas ligand participates in ROS production, subsequently recruiting the Fas-associated death domain and initiating apoptosis. In the endogenous pathway, mitochondrial damage, along with a cascade of caspase activation and oxidative stress, leads to the release of damaged cytochrome c and DNA, triggering apoptosis. In septic cardiomyopathy, excessive ROS can open mitochondrial permeability transition pores (mPTPs), resulting in the release of cytochrome c, apoptosis-inducing factor, mtDNA, and other factors into the extracellular space, which in turn activates the NLRP3 inflammasome and induces septicemia and septic myocardial injury. Additionally, caspase-1 activation following NLRP3 inflammasome stimulation exacerbates mitochondrial damage, increases cell membrane permeability, and enhances endothelial permeability to small molecules, thereby promoting apoptosis through a positive feedback loop.[112] Song et al demonstrated that geniposide (GE) activates AMPKα to inhibit myocardial ROS accumulation, thereby blocking NLRP3 inflammasome-mediated cardiomyocyte apoptosis and improving cardiac function in septic mice.[113] Similarly, Atractylenolide I was found to downregulate the PARP1/NLRP3 signaling pathway, inhibit LPS-induced M1 polarization in RAW 264.7 cells, and reduce oxidative stress and apoptosis in H9c2 cells, thus alleviating septic myocardial injury.[114]

Taken together, the prevailing view suggests that ROS and the NLRP3 inflammasome exert a reciprocal enhancing effect. However, some studies have also found that ROS can participate in autophagy to inhibit DAMPs and PAMPs, thereby limiting NLRP3-mediated inflammatory responses. Therefore, the interaction between ROS and the NLRP3 inflammasome in the pathogenesis of septic cardiomyopathy is complex. Further research is needed to elucidate the specific molecular mechanisms underlying this process.

The Role of NLRP3 Inflammasome via Mitochondrial Damage in SIMD

The myocardium, characterized by its high mitochondrial content, plays a crucial role in cellular energy metabolism. In the pathogenesis and progression of sepsis, myocardial hypoxia triggers mitochondrial damage or dysfunction, leading to metabolic disturbances, oxidative stress, immune dysregulation, and energy depletion in cardiomyocytes. Ultimately, this results in myocardial injury and functional failure, severely impacting the prognosis of septic patients. In the pathophysiology of SIMD, mitochondrial dysfunction is primarily characterized by the activation of oxidative stress, increased mitochondrial membrane permeability, mitochondrial uncoupling, disturbances in mitochondrial bioenergetics, and mitochondrial autophagy. Recent studies suggest that cellular stress, induced by factors such as infection or external stimuli, can precipitate mitochondrial dysfunction, which, in turn, triggers the activation of the NLRP3 inflammasome through multiple signaling pathways. This process further exacerbates septic myocardial damage. In SIMD, the interplay

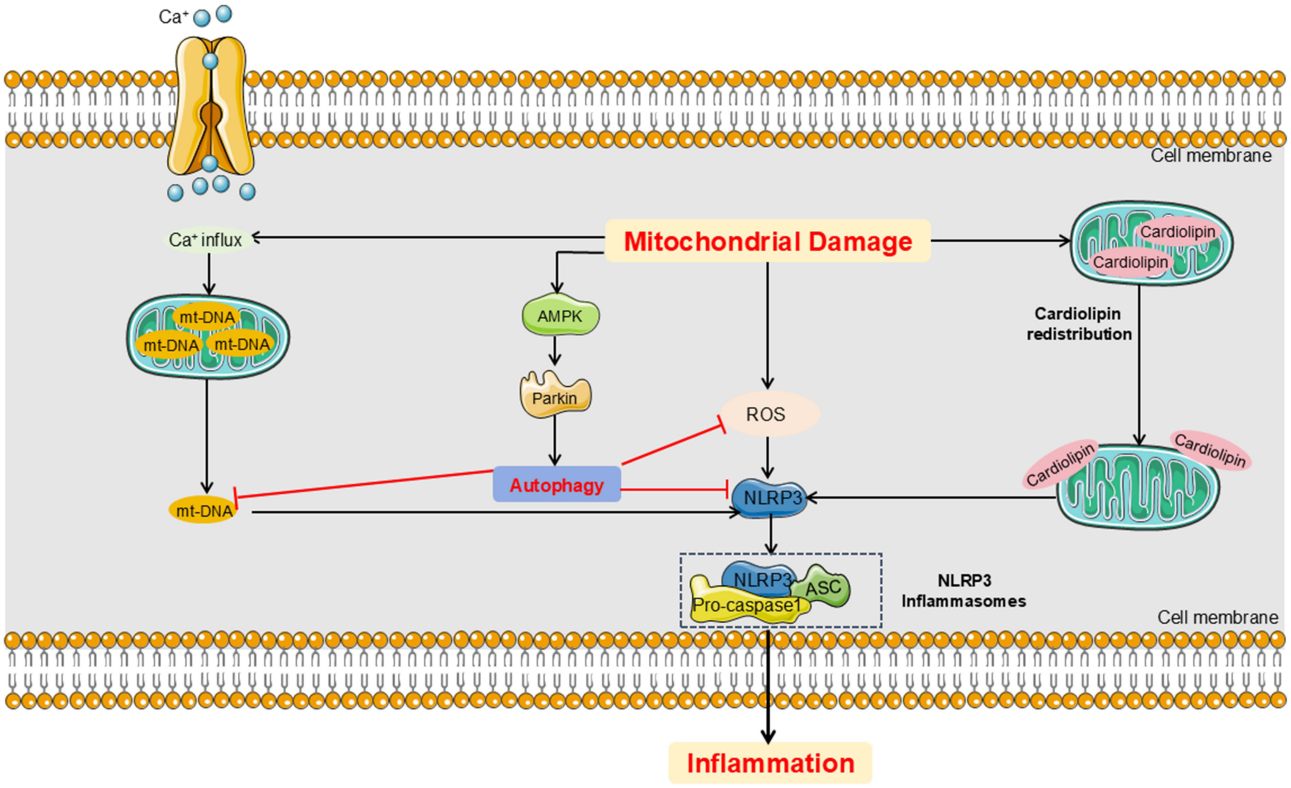

Figure 3 The Role of NLRP3 Inflammasome via mitochondrial damage in SIMD. Mitochondrial damage leads to the accumulation of ROS within the cell. ROS are released into the cytoplasm, where they interact with NLRP3 proteins, thereby triggering the activation of the NLRP3 inflammasome. Impaired mitochondria can also induce a high influx of Ca^{2+} through the mitochondrial calcium uniporter and produce large amounts of ROS, leading to the release of mtDNA into the cytoplasm, which further activates the NLRP3 inflammasome and induces apoptosis. However, the activation of the kinase 1/Parkin pathway promotes the removal of damaged and dysfunctional mitochondria, reduces the levels of ROS and mtDNA, and inhibits the activity of the NLRP3 inflammasome. After mitochondrial damage, cardiolipin redistributes to the outer mitochondrial membrane and directly interacts with the LRR domain of NLRP3 to activate the inflammasome.

between mitochondrial dysfunction and NLRP3 inflammasome activation is primarily manifested in two central mechanisms (Figure 3).

Mitochondrial Damage Activates the NLRP3 Inflammasome in SIMD

Mitochondria represent the primary source of mtROS, which play a critical role in cellular stress responses. The accumulation of ROS within the mitochondria subsequently spills over into the cytoplasm, where it interacts with the NLRP3 protein, thereby initiating the activation of the NLRP3 inflammasome.[115] Excessive ROS production not only triggers the inflammasome pathway but also activates downstream inflammatory cascades mediated by TLRs, contributing to the exacerbation of myocardial injury in the context of sepsis.[116] In addition to inflammasome activation, ROS accumulation promotes oxidative modifications of cellular macromolecules, such as proteins and DNA, which leads to structural damage to mitochondria.[117] This damage increases mitochondrial membrane permeability and activates apoptotic pathways, including the release of cytochrome c, which triggers cardiomyocyte apoptosis.[117] Recent studies by Bronner et al have shown that inositol-requiring enzyme 1α (IRE1α) can mediate ROS-dependent translocation of NLRP3 to the mitochondrial-associated endoplasmic reticulum membrane, thereby facilitating the activation of the caspase signaling axis and the pro-apoptotic protein Bid.[118] This interaction further enhances the release of mitochondrial DAMPs, which contribute to the amplification of NLRP3 inflammasome formation. In the pathophysiology of SIMD, mitochondrial dysfunction is central to disease progression. Moreover, damaged mitochondria facilitate excessive calcium influx via the mitochondrial calcium uniporter (MCU), further elevating ROS levels and promoting the release of mitochondrial DNA into the cytoplasm. These events converge to activate the NLRP3 inflammasome, driving an inflammatory response and ultimately leading to cardiomyocyte apoptosis, which plays a pivotal role in SIMD.[112]

It is noteworthy that sepsis and organ dysfunction are primarily characterized by hypoxia and ROS production. Hypoxia-induced mitochondrial dysfunction not only activates the NLRP3 inflammasome but also alters cellular metabolic pathways, inducing metabolic reprogramming. Under normal conditions, cells utilize transport proteins to uptake long-chain fatty acids, facilitating their oxidation within the mitochondria to generate acetyl-CoA, FADH2, and NADH. These metabolites further participate in the tricarboxylic acid (TCA) cycle and enter the electron transport chain to produce ATP. However, during sepsis, cellular hypoxia and metabolic alterations lead to a metabolic shift from fatty acid oxidation (FAO)-driven oxidative phosphorylation (OXPHOS) to glycolysis via the activation of the HIF-α (hypoxia-inducible factor) signaling pathway. Glycolysis provides ATP by generating pyruvate, which is subsequently converted to lactate, in order to meet the energy demands of immune responses.[119] Studies have shown that lidocaine significantly inhibits the secretion of inflammatory cytokines induced by LPS, exerting anti-inflammatory effects through the suppression of hypoxia inducible factor-1(HIF-1α)-mediated glycolysis.[120] In conclusion, mitochondrial dysfunction induced by cellular hypoxia not only activates the NLRP3 inflammasome but also induces metabolic reprogramming, playing a crucial role in the pathogenesis of septic cardiomyopathy.

Mitochondrial Autophagy Can Suppress the Activation of the NLRP3 Inflammasome in SIMD

As previously discussed, mitochondrial dysfunction can trigger excessive ROS release, leading to the activation of the NLRP3 inflammasome. However, in sepsis-induced cardiomyopathy, mitochondrial damage can also activate mitochondrial autophagy mechanisms. Specifically, this occurs through the activation of the AMPK/Parkin pathway, which facilitates the clearance of damaged and dysfunctional mitochondria, thereby reducing ROS and mtDNA levels, and inhibiting NLRP3 inflammasome activation.[121] The application of mitochondrial autophagy inhibitors has been pointed to facilitate NLRP3 inflammasome activation.[122]

Based on the interaction between mitochondrial dysfunction and NLRP3 inflammasome activation, this mechanism can be considered as a potential novel therapeutic target for SIMD. For instance, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and Nrf2 are critical factors regulating mitochondrial biogenesis.[123] Studies have shown that Nrf2 modulates NLRP3 inflammasome activity through two pathways. First, Nrf2 suppresses NLRP3 inflammasome activation by upregulating the expression of antioxidant genes, thereby reducing the generation of ROS.[124] Second, Nrf2 inhibits the activation of the NF-κB signaling pathway, reducing the expression of inflammatory mediators such as caspase-1, IL-1β, and IL-18, further suppressing NLRP3 inflammasome activity. It is worth mentioning cardiolipin. Cardiolipin is a unique phospholipid that does not form bilayers, with a specific structure consisting of two acylated phosphatidyl groups connected by a glycerol bridge.[125] It is localized to the inner mitochondrial membrane and redistributes to the outer mitochondrial membrane upon mitochondrial destabilization.[126] Given that mitochondria are endosymbionts of early eukaryotic cells and cardiolipin is exclusively found in mitochondria and bacteria, it is hypothesized that cardiolipin may be revealed as an endogenous PAMP during mitochondrial dysfunction and sensed by NLRP3.[127] Currently, it is believed that cardiolipin may play a role in the activation of the NLRP3 inflammasome, either by serving as a docking site for inflammasome assembly and subsequent activation on mitochondria, or as a direct activating ligand for NLRP3.[127] Furthermore, experimental studies by Shankar S. Iyer et al have shown that under various stress conditions, cardiolipin redistributes to the outer mitochondrial membrane, where it directly binds to the LRR domain of NLRP3, positioning NLRP3 on the mitochondria and activating the NLRP3 inflammasome.[127] Nonetheless, the exact mechanism of cardiolipin translocation to the outer mitochondrial membrane and its role in the pro-inflammatory pathway of NLRP3 inflammasome activation remains unclear and requires further investigation.[128]

The Role of NLRP3 Inflammasome via Exosome in SIMD

Exosomes are extracellular vesicles derived from endosomes, typically ranging in size from 30 to 150 nanometers, making them one of the smallest types of extracellular vesicles, which may contain a diverse array of complex molecules provided by the parent cell, including proteins, lipids, mRNA, miRNA, and DNA.[129,130] Unlike other extracellular vesicles, exosomes are formed by the fusion of intracellular multivesicular bodies with the plasma membrane, thereby releasing their contents into the extracellular space. In contrast, other extracellular vesicles are actively released by the cell. Furthermore, exosomes exhibit greater complexity in terms of both molecular weight and the variety of molecules

they contain.[129] In recent years, exosomes have been recognized for their significant roles in the pathogenesis and progression of various diseases, including neurodegenerative diseases, cancer, liver diseases, and heart failure. Similar to other extracellular vesicles, exosomes selectively capture their "cargo" rather than passively packaging it. The uptake of this cargo is dependent on the type of cell that produces the exosomes.[131] Exosomes have increasingly been identified as key carriers of signaling molecules during inflammation, effectively transferring proteins, lipids, and nucleic acids to regulate the metabolic state of target cells in numerous diseases such as cancer, cardiovascular diseases, and neurodegenerative disorders. In the context of inflammasomes, the interaction between exosomes and the NLRP3 inflammasome is considered to play a critical role in the onset and progression of inflammation-related diseases, particularly in systemic inflammatory responses (eg, systemic inflammatory myocardial injury, SIMD). For instance, Xu et al observed that inhibiting miR-484 in an LPS-induced sepsis cardiomyocyte model effectively reduced the formation of NLRP3 inflammasomes, thereby downregulating the expression of pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-6), alleviating cardiomyocyte apoptosis, and promoting cardiomyocyte viability recovery.[132] Similarly, miR-495 has been shown to improve damage and inflammation in cardiac microvascular endothelial cells by inhibiting the NLRP3 inflammasome signaling pathway.[133] Liu et al's research demonstrated that miR-129-5p, by targeting TRPM7 and inhibiting NLRP3 inflammasome activation, alleviated cardiomyocyte injury.[134] Further molecular studies have suggested that miRNAs may regulate the transcriptional expression of NLRP3 by directly binding to its 3' untranslated region (UTR). For example, Li et al discovered that in sepsis cardiomyopathy patients and in septic cardiomyocyte injury models, long non-coding RNA ZFAS1, acting as a competing endogenous RNA (ceRNA), indirectly modulates the expression of SESN2, thereby reducing sepsis-induced myocardial cell damage.[135]

Current literature suggests that exosome-mediated interactions with the NLRP3 inflammasome play a significant role in the pathophysiology of SIMD, highlighting their potential as promising therapeutic targets for SIMD. However, the precise molecular mechanisms governing these interactions remain poorly understood. Consequently, further research is warranted to elucidate the underlying mechanisms and their implications for future therapeutic strategies.

The Role of NLRP3 Inflammasome via ER Stress in SIMD

ER stress is a cellular response activated to cope with conditions such as the accumulation of misfolded and unfolded proteins within the ER lumen and dysregulation of calcium homeostasis.[136] This response involves pathways such as the unfolded protein response (UPR), the ER overload response, and caspase-12 mediated apoptosis.[136] Physiological UPR refers to the process by which cells manage mild ER stress under normal physiological conditions.[137] During this process, the ER senses the accumulation of misfolded or unfolded proteins and activates a series of signaling pathways to initiate the stress response.[137] The goal of this response is to restore ER function, promote proper protein folding, and adjust protein synthesis to maintain normal cellular function.[137] This stress response is typically reversible and helps cells cope with transient stress. However, when the stress load becomes overwhelming and intracellular homeostasis is disrupted, physiological UPR may no longer maintain normal cellular function.[137,138] Excessive ER stress triggers inflammatory signals within the cell, activating the NLRP3 inflammasome and leading to widespread inflammatory responses[137,138](Figure 4).

The UPR is a cellular mechanism that helps mitigate ER stress by enhancing the ER's protein-folding capacity, repairing mildly misfolded proteins, and ultimately clearing irreversibly misfolded proteins.[139] The UPR involves multiple signaling pathways aimed at promoting the proper folding of proteins in the ER, reducing overall protein synthesis, and activating ER-associated degradation (ERAD) pathways to remove accumulated misfolded proteins. In cases of excessive or unresolved ER stress, the UPR also triggers apoptotic cascades. A key protein in the UPR process is the chaperone GRP78, which regulates protein synthesis, folding, and assembly.[140] GRP78 acts not only as a sensor of misfolded proteins but also as an initiator of UPR signaling cascades.[141] Under normal conditions, GRP78 binds to and inhibits the activity of three ER-resident transmembrane UPR signaling proteins: inositol-requiring enzyme 1 (IRE1), activating transcription factor 6 (ATF6), and protein kinase RNA-like endoplasmic reticulum kinase (PERK). However, upon the accumulation of misfolded proteins during ER stress, GRP78 recognizes the error and releases these signaling factors, allowing them to bind to misfolded proteins, thus activating UPR signaling and downstream cascades.[142] These factors cooperate to promote correct protein folding and clear misfolded proteins. Although this is the classical

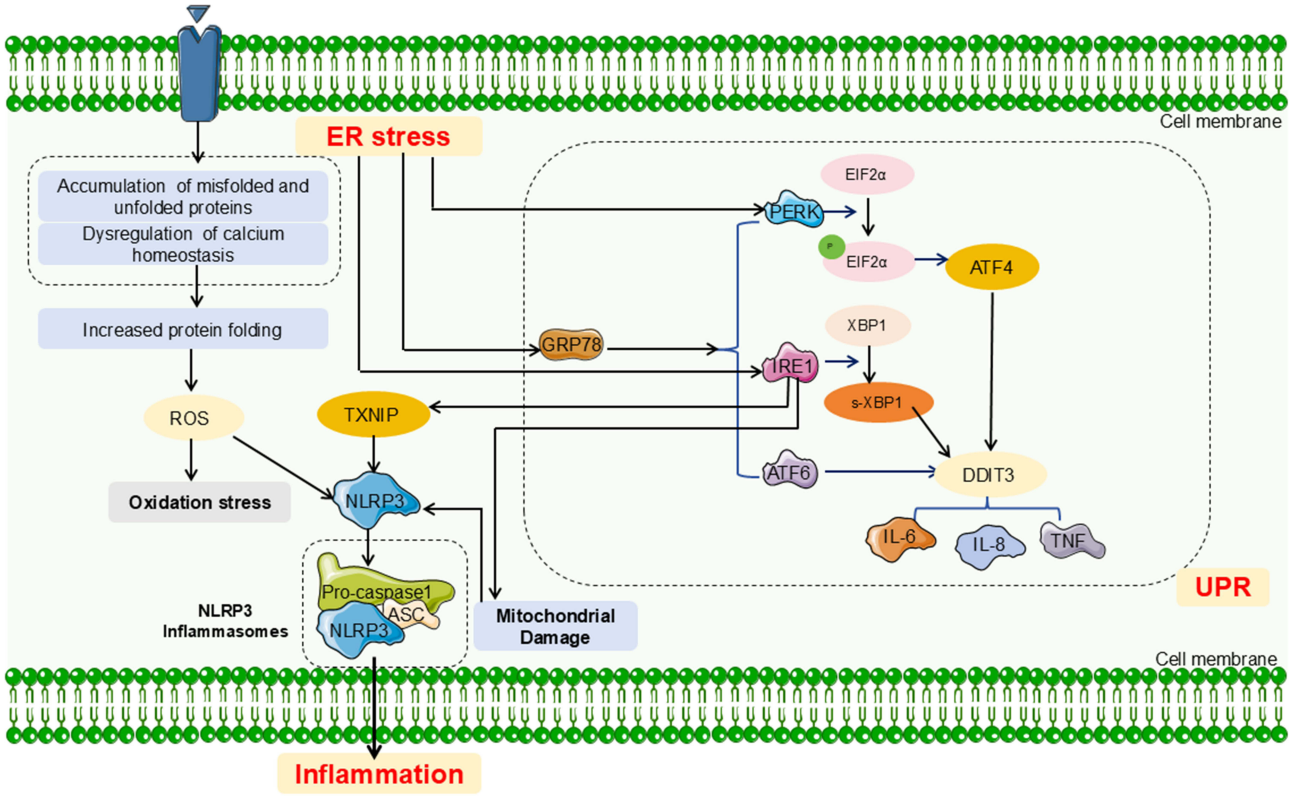

Figure 4 The Role of NLRP3 Inflammasome via ER stress in SIMD. Under normal conditions, GRP78 binds to and inhibits three transmembrane UPR signaling factors localized in the ER: IRE1, ATF6, and PERK. However, during ER stress, the UPR is activated through these three ER sensors—PERK, IRE1, and ATF6—which subsequently trigger the activation of the NLRP3 inflammasome. Excessive ROS production can induce ER stress. Moreover, ER stress activates PERK and IRE1, which promote the expression of TXNIP, thereby activating the NLRP3 inflammasome.

Abbreviations: TXNIP, Thioredoxin-interacting protein; XBP1, X-box Binding Protein 1; sXBP1, spliced XBP1; ATF4, Activating transcription factor 4; ATF6, Activating Transcription Factor 6; DDIT3, DNA Damage-Inducible Transcript 3; EIF2α, Eukaryotic Initiation Factor 2α; GRP78, Glucose-Regulated Protein 78.

mechanism of recognizing misfolded proteins in the ER, increasing evidence suggests that misfolded proteins may also directly interact with IRE1 or PERK, initiating the UPR.[143,144] Moreover despite being a protective response, in cases of severe and prolonged ER stress, the UPR can lead to cellular toxicity.[145]

Recent studies have revealed a close relationship between ER stress, UPR, and inflammatory responses.[146,147] A number of investigations have shown that sepsis and sepsis-induced cardiomyopathy are closely linked to excessive ROS production. Thus, enhancing cellular antioxidant defenses or promoting ROS clearance may help restore redox balance and improve pathological conditions in various disease models.[148] Excessive ROS generation can induce ER stress, referred to as ROS-induced ER stress,[149] which is one of the mechanisms of cell apoptosis mediated by ROS. ER stress -induced apoptosis in cardiomyocytes has been recognized as a primary mechanism of myocardial injury.[150,151] Further research has also highlighted the role of the NLRP3 inflammasome in the development of various inflammatory diseases, including sepsis and sepsis-induced cardiomyopathy. In this context, the interplay between ER stress and the NLRP3 inflammasome and their potential synergistic roles in the pathogenesis of sepsis and SIMD have become important areas of investigation.

The UPR is the most significant and widely studied pathway for ER stress. In mammals, UPRs are mediated by three ER stress sensors: IRE1, PERK, and ATF6. Research suggests that ER stress serves as an endogenous trigger for the NLRP3 inflammasome.[152] These three ER stress sensors can activate the NLRP3 inflammasome through complex mechanisms, leading to cellular damage, often involving the TXNIP/NLRP3 pathway.

Upon activation, IRE1α phosphorylates and dimerizes, activating its RNase domain and catalyzing the removal of 26 nucleotides from the XBP1 mRNA sequence, allowing its translation.[153] X-box binding protein 1 (XBP1) is a key regulator of genes involved in ER-associated degradation (ERAD) and protein folding.[153] Additionally, IRE1α activation

triggers the TNF receptor-associated factor 2 (TRAF2) and c-Jun N-terminal kinase (JNK) signaling modules, which initiate inflammatory responses.[154] Studies indicate that IRE1α overexpression due to ER stress activates XBP1s or stimulates JNK phosphorylation through ASK1, which in turn activates C/EBP homologous protein (CHOP), inducing TXNIP overexpression. TXNIP is then translocated to the mitochondria, where it forms a complex with TRX2.[103] This process promotes ROS accumulation and the oxidation of TRX2, releasing TXNIP, which subsequently activates the NLRP3 inflammasome through interaction with NLRP3, triggering an inflammatory response.[104] Second, PERK, a type I transmembrane kinase, is activated under ER stress. Its activation induces the phosphorylation of the eukaryotic initiation factor 2α (eIF2α) subunit, which inhibits protein synthesis.[155] Under ER stress, sustained phosphorylation of eIF2α induces ATF4 expression, leading to the activation of CHOP and the subsequent activation of the TXNIP/NLRP3 inflammasome.[155,156] Third, upon activation of the UPR, ATF6 directly encodes XBP1, which enhances CHOP expression.[157] Similar to the IRE1α and PERK pathways, overexpression of CHOP leads to TXNIP overexpression and activation of the NLRP3 inflammasome.[101] Liu et al found that silencing TXNIP inhibited NLRP3 inflammasome activation and reduced cardiomyocyte apoptosis induced by ischemia/reperfusion.[158] Similarly, studies in a SIMD rat model observed increased expression of TXNIP, NLRP3, IL-1β, and IL-18.[106]

In addition to the TXNIP/NLRP3 pathway, Yang et al found that inhibiting the IRE1α pathway alleviates NLRP3 activity and IL-1β production, thereby reducing inflammation and ROS in sepsis and organ injury models.[152] Activated IRE1 also triggers mitochondrial damage through caspase-2 and BID, leading to NLRP3 inflammasome activation.[159] The ER is a calcium ion reservoir, and during ER stress, an imbalance in the ER leads to excessive calcium influx into the mitochondria through the ER-mitochondria contact points (MAM), resulting in mitochondrial calcium overload and damage.[160] This overload causes excessive mtROS production, mitochondrial DNA damage, and cardiolipin damage, all of which activate the NLRP3 inflammasome.[44,128,161] Consequently, calcium dysregulation serves as a secondary effect of ER membrane instability and subsequent inflammatory responses, rather than directly inducing membrane instability.[162] Calcium changes are critical signaling events in cellular stress responses, indirectly promoting NLRP3 inflammasome activation.[162] In experimental models of various inflammatory diseases, including sepsis, reducing ER stress and the interaction between ER stress and the NLRP3 inflammasome through pharmacological or gene therapy strategies has successfully alleviated pathology associated with inflammation.[118,163] Melatonin and liver X receptor agonists have been shown to attenuate sepsis-induced myocardial dysfunction by inhibiting ER stress.[164,165]

The aforementioned findings highlight the critical role of the interaction between ER stress and the NLRP3 inflammasome in the pathogenesis of septic myocardial injury. However, the precise mechanisms by which ER stress triggers the activation and inflammatory functions of the NLRP3 inflammasome remain unclear. To date, there has been no in-depth investigation directly exploring the role of ERS markers, such as GRP78, IRE1α, PERK, or ATF6α, within the NLRP3 inflammasome signaling cascade. Future research is required to further elucidate the specific molecular mechanisms underlying the interplay between ER stress and the NLRP3 inflammasome in septic cardiomyopathy. This will be crucial for the development of targeted therapeutic strategies for SIMD.

Targeted Therapy for SIMD Focusing on the NLRP3 Inflammasome

As previously highlighted, the activation of the NLRP3 inflammasome is a critical factor in the pathogenesis of sepsis and SIMD, contributing to disease progression through mechanisms such as pyroptosis, ROS, mitochondrial dysfunction, exosome release, and ERS stress. These interconnected pathological processes play a significant role in the onset and advancement of SIMD. Consequently, targeting the NLRP3 inflammasome has emerged as a promising therapeutic strategy for both the prevention and treatment of SIMD (Table 1). For instance, melatonin has been shown to modulate the Nrf2 signaling pathway, thereby inhibiting NLRP3 inflammasome activation and mitigating myocardial injury induced by sepsis.[80] In a similar vein, geniposide (GE) exerts its effects by activating AMPKα, which suppresses the accumulation of myocardial ROS and prevents NLRP3 inflammasome-mediated cardiomyocyte apoptosis, leading to improved outcomes in SIMD.[113] Given the pivotal role of NLRP3 inflammasome activation and its involvement in multiple pathological processes, including pyroptosis and oxidative stress, targeting the NLRP3 inflammasome represents a promising therapeutic approach and an important area for future research in the treatment of SIMD.

Table 1 Therapeutic Strategies Based on NLRP3 Inflammasome in SIMD

Mechanism	Therapy	Target/Signaling Pathway	Effect for Target/ Signaling Pathway	In-vivo model	In-vivo Subject	In-vitro Model	In-vitro Subject	Effect	References
Pyroptosis	Melatonin (MT)	NLRP3, caspase-1, GSDMD	Downregulation	LPS	-	LPS	H9C2	Inhibition	[80]
	Carvacrol (CVL)	NLRP3, caspase-1, GSDMD	Downregulation	LPS	Mouse	LPS	H9C2	Inhibition	[166]
	Recombinant human angiotensin-converting enzyme 2 (rhACE2)	NLRP3	Downregulation	LPS	Mouse	-	-	Inhibition	[167]
	Sodium tanshinone IIA sulfonate (STS)	NLRP3	Downregulation	LPS	Mouse	-	-	Inhibition	[168]
	Geniposide (GE)	NLRP3	Downregulation	LPS	Mouse	-	-	Inhibition	[113]
	MCC950	NLRP3/Caspase-1/IL-1β	Downregulation	CLP	Rat	LPS	H9C2	Inhibition	[169]
	Emodin	NLRP3, GSDMD	Downregulation	LPS	Mouse	-	-	Inhibition	[170]
	Irisin	NLRP3	Downregulation	LPS	Mouse	-	-	Inhibition	[171,172]
	Syringaresinol (SYR)	ER/SIRT1/NLRP3/ GSDMD	Upregulation	CLP	Mouse	-	-	Inhibition	[173]
	Dehydrogenase (ALDH2)	NLRP3, caspase-1, GSDMD	Downregulation	LPS	Mouse	-	-	Inhibition	[174]
	Necrosulfonamide	GSDMD	Downregulation	LPS	Mouse	-	-	Inhibition	[175]
	HSP70	NLRP3, caspase-1, GSDMD	Downregulation	CLP	Mouse	LPS	H9C2	Inhibition	[16]
ROS	Minocycline (Min)	NLRP3/Caspase-1	Downregulation	LPS	Mouse	LPS	H9C2	Inhibition	[176]
	GYY4137	NLRP3	Downregulation	LPS	Mouse	LPS	H9C2	Inhibition	[89]
	Atractylenolide	PARP1/NLRP3	Downregulation	LPS	Mouse	-	-	Inhibition	[114]
	Geniposide (GE)	AMPKα	Downregulation	-	-	LPS	H9C2	Inhibition	[113]
	Cortistatin (CST)	SSTR2/AMPK/Drp1/ NLRP3	Downregulation	LPS	Mouse	-	-	Inhibition	[177]
	Melatonin (MT)	Inos, COX-2, NLRP3	Downregulation	-	-	LPS	H9C2	Inhibition	[80]
Mitochondrial dysfunction	HSP70	NLRP3 inflammasome, caspase-1, GSDMD	Downregulation	CLP	Mouse	LPS	H9C2	Inhibition	[16]
	SESN2 (sestrin 2)	NLRP3 inflammasome	Downregulation	LPS	Mouse	-	-	Inhibition	[178]
	Growth arrest-specific gene 6 (GAS6)	GAS6/AXL-NLRP3	Downregulation	CLP	Mouse	-	-	Inhibition	[179]
	Chicoric acid (CA)	α-tubulin acetylation	Downregulation	-	-	LPS	Macrophages	Inhibition	[180]
	Vaccarin (VAC)	NLRP3 inflammasome	Downregulation	LPS	Mouse	-	-	Inhibition	[181]

(*Continued*)

Table 1 (Continued).

Mechanism	Therapy	Target/Signaling Pathway	Effect for Target/ Signaling Pathway	In-vivo model	In-vivo Subject	In-vitro Model	In-vitro Subject	Effect	References
	NR1H3	NLRP3	Downregulation	CLP	Mouse	-	-	Inhibition	[182]
	Aldehyde dehydrogenase (ALDH2)	NLRP3 inflammasome	Downregulation	LPS	Mouse	-	-	Inhibition	[174]
Exosome	PSSM1443	TXNIP-NLRP3 interaction	Downregulation	LPS	Mouse	-	-	Inhibition	[183]
ER stress	Thioredoxin-1	NLRP3 inflammasome	Downregulation	-	-	LPS	Raw 264.7	Inhibition	[152]
	Melatonin	ERK/BAP31 pathway	Downregulation	LPS	Mouse	-	-	Inhibition	[184]
	Sestrin2	NLRP3	Downregulation	CLP	Mouse	-	-	Inhibition	[185]
	Liver X receptor (LXR)	SIRT1	Upregulation	CLP	Mouse	-	-	Inhibition	[186]
	4-Phenylbutyric acid (4-PBA)	IP3R2, NLRP3	Downregulation	LPS	Rat	LPS	Primary neonatal rat cardiomyocytes (NRCMs)	Inhibition	[187]

https://doi.org/10.2147/JIR.S521655

Limitation

In this review, while we have thoroughly explored the role of the NLRP3 inflammasome in septic cardiomyopathy, several limitations remain to be addressed. First, our research lacks clinical trial data, and as a result, our conclusions are primarily based on animal models and in vitro experiments. Although these experimental findings provide important insights into the mechanisms of the NLRP3 inflammasome, their validation in clinical settings remains insufficient. Therefore, future studies should design and conduct more clinical trials to verify the theories and discoveries we have proposed. Secondly, our research identified the involvement of the NLRP3 inflammasome in multiple intracellular signaling pathways, including mitochondrial dysfunction, oxidative stress, and endoplasmic reticulum stress. These pathways may exhibit overlapping and interactive effects to some extent. However, the current study has not fully elucidated the precise relationships and interactions between these pathways. Therefore, future research needs to further investigate the cross-talk between these signaling pathways in order to gain a more comprehensive understanding of the multifaceted role of the NLRP3 inflammasome in septic cardiomyopathy. In conclusion, although this study provides new insights into the role of the NLRP3 inflammasome in septic cardiomyopathy, we acknowledge the limitations of the current research. We look forward to future studies that will complement and refine these findings through more clinical investigations and in-depth mechanistic studies.

Conclusion

In summary, we explored the activation of the NLRP3 inflammasome as a central mechanism in the pathogenesis of SIMD, with a particular focus on its interactions with various pathological processes, including pyroptosis, oxidative stress, mitochondrial damage, exosome release, and endoplasmic reticulum stress. The findings suggest that the NLRP3 inflammasome may serve as a potential therapeutic target or a preventive approach for SIMD. While significant progress has been made in the development of NLRP3 inflammasome-targeted therapies, existing research has predominantly been confined to cell lines and animal models, with a lack of clinical evidence to support these findings. Therefore, there is an urgent need for more clinical studies focusing on the application of NLRP3 inflammasome-based therapies.

Acknowledgments

The authors thank Department of Emergency Medical, General Hospital of Ningxia Medical University, Department of Nuclear Medical, General Hospital of Ningxia Medical University and Department of Pediatrics Emergency Medical, General Hospital of Ningxia Medical University for supporting this work.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors declare that there is no conflict of interest in this work.

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