Acupuncture and Herbal Medicine

The mechanism and treatment strategies of GSDMD-mediated pyroptosis in myocardial infarction

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Abstract

Acute myocardial infarction (MI) is associated with high morbidity and mortality and poses a significant challenge to human health. Despite advances in medicine, effective treatment options for MI are still associated with adverse outcomes, such as heart failure. Consequently, identifying the pathogenesis of MI is a promising avenue for developing practical treatments. The inflammatory response plays a critical role in the pathogenesis of MI. Gasdermin D (GSDMD)-mediated pyroptosis regulates the inflammatory response, which is a pathogenic and potential therapeutic target for MI. Therefore, anti-pyroptosis treatment is emerging as a promising therapeutic approach for MI. Overall, this article reviews the mechanism and treatment strategies for GSDMD-mediated pyroptosis in MI, with the hope of providing insights into pathogenic interventions.

Keywords: GSDMD inhibitors, Myocardial infarction, Pyroptosis, Traditional Chinese medicine

Graphical abstract: http://links.lww.com/AHM/A134.

Introduction

Acute myocardial infarction (MI) is a necrotic disease caused by acute and sustained ischemia and hypoxia of the coronary arteries. This condition is associated with high mortality and morbidity and poses a significant threat to public health. Established treatment modalities, including combined surgical and pharmacological thrombolytic therapies, such as percutaneous coronary intervention and coronary artery bypass grafting, in conjunction with antithrombotic and antiplatelet medications (eg, aspirin, angiotensin-converting enzyme inhibitors, and β-blockers), have been shown to improve MI prognosis[1]. Nevertheless, current therapies often fail to address adverse pathological outcomes, such as heart failure, emphasizing the need to explore treatments derived from a deeper understanding of the pathogenesis.

Inflammation plays a pivotal role in the pathological process of MI. Moderate inflammatory reactions promote tissue repair after MI. However, an excessive inflammatory response can exacerbate myocardial injury[2]. Thus, modulation of the inflammatory response is a potential method for alleviating myocardial damage. Previous studies have shown that the inflammatory response to MI is influenced by various inflammatory cell death pathways, including necrosis, necroptosis, ferroptosis, and apoptosis[3]. Pyroptosis, a novel inflammatory programmed cell death pathway, is particularly important in MI.

Pyroptosis is mediated by damage-associated molecular patterns (DAMPs) released by damaged cardiac tissues in MI, including HMGB1, RNA, nucleotides, heat shock proteins (HSP), members of the S100 family, and interleukin (IL)-1α. In 2022, a groundbreaking study published in *Circulation* and the *Journal of Clinical Investigation* elucidated the central regulatory role of gasdermin D (GSDMD) in the pyroptosis pathway in MI[4–5]. Inhibition of the function of GSDMD can significantly improve myocardial injury, indicating that GSDMD is a promising therapeutic target for the treatment of MI. However, GSDMD inhibitors have not yet been used for the clinical treatment of MI. This review systematically discusses the recent progress and future potential of therapeutic strategies for MI based on the GSDMD-mediated pyroptosis signaling pathway, with the aim of providing a reference for alleviating MI damage.

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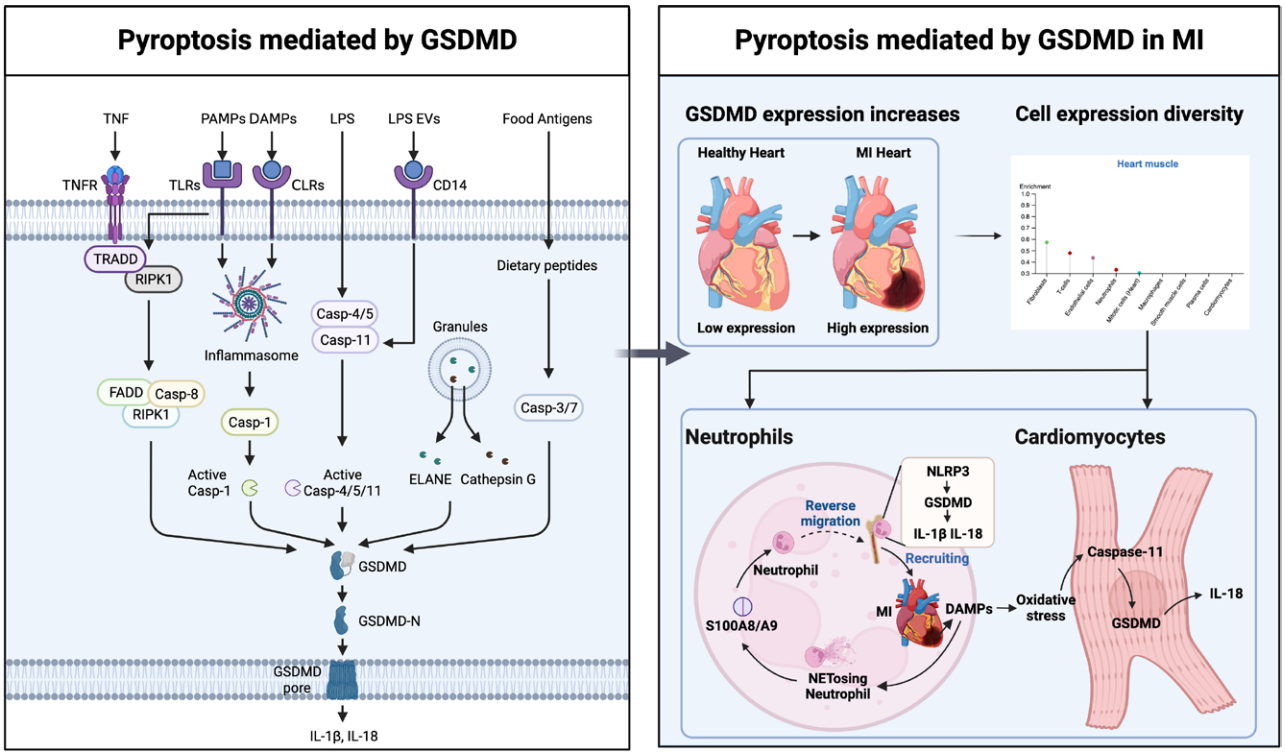

Figure 1. The GSDMD-mediated pyroptosis signaling pathway exhibits complexity and specificity in its mechanisms, particularly in MI. Post-MI, there is an observed upregulation of GSDMD expression in cardiac tissues. This expression alteration involves various cell types, each mediating distinct signaling pathways. Notably, the pyroptosis mechanism of GSDMD in neutrophils and cardiomyocytes has been elucidated. CLRs: C-type lectin receptors; DAMP: Damage-associated molecular pattern; EVs: Extracellular vesicles; FADD: Fas-associated death domain protein; GSDMD: Gasdermin D; IL: Interleukin; LPS: Lipopolysaccharide; MI: Myocardial infarction; PAMP: Pathogen-associated molecular pattern; RIPK1: Recombinant receptor interacting serine threonine kinase 1; TLRs: Toll-like receptors; TNF: Tumor necrosis factor; TNFR: Tumor necrosis factor receptor; TRADD: TNF receptor 1 associated via death domain.

GSDMD-mediated pyroptosis in MI

Inflammatory disorders can intensify the damage following MI. Pyroptosis, an important pro-inflammatory cell death mechanism, facilitates the release of inflammatory cytokines *via* gasdermin pores, contributing to the post-MI inflammatory response and aggravating cardiac injury[6]. Various gasdermin proteins mediate pyroptosis, among which GSDMD-mediated pyroptosis significantly influences the post-MI damage and repair processes. Previous studies have established that both genetic knockout and pharmacological inhibition of GSDMD markedly ameliorate post-MI damage, highlighting GSDMD as a viable therapeutic target for MI. The exploration of the mechanisms underlying GSDMD in MI is of substantial significance. In summary, our findings indicate that the mechanism of pyroptosis associated with GSDMD is highly intricate, varies across diseases, and exhibits unique characteristics in MI, which are potentially linked to differential GSDMD expression in cells affected by MI.

In general, the pyroptosis pathway mediated by GSDMD can be divided into canonical and non-canonical pathways, depending on the membrane receptor recognition patterns. In the canonical pathway, pathogen-associated molecular patterns (PAMPs) and DAMPs are identified by pattern recognition receptors that trigger the assembly of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3)-apoptosis-associated speck-like protein containing a CARD (ASC)-caspase-1 inflammasome. Subsequently, caspase-1 cleaves GSDMD, producing GSDMD-N, and converts the cytokines pro-IL-1β and pro-IL-18 into their mature forms. GSDMD-N then oligomerizes and forms a gasdermin pore in the membrane, and the mature IL-1β and IL-18 are released from the gasdermin pore. Conversely, the non-canonical pathway, governed by caspase-4/5/11, entails the direct recognition of DAMPs/PAMPs by caspase, leading to GSDMD cleavage and release of mature IL-1β and IL-18[7,8]. Furthermore, GSDMD can be recognized by caspase-3/7 at D88 in duodenal intestinal epithelial cells (IECs)[9]. Tumor necrosis factor (TNF) can also activate the FADD-RIPK1-caspase 8 complex, which facilitates the cleavage of GSDMD[10,11]. In addition, GSDMD may be (Figure 1, left) cleaved by cathepsin G or ELANE in neutrophils[12–14].

During MI, various cell types exhibit varying GSDMD expression levels. GSDMD is predominantly expressed in immune cells, notably neutrophils, which play a critical role in MI. Despite the low expression of GSDMD in cardiomyocytes, its distinct role in MI has been elucidated. During MI, circulating neutrophils are recruited to the heart, undergo NETosis, and release S100A8/A9. This release heightens CXCR4 expression in other neutrophils, causing their reverse migration to the bone marrow. Within the bone marrow, neutrophils accumulate, and activated neutrophils secrete IL-1β through GSDMD-mediated pyroptotic pores, promoting granulopoiesis[5]. In myocardial ischemia-reperfusion (MI/R) injury, GSDMD can regulate cardiomyocyte pyroptosis

and aggravate MI/R injury, wherein oxidative stress is induced and the expression of caspase-11 and cleavage of GSDMD are promoted. GSDMD-N is then oligomerized to form GSDMD membrane pores[15] (Figure 1, right).

In conclusion, GSDMD-mediated pyroptosis plays a critical role in MI. While the fundamental aspects of pyroptosis in MI, including GSDMD cleavage and the release of the inflammatory cytokines IL-1β and IL-18, align with the general pathway, there are distinct differences that are attributed to cell-specific expression patterns in MI. Additionally, a literature review revealed that specific danger signals that initiate pyroptosis in MI have not yet been identified.

Pyroptosis inhibition as a strategy to ameliorate MI symptoms

Targeting pyroptosis is a viable therapeutic strategy to reduce MI damage. Consequently, we delineated two therapeutic approaches: inhibition of the GSDMD-mediated pyroptotic pathway and targeted suppression of GSDMD. Our review encompasses the utilization of small-molecule inhibitors and Chinese herbal medicines, emphasizing their efficacy and mechanism in inhibiting pyroptosis and reducing MI-related injury, as well as attempting to provide a systematic pyroptosis inhibition-oriented therapeutic solution to ameliorate MI symptoms.

Small-molecule inhibitors for pyroptosis and MI symptom alleviation

Pyroptosis pathway inhibitors

Pyroptosis is a form of programmed cell death that occurs after MI and exacerbates cardiac damage. Inhibiting key components of pyroptosis, such as NLRP3, caspase-1, and IL-1β, has been shown to relieve damage post-MI.

Studies have indicated that targeting the NLRP3 domain, such as the NACHT region with adenosine triphosphate (ATP)ase activity, or the processes of NLRP3 oligomerization and activation effectively reduces cardiac damage. OLT1177, an NLRP3 inhibitor, suppresses the catalytic and ATP-binding activities of the enzyme in the Walker A region, thereby reducing the recruitment of NLRP3 to ASC. Furthermore, inhibiting the NLRP3 inflammasome helps prevent left ventricular diastolic dysfunction and reduces infarct size post-MI in mice[16–18]. Moreover, the NLRP3 ATPase inhibitor BAY 11-7082 decreases neutrophil and macrophage infiltration in MI, thereby reducing the fibrotic area and enhancing cardiac function[19]. INF4E, which targets the NLRP3 inflammasome, promotes survival, sustains mitochondrial health, reduces ischemic injury, and improves cardiac function[20–21].

MCC950 (CP-456773), which consists of two arylsulfonylurea moieties, binds noncovalently to the hydrolysis site of Walker B within the NACHT region of NLRP3. This binding impedes the formation of a stable Walker B-ATP complex in NLRP3, inhibits ATPase activity, and prevents hydrolysis of ATP to ADP. Additionally, Walker B, upon ATP binding, shifts NLRP3 from an "open" to a "closed" conformation, hindering the assembly and activation of inflammasomes, thereby reducing the release of IL-1β[22,23]. In a pig model of MI, MCC950 effectively minimized cardiac infarction size and maintained cardiac function[24]. Compound 16673-34-0 also effectively inhibited NLRP3 inflammasome formation in cardiomyocytes and improved the fibrotic area in mice post-MI[25].

VX-765 (Belnacasan/VRT-043198), a selective caspase-1 inhibitor, blocks caspase-1 by covalently modifying the cysteine residue in its active site. This modification inhibits the cleavage of pro-IL-1β and pro-IL-18[26,27]. In MI, VX-765 has been shown to significantly reduce infarct size and improve cardiomyocyte function[28–30].

IL-1β, initially identified as a downstream effector of the inflammasome, plays a crucial role in the progression of ischemic heart diseases, including MI and MI/R injury[31]. Consequently, drugs such as Canakinumab (ACZ885), Anakinra (Kineret, an IL-1β monoclonal antibody), and Rilonacept (Arcalyst, an IL-1α/IL-1β soluble trap receptor drug) have been developed[32]. These medications were administered as a part of the CANTOS trial. The trial demonstrated that IL-1β inhibitors significantly reduce IL-6 and CRP levels in plasma, lower adverse vascular events by approximately 15%[33], and effectively prevent recurrent ischemic events in patients with prior MI, along with a reduction in hospitalization rates. However, owing to statistically insignificant clinical data and the risk of fatal infections as adverse reactions, these drugs have not been approved for the treatment of myocardial injury post-MI (NCT01327846)[34,35] (Figure 2).

Although some inhibitors targeting the pyroptosis pathway have demonstrated the potential for alleviating MI damage, their effectiveness is currently limited to animal experiments and clinical trials, with no market approval. For example, IL-1β inhibitors, while utilized in clinical trials, have not progressed to drug development, mainly due to concerns regarding their efficacy. As a result, although the pyroptosis pathway holds significant promise for MI treatment, it also poses considerable challenges in the development of drugs related to GSDMD.

GSDMD inhibitors

Given the critical role of GSDMD in this pathway, it may be a potential target for the therapeutic repair of MI damage. Existing research has indicated that the GSDMD chemical inhibitor necrosulphonamide (NSA) improves MI injury[4]. Administration of NSA (20 mg/kg) at both MI onset and 8 hours post-MI reduced the cardiac fibrotic area from 52% to 42%. Further results indicated that administration of NSA effectively improved cardiac function in mice, with a decrease in the cardiac fibrotic area from 58.3% to 21.6%. These findings confirm the potential of the GSDMD inhibitor NSA in alleviating MI injury. Additionally, disulfiram is another drug that targets GSDMD. Administration of disulfiram at the onset and 4 hours after MI improved the survival rates in MI mice, although the differences were not statistically significant[4]. Low bioavailability of NSA and disulfiram affects their performance in improving survival rates. Therefore, GSDMD inhibitors provide a potential

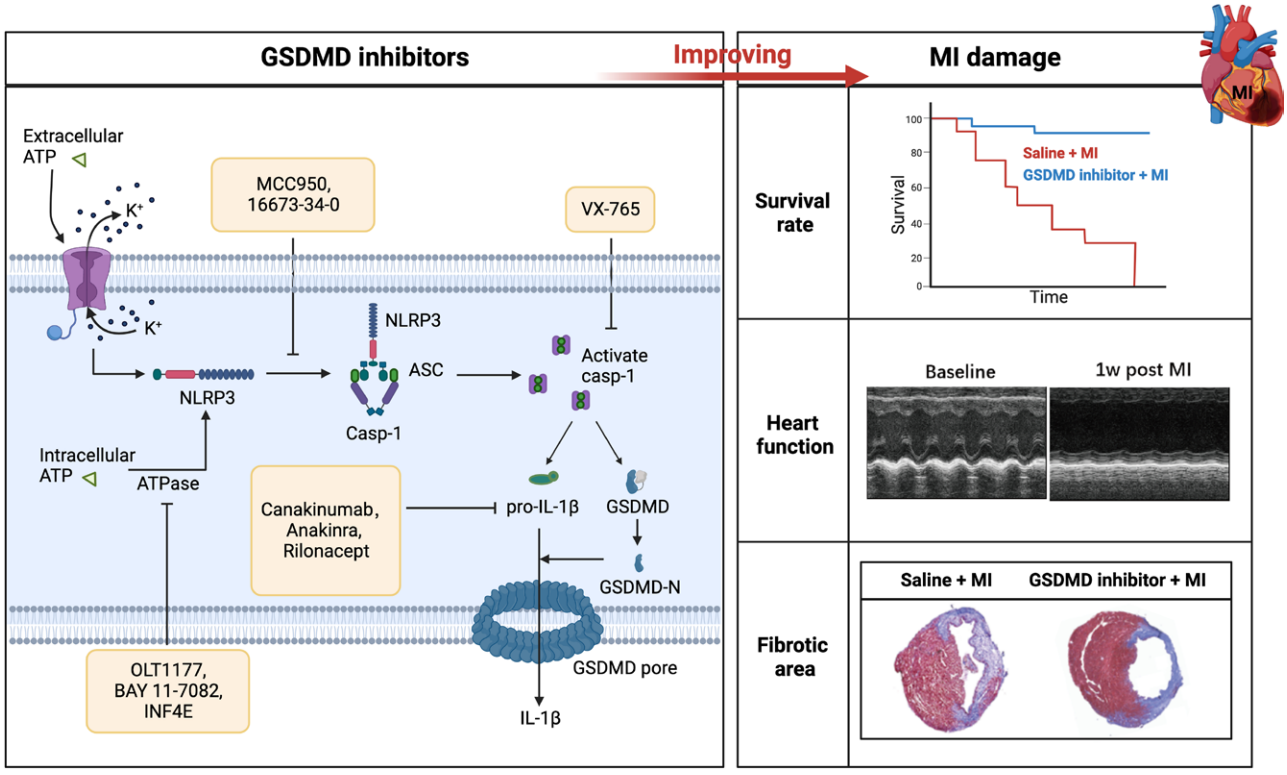

Figure 2. Inhibitors targeting the GSDMD pathway components, including NLRP3, caspase-1, and IL-1β, have been shown to effectively enhance survival rates, cardiac function, and reduce cardiac fibrotic area following MI[4]. ASC: Apoptosis-associated speck-like protein containing a CARD; GSDMD: Gasdermin D; IL-1β: Interleukin-1β; MI: Myocardial infarction; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3.

therapeutic option for MI; however, new drug delivery strategies and drug formulations are needed to improve their performance and potential for the treatment of MI.

These inhibitors target mouse-GSDMD Cys192/human GSDMD Cys191 and inhibit the oligomerization of p30-GSDMD and subsequent pyroptosis[36]. The GSDMD domain may be selected owing to the location of Cys191/Cys192 in the distal tip of the membrane-spanning region starting from the β8 strand within the β7-β8 hairpin. This location is pivotal for pyroptotic pore formation within the β-barrel[37]. In summary, targeting Cys191/Cys192 is crucial for inhibiting GSDMD p30 oligomerization and triggering pyroptosis (Figure 3).

In addition, we found that GI-Y1 targets the GSDMD Arg7 site. Nevertheless, the other active sites require further investigation[39].

Chinese herbal interventions for pyroptosis and MI symptom alleviation

Pyroptosis pathway inhibition

Through a search using keywords such as "traditional Chinese medicine" "pyroptosis" and "acute myocardial infarction" we ascertained that Chinese herbal formulas, extracts, and monomers potentially inhibit pyroptosis by inhibiting the pyroptosis process or targeting GSDMD[40–45]. However, upon reviewing related studies, it became evident that many investigations have linked herbs to pyroptosis inhibition, and they often did so based on the evaluation of specific proteins without identifying the exact targets. A detailed summary of these findings is provided in the following paragraph.

At the cellular level, research on the impact of traditional Chinese medicine in inhibiting pyroptosis has primarily focused on cardiomyocytes, macrophages, and mesenchymal stem cells. The Chinese medicine formula "Simiao Yongan decoction" has demonstrated its ability to relieve H9c2 cardiac injury caused by hypoxia/reoxygenation; suppress the expression of NLRP3, caspase-1, and IL-1β; and also stimulate autophagy; thus further preventing MI/R injury[40]. Similarly, the Chinese herbal extract, namely the total glucosides of paeony, has been shown to dose-dependently reduce the expression of NLRP3, caspase-1, GSDMD-N, and IL-1β/IL-18, consequently ameliorating the damage to HL-1 cardiomyocytes due to hypoxia/reoxygenation[41]. The Chinese herbal monomer irisin inhibited NLRP3 inflammasome-mediated pyroptosis and oxidative stress in a co-culture model of bone marrow-derived mesenchymal stem cells (BMMSCs) and cardiomyocytes[46]. Moreover, AS-IV has a similar mechanism in macrophages[47] (Table 1).

At the animal level, the Chinese herbal formula Simiao Yongan decoction has been observed to modulate the expression of type I collagen, Matrix metalloprotein-9 (MMP9), and TNFα in the myocardial tissue of rats suffering from MI/R injury. This modulation enhanced the cardiac function (ventricular volume and ejection fraction)[40]. Additionally, the ethyl acetate extract from *Cinnamomi ramulus* has demonstrated efficacy in shrinking infarct areas and decreasing inflammatory reactions by inhibiting the activation of NLRP3, caspase-1, GSDMD, and IL-1β in rat myocardial tissue[42]. Cinnamic acid, a Chinese herbal monomer, can effectively improve cardiac diastolic function and reduce myocardial infarct size by inhibiting protein

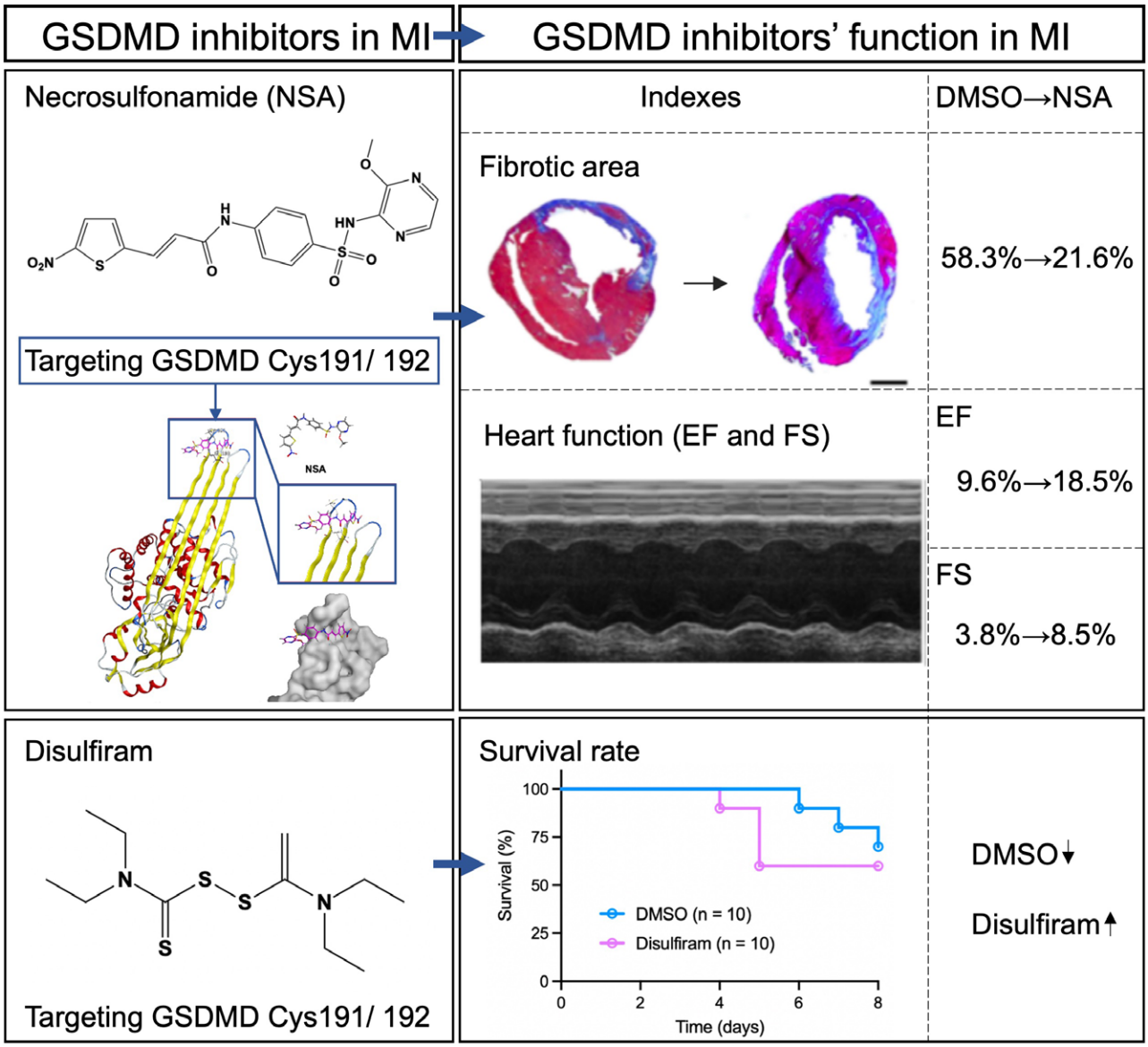

Figure 3. Role and mechanism of GSDMD inhibition in MI[4,38]. DMSO: Dimethyl sulfoxide; EF: Ejection fraction; FS: Fraction shorting; GSDMD: Gasdermin D; MI: Myocardial infarction.

and mRNA changes in the NLRP3-caspase 1-GSDMD signaling pathway[43] (Table 2).

Cell and animal assays have indicated that Chinese herbal medicines can relieve MI injury by targeting the pyroptosis signaling pathway. Numerous studies have suggested that Chinese herbal medicines can inhibit pyroptosis, without identifying GSDMD. Consequently, the direct role of Chinese herbal medicines in the inhibition of pyroptosis warrants further comprehensive research and validation (Figure 4).

Targeting GSDMD

Research indicates that Chinese herbal formulas and monomers can decrease MI injury by directly targeting GSDMD. For instance, punicalagin, a polyphenol extract of pomegranate, can effectively block lipopolysaccharide (LPS)- and ATP-induced pyroptosis in BMDMs, suggesting GSDMD as a potential target[57]. Besides, in an earlier investigation conducted by our team, 177 Chinese herbal formulas and extracts were assessed for their potential to inhibit pyroptosis in J774A.1 cells treated with LPS and nigericin. Our findings revealed that Danhong injection, an approved medicinal formulation, suppressed pyroptosis by targeting the GSDMD-N domain. Further investigation using both infectious and sterile inflammation models validated the inhibitory effects of Danhong injections on pyroptosis. Liquid chromatography tandem-mass spectrometry (LC-MS/MS) analytical procedures and subsequent activity tests identified salvianolic acid E as the primary active component, which exhibited a pronounced affinity for human Cys191/mouse Cys192 and attenuated GSDMD-N oligomerization to some extent[38] (Figure 5).

Recent studies have indicated that GSDMD is a target of Chinese herbal formulas, offering a novel avenue for exploring the mechanisms of action of these compounds and paving the way for the development of GSDMD inhibitors. This raises further considerations: Can multiple components within a Chinese herbal formula synergistically inhibit GSDMD? Such insights may offer

Table 1

Role of traditional Chinese medicine in inhibiting pyroptosis and decreasing MI injury at the cellular level

Category	Cell	Model	Mechanisms	References
Formula				
Simiao Yongan decoction	H9c2 cell	Hypoxia/reoxygenation treatment	Increasing the survival rate of H9c2 cardiomyocytes by reducing expression of NLRP3, caspase 1, and IL-1β	[40]
Danhong injection	J774A.1, BMDMs	LPS + ATP/ LPS + nigericin stimulation	Inhibiting monocyte/macrophage pyroptosis by targeting GSDMD-N	[38]
Extract				
Total glucosides of paeony	HL-1	Hypoxia/reoxygenation treatment	Inhibiting cardiomyocyte pyroptosis *via* miR-181a-5p/ ADCY1/NLRP3/GSDMD axis	[41]
Ingredient				
Aesculin	Neonatal rat cardiomyocytes	Oxygen-glucose deprivation/restoration	Inhibiting cardiomyocyte death *via* Akt/GSK3β/NF-κB/ NLRP3 pathway	[44]
Sweroside	H9c2 cells	Hypoxia/reoxygenation treatment	Inhibiting oxidative stress and cell death *via* Keap1/ Nrf2 axis	[45]
Emodin	Primary cardiomyocytes	Hypoxia/reoxygenation treatment	Increasing cell survival *via* TLR4/MyD88/NF-κB/ NLRP3 pathway	[48]
Oridonin	Neonatal rat cardiomyocytes	Hypoxia/reoxygenation treatment	Inhibiting cardiomyocyte pyroptosis *via* NF-κB/NLRP3 signaling pathway	[49]
Irisin	Cardiomyocytes and bone marrow-derived mesenchymal stem cells	Hypoxia/reoxygenation treatment	Repressing cardiomyocyte pyroptosis and oxidative stress by suppressing NLRP3 expression	[46]
Kanglexin	Neonatal mouse ventricular cardiomyocytes	Hypoxia and LPS treatment	Inhibiting cardiomyocyte pyroptosis by suppressing NLRP3 inflammasome and GSDMD expression	[50]
Astragaloside IV	BMDMs	LPS and nigericin treatment	Reducing macrophage pyroptosis *via* ROS/caspase-1/ GSDMD axis	[47]
Apigenin	H9c2 cells	Ischemia/hypoxia stimulation	Reversing ischemia/hypoxia-induced cell death by inhibiting NLRP3 inflammasome expression	[51]

Akt/GSK3β/NF-κB: Protein kinase B/Glycogen synthase kinase-3β/Nuclear factor-κB; ATP: Adenosine triphosphate; BMDMs: Bone marrow-derived macrophages; GSDMD-N: Gasdermin D; HL-1: HL-1 mouse atrial myocytes; IL-1β: Interleukin-1β; I/R: Ischemia-reperfusion; LPS: Lipopolysaccharide; MI: Myocardial infarction; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; ROS: Reactive oxygen species.

new perspectives for the development of novel GSDMD inhibitors.

Challenges and future potential

Numerous studies have investigated inhibitors of GSDMD-mediated pyroptosis in MI; however, significant limitations and challenges remain. Existing pyroptosis inhibitors can be categorized into two main types: small-molecule inhibitors and traditional Chinese medicine-based interventions. However, clinical trials of small-molecule inhibitors are yet to be conducted. Research on traditional Chinese medicine interventions has predominantly occurred at the cellular and animal levels, leaving the molecular mechanisms largely unexplored. Furthermore, focusing on GSDMD mechanisms has highlighted a significant oversight in numerous studies: the tendency to target GSDMD directly while neglecting the intricacies of its systemic processes and upstream signaling pathways. Research has indicated that the mechanism of action of GSDMD extends beyond conventional pyroptosis, including its roles in neutrophil autophagy and necroptosis. Moreover, the present GSDMD inhibitors have relatively high IC_{50} values and low target specificity; therefore, their druggability is poor.

Considering the complex GSDMD-mediated mechanisms involved in MI and the less-than-ideal chemical properties of the current inhibitors, this study proposes various approaches for improving the development of GSDMD inhibitors to reduce the damage caused by MI. These strategies encompass the following: (1) an in-depth study of the mechanisms of pyroptosis and the coordination between pyroptosis and multiple types of cell death. (2) Focusing on post-translational modifications of GSDMD for drug discovery, (3) promoting cell-specific pyroptosis inhibition, and (4) improving drug bioavailability through responsive release systems regulated by external energy fields.

In-depth study of the mechanisms of pyroptosis and the coordination between pyroptosis and multiple forms of cell death

The cellular mechanisms mediated by GSDMD are intricate and cell-specific. In MI, GSDMD is typically recognized as a critical element in the NLRP3 inflammasome pathway, crucial for the release of IL-1β and IL-18. This process influences the subsequent inflammatory responses and contributes to MI-related inflammatory damage. Recent studies have expanded our understanding of the

Table 2

Role of traditional Chinese medicine in inhibiting pyroptosis and reducing MI injury in laboratory animal models

Category	Animal	Model	Mechanisms	References
Formula				
Simiao Yongan decoction	Mice	I/R	Improving cardiac function by reducing expression of NLRP3, caspase 1, and IL-1β	[40]
Danhong injection	Mice	MI, MI + T2DM	Decreasing fibroblast area by targeting GSDMD-N	
Extract				
Ethyl acetate extract of *Cinnamomi ramulus*	Mice	I/R	Decreasing myocardial infarct size and improving cardiac function, mitigating myocardial damage by inhibiting NLRP3 inflammasome activation and GSDMD expression	[42]
Ingredient				
Cinnamic acid	Rats	I/R	Improving cardiac diastolic function and decreasing cardiac infarct size *via* NLRP3/caspase 1/GSDMD signaling pathway	[43]
Aesculin	Rats	I/R	Attenuating reperfusion arrhythmias and myocardial damage, improving the hemodynamic function by suppressing the NLRP3 inflammasome-mediated pyroptosis *via* the Akt/GSK3β/NF-κB pathway	[44]
Sweroside	Rats	I/R	Inhibiting oxidative stress by inhibiting Keap1/Nrf2 axis	[45]
Cinnamaldehyde	Mice	I/R	Improving cardiac diastolic function, decreasing cardiac infarct size and myocardial injury enzyme by inhibiting NLRP3 inflammasome and GSDMD expression	[52]
Geniposide	Mice	I/R	Reducing the myocardial infarct area, improving heart function by suppressing NLRP3 inflammasome and GSDMD expression *via* the AMPK pathway	[53]
Emodin	Rats	I/R	Improving survival rate, decreasing infarct size by suppressing TLR4/MyD88/NF-κB/NLRP3 pathway	[48]
Oridonin	Mice	I/R	Improving cell survival and decreasing the myocardial infarct size *via* the regulation of GSDMD-mediated pyroptosis	[49]
Beta-Asarone	Rats	I/R	Decreasing infarct size, preserving the left ventricular performance with higher ejection fraction and fractional shortening by inhibiting the expression of GSDMD	[54]
Kanglexin	Mice	MI	Decreasing infarct area, improving cardiac function by suppressing NLRP3 inflammasome and GSDMD expression	[50]
Astragaloside IV	Mice	MI	Attenuating MI-induced myocardial fibrosis and cardiac remodeling by inhibiting ROS/caspase-1/GSDMD expression	[47]
Ginsenoside Rh2	Rats	MI	Relieving the focal death of cardiomyocytes by inhibiting NLRP3/caspase-1/GSDMD/IL-1β pathway	[55]
Tanshinone IIA	Rats	MI	Improving cardiac function and decreasing myocardial microinfarct size by inhibiting the TLR4/MyD88/NF-κB/NLRP3/GSDMD pathway	[56]

Akt/GSK3β/NF-κB: Protein kinase B/Glycogen synthase kinase-3β/Nuclear factor-κB; AMPK: Adenosine 5'-monophosphate (AMP)-activated protein kinase; GSDMD: Gasdermin D; IL-1β: Interleukin-1β; I/R: Ischemia-reperfusion; MI: Myocardial infarction; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; ROS: Reactive oxygen species; T2DM: Type 2 diabetes mellitus.

roles of GSDMDs. For instance, Jiang et al.[4] demonstrated that in neutrophils, GSDMD controls the release of IL-1β through an autophagy-dependent mechanism, indicating a potential non-pyroptotic function of GSDMD in MI. Consistent with this finding, a study by Weindel et al. revealed that mutations in specific kinases can cause an accumulation of GSDMD-N in the mitochondria, increasing mitochondrial reactive oxygen species (ROS) generation and shifting toward necroptosis rather than pyroptosis[58]. Moreover, GSDMD-mediated cell death is not an isolated phenomenon but interacts with other cell death pathways, such as apoptosis and necroptosis, collectively influencing cell fate. Nevertheless, the implications and importance of this type of cell death in MI remain to be further elucidated[59].

Focusing on post-translational modifications of GSDMD for drug discovery

The current focus of drug research is on the post-translational modifications of the core proteome. Modifications in the GSDMD protein, including ubiquitination, phosphorylation, acetylation, and oxidation, play pivotal roles in its functionality. These modifications facilitate the recruitment of proteins that recognize the modification sites, thereby influencing the conformation, stability, and solubility of GSDMDs. These findings highlight the critical role of post-translational modifications in maintaining GSDMD expression and function. However, the effects of post-translational modifications of GSDMD on MI are not fully understood.

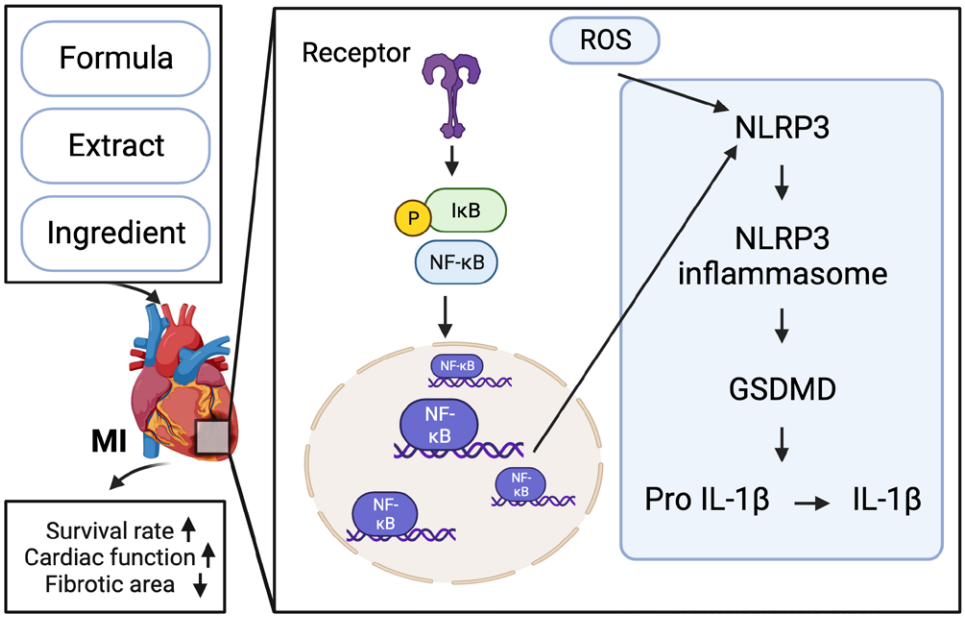

Figure 4. Traditional Chinese medicine (formula, extract, and ingredient) for MI treatment inhibits the GSDMD pyroptosis pathway mediated by ROS and NF-κB, consequently increasing survival rates, enhancing heart function, and reducing fibrotic areas in MI. GSDMD: Gasdermin D; IL-1β: Interleukin-1β; IκB: Recombinant inhibitory subunit of NF kappa B; MI: Myocardial infarction; NF-κB: Nuclear factor-κB; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; ROS: Reactive oxygen species.

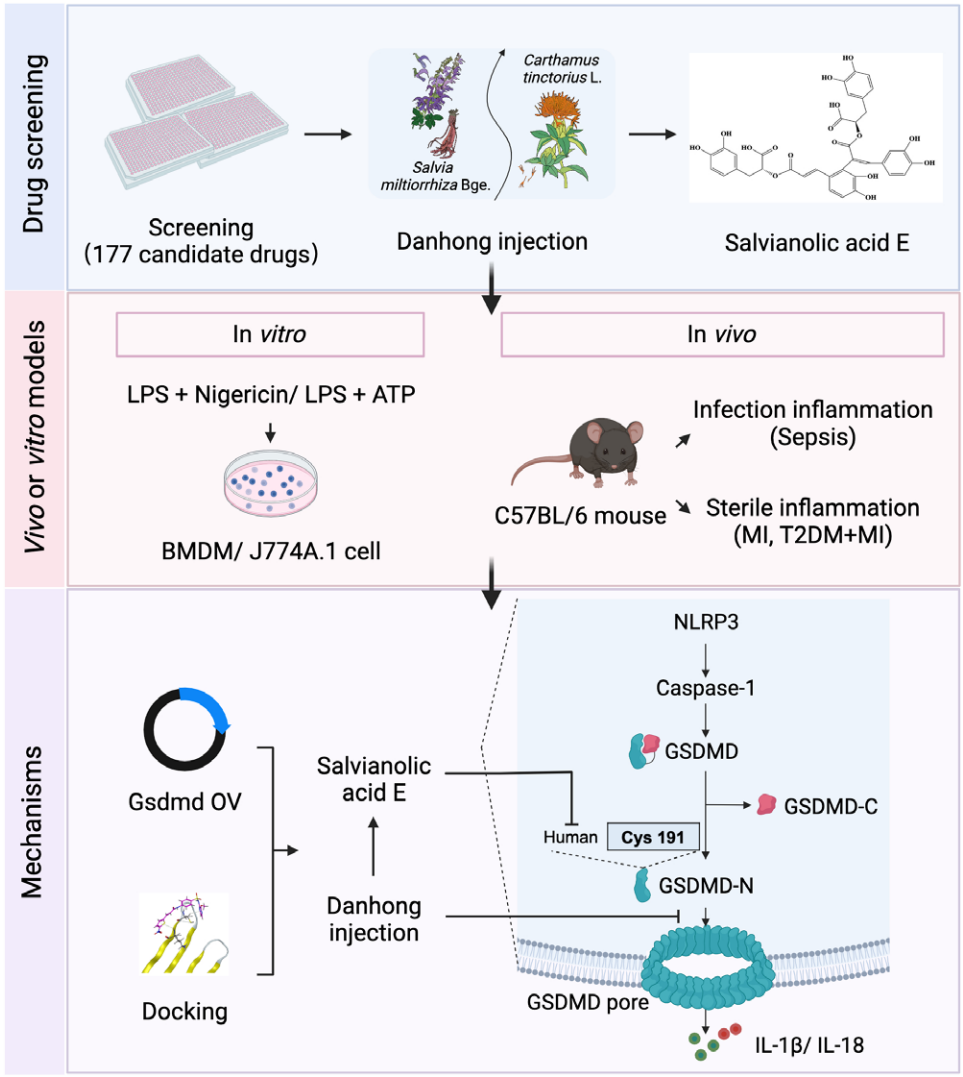

Figure 5. Research scheme: inhibition of pyroptosis by the traditional Chinese medicine formula danhong[38]. GSDMD: Gasdermin D; IL-1β: Interleukin-1β; LPS: Lipopolysaccharide; MI: Myocardial infarction; NLRP3: NOD-, LRR- and pyrin domain-containing protein 3; T2DM: Type 2 diabetes mellitus.

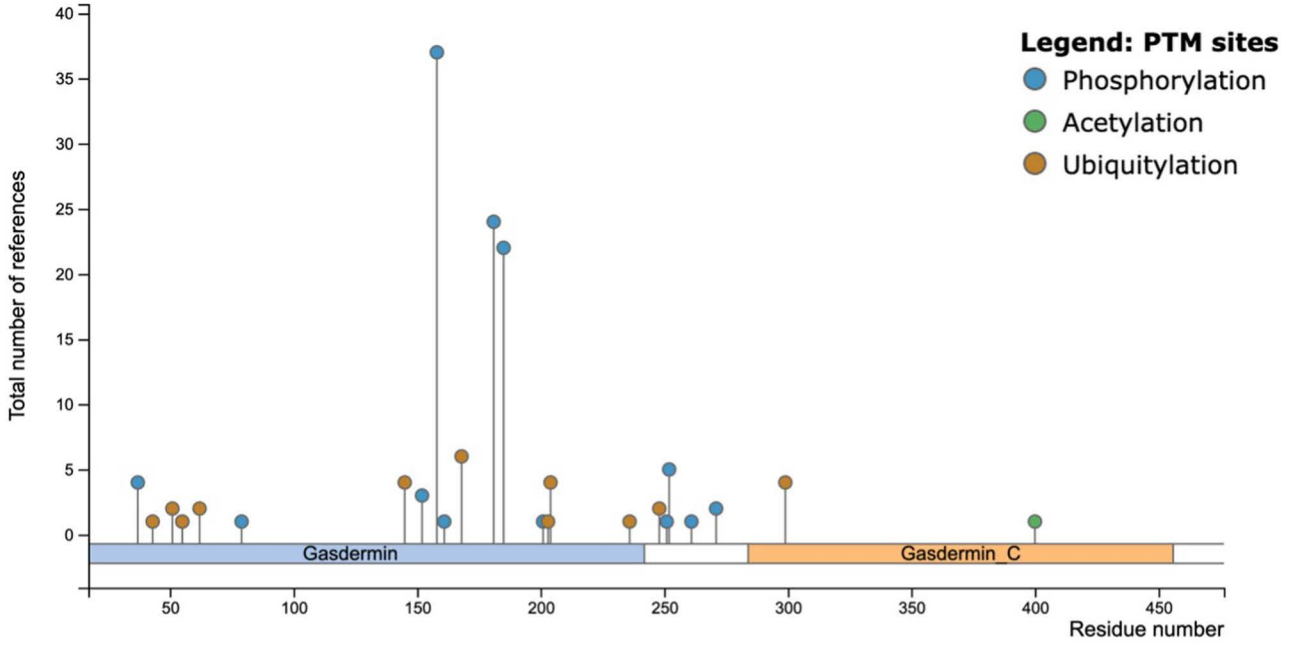

Figure 6. Post-translational modifications of GSDMD. A total of 11 phosphorylation sites, one acetylation site, and 12 ubiquitylation sites were detected in GSDMD. GSDMD: Gasdermin D; PTM: Post translational modification.

The Shigella ubiquitin ligase IpaH7.8 initiates ubiquitin-mediated degradation of human GSDMD by mediating the interaction of 15 lysine residues with GSDMD[60]. Proteomic analyses have revealed that protein phosphatase 1 (PP1) colocalizes with GSDMD and that phosphorylation at sites such as Thr213 can alter GSDMD pore formation[61]. Succinic acid may modify the Cys77 residue of GSDMD to influence the processing level of GSDMD[62–64]. ROS released by the lysosomal Ragulator-Rag complex can directly modify the Cys192 residue of GSDMD, subsequently affecting GSDMD oligomerization and pore formation, leading to pyroptotic cell death[65]. In addition to Cys192, other residues in human GSDMD, such as Cys38, Cys56, Cys268, and Cys467, play significant roles in GSDMD cleavage upon oxidative stress in macrophages[66].

Beyond these known modifications, an exploration at https://www.phosphosite.org revealed potential sites for phosphorylation, acetylation, and ubiquitination of human GSDMD, offering insights into the development of GSDMD inhibitors (Figure 6). Nevertheless, the identification of drugs targeting post-translational modifications necessitates further research. A comparative analysis of the efficacy of drugs targeting post-translational modifications of GSDMD and those targeting GSDMD warrants further investigation.

Promoting cell-specific pyroptosis inhibition

Studies have indicated that GSDMD expression varies across cell types and exhibits distinct functions during MI. In cardiomyocytes, pyroptosis negatively affects cardioprotection following MI. Conversely, neutrophil GSDMD in the heart can trigger a cardiac inflammatory response post-MI. While GSDMD inhibitors show potential for treating MI, the existing options are broad-spectrum GSDMD inhibitors that lack cellular specificity. Previous studies have indicated a vital role for GSDMD in neutrophils and cardiomyocytes during MI injury and repair. Single-cell sequencing revealed that GSDMD expression in MI involves various cell types. Nevertheless, the exact roles of these cells in cardiac remodeling and the function of specifically targeting GSDMD for cardiac repair remain unclear. Thus, the development of cell-specific GSDMD inhibitors to enhance the repair of MI injuries is promising.

A notable advancement in this field is the use of engineered T-cells targeting cardiac fibrosis, a pioneering therapy for cardiovascular diseases. This study initially identified fibroblast activation protein (FAP) as a target[67]. Engineered CAR-T cells, formulated based on FAP, employ lipid nanoparticles (LNPs) to deliver CAR mRNA-targeting T-cells (CD5). The results demonstrated significant potential for modulating activated cardiac fibroblast phenotypes[68,69]. The above research highlights the specific fibroblast subpopulations and macrophages involved in cardiac fibrosis, presenting promising targets for MI treatment[70]. Researchers have devised a macrophage shell with a polydopamine nucleus, which is a biodegradable nanomaterial, to create a structure that retains the natural migration capabilities of macrophages. This design aimed to target the infarcted myocardium, inhibit pyroptosis *via* the NLRP3/caspase-1 pathway, protect the myocardium, and minimize infarct size post-MI[71]. Such studies offer valuable insights for refining GSDMD drug design strategies for targeting specific cells.

Improving drug bioavailability through a responsive release system regulated by external energy fields

Utilizing ultrasound-assisted therapy, near-infrared light, magnetic field nano-drug release platforms, metal ions, and pH-responsive systems combined with small-molecule GSDMD inhibitors can effectively control drug release rates, enhance biological efficacy, and reduce side effects[72]. Specifically, developing sustained- and

controlled-release formulations for GSDMD inhibitors may further decrease adverse effects such as infections caused by excessive suppression of the inflammatory response.

Although the potential efficacy of GSDMD is notable, no drugs for GSDMD delivery have yet been developed. Drug-free tea polyphenol nanoparticles have been shown to improve septic injury by inhibiting GSDMD oligomerization. However, the efficacy of drug-loaded nanoformulations versus that of small-molecule drugs remains unexplored and warrants further investigation[73].

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Yang Chen and Yaozu Xiang conceived and supervised this study. Yujuan Li designed and drafted the manuscript. Jiayi Liang polished the language of the manuscript. All the authors contributed to the review, revision, and finalization of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

All data generated or analyzed during this study are included in the published article.

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