Am J Cardiovasc Dis 2025;15(6):477-508
www.AJCD.us /ISSN:2160-200X/AJCD0168800

Review Article

Pyroptosis in cardiovascular diseases: molecular mechanisms, pathological roles, and therapeutic implications

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Received September 15, 2025; Accepted December 8, 2025; Epub December 15, 2025; Published December 30, 2025

Abstract: Each year, cardiovascular diseases (CVDs) claim millions of lives worldwide, making them one of the biggest causes of deaths globally. More often than not, the inflammatory response is the principal disease mechanism behind the onset and development of CVDs. The study seeks to elucidate the mechanistic role of pyroptosis in CVDs and to summarize the current progress of potential therapeutic strategies targeting pyroptotic pathways. Pyroptosis is a form of PCD, which is inflammatory and mediated through an inflammasome and gasdermin complex. In the past few years, it has emerged as a crucial mechanism possibly explaining protracted inflammation and tissue damage. There is evidence suggesting that pyroptosis contributes to multiple CVDs. Indeed, it may induce disruption of endothelial barrier and plaque instability in atherosclerosis (AS). Also, it may aggravate ischemia-reperfusion injury (IRI) and reduce repair processes in case of myocardial infarction (MI). Finally, it may drive ventricular remodeling and functional impairment in heart failure (HF). Cell death and immune activation are further aggravated by a vicious cycle between pyroptosis and inflammation. Recent studies indicate that therapeutic interventions focused on key molecules, including the NLRP3 inflammasome, caspase-1, and gasdermin D (GSDMD), along with combination therapies consisting of antioxidants and inflammation inhibitors, exhibit significant cardioprotective effects. Additionally, one's diet, exercise and other lifestyle choices impact pyroptotic pathways and influence the risk of CVD. We should include pyroptosis as a form of cell death in future research only. Further, it would be necessary to identify reliable biomarkers for all of these forms of cell death for their therapeutic mechanisms.

Keywords: Pyroptosis, inflammation, atherosclerosis, myocardial infarction, heart failure, cardiovascular diseases

Introduction

CVDs are still one of the main causes of illness and death around the world. Threatens human health severely major subtypes like coronary artery disease (CAD), MI, HF, arrhythmias, along with risk factors such as hypertension, diabetes, obesity, and smoking. At the mechanistic level, inflammation is recognized as a crucial instigator in CVD initiation and progression. It occurs through the whole process from plaque formation and rupture to myocardial injury and ventricular remodeling. Elevated levels of inflammatory cytokines such as interleukin (IL)-1β, IL-18, and tumor necrosis factor-α (TNF-α) have been detected in various CVDs, directly inducing vascular endothelial dysfunction, macrophage infiltration, myocardial fibrosis, and electrophysiological abnormalities. Myocardial atrophy and contractile dysfunction are caused

https://doi.org/10.62347/MTTP3167

by IL-1β. NLRP3/IL-1β inhibition lessens sepsis damage. Thus, it may be a therapeutic target for septic cardiomyopathy (SIC) [1].

In recent years, gasdermin-mediated pore-forming programmed cell death, which is mediated by inflammatory caspases (caspase-1, caspase-4/5/11) and marked with inflammation has gained similar attention. Unlike apoptosis and necrosis, pyroptosis is a type of programmed cell death characterized by cell lysis with the concomitant release of IL-1β, IL-18 and other pro-inflammatory mediators, resulting in intense amplification of inflammatory processes. Pyroptosis has been implicated in various CVD pathologies. Firstly, macrophage pyroptosis is activated by cholesterol crystals and this subsequently destabilizes the atherosclerotic plaque. Secondly, under the stimulation of TNF-α, salvianolic acid B (SAB) stops the production of reactive oxygen species (ROS) and thereby inhibits inflammation by inhibiting the NF-κB/NLRP3 pathway [2]; hypoxia-inducible factor-1α (HIF-1α) - induced upregulation of the lncRNA TUG1 exacerbates MI by promoting mitochondrial dysfunction and cardiomyocyte pyroptosis through FUS binding [3]; in addition, IRI and DUOX1-derived oxidative stress can trigger pyroptosis in cardiomyocytes and immune cells, accelerating the progression of HF [4, 5]. Together, these data indicate pyroptosis is a downstream effector of inflammation and amplifies the injury in CVD.

Significantly, a self-inducing 'vicious cycle' is formed between pyroptosis and inflammation. Pyroptotic cells release IL-1β, IL-18, and DAMPs that induce inflammasomes in neighbouring cells. This, in turn, amplifies cell death and inflammation that drives the disease further. Breaking this cycle of 'pyroptosis-inflammation' would prove to be a great target. Inhibitors targeting the NLRP3 inflammasome, caspase-1, or GSDMD has been shown to be effective in preclinical and first-in-human studies. For instance, GZTLT is said to reduce vascular inflammation and macrophage pyroptosis through Piezo1NLRP3 signaling pathway, and thus delay AS development [6].

CVD represents one of the most important public health challenges worldwide, with inflammation playing a key role in the pathophysiology of CVD. Pyroptosis shows novel inflammatory cell death, and it is becoming increasingly accepted in AS, MI, and HF. By revealing the connection between pyroptosis, inflammation and CVDs, we can potentially provide a deeper understanding of disease mechanisms. This can later help in the discovery of novel biomarkers and therapeutic targets. As a result, the mechanistic involvement of pyroptosis and its inflammation in CVD is greatly important scientifically and clinically.

Apart from pyroptosis, apoptosis is another important type of programmed cell death in CVDs. It affects processes including cardiomyocyte loss, plaque instability and adverse ventricular remodeling. The mitochondrial intrinsic and death receptor extrinsic pathways initiate apoptosis that targets the apoptosis process by disassembly through caspase-3. In the dilated cardiomyopathy model, this process is favorably improved with the depletion of cells and structural remodeling. This supports left ventricular remodeling and results in worsened HF [7]. In response to DOXO-induced oxidative stress, mobilization of intracellular Ca^{2+}, and activation of immune signaling, there is marked upregulation of pro-inflammatory IL-1β, IL-6, and TNF-α alongside the activation of NLRP3 and MyD88 inflammatory pathways. Endothelial and cardiomyocyte injury caused by these events maintains a chronic inflammatory microenvironment that drives the development of AS, myocardial fibrosis, and HF [8]. Although partial benefit has been observed with statins, RAAS inhibitors, antiplatelet treatment, and novel anti-inflammatory approaches, there still remains an unrelenting inflammatory response and cell death in clinical practice, signaling for a better understanding of the apoptotic and inflammation mechanisms which may help develop more targeted intervention strategies.

Biomarkers of pyroptosis and their detection

Roles of iron metabolism-related enzymes and their biomarkers

A major role in ferroptosis and CVD is played by dysregulation of iron. The wrong regulation of enzymes that handle iron, as well as the molecules involved in signaling, can worsen inflammation and hurt the heart. They may also be markers of disease. Ferroptosis is a type of cell death that is caused by lipid peroxidation which is iron dependent. Oxidative stress levels and

the fate and function of cells are dictated by changes in the activities of some enzymes and regulators of iron metabolism.

In IRI, FUNDC2 sustains mitochondrial glutathione (mitoGSH) levels, inhibiting ferroptosis, thereby indicating that FUNDC2 could work as a measurable inhibitor of ferroptosis [9]. Moreover, iron overload and stimulation of ferroptosis, as well as local inflammation, result from heme iron released by macrophages that phagocytose extravasated erythrocytes in atherosclerotic plaques. This implies that heme iron and its degradation products could be potential risk biomarkers of plaque instability [10].

Regulatory factors regulate ferroptosis at the metabolic and Signaling levels via iron metabolism enzymes. CircRNA FEACR, for instance, activates the NAMPT-Sirt1-FOXO1-FTH1 signaling axis to upregulate ferritin heavy chain 1 (FTH1) expression, limiting ferroptosis and preserving cardiac function [11]. Plant-derived alkaloid solanine (LQF) inhibits ferroptosis via activating Nrf2/GPX4 pathway and downregulating SLC7A11 and HO-1, while monitoring GPX4 and SLC7A11 levels can reflect the effect of LQF [12]. Raising NAD^+ levels activates the SIRT-PINK1 and SIRT1-GPX4 pathways, promoting mitophagy while inhibiting ferroptosis, indicating that NAD^+ levels and deacetylase activity can be used as biomarkers [13]. Otherwise, the RNA methyltransferase METTL3 inhibits SLC7A11 and FSP1 expression. METTL3 promotes vascular smooth muscle cell (VSMCs) ferroptosis. Moreover, epigenetic modifiers serve as predictive markers [14].

Ubiquitination also affects the stability of enzymes involved in iron metabolism and their biomarkers. OTUD5 inhibits ferroptosis by deubiquitinating GPX4 and stabilizing it, reversing 4-HNE-induced ferroptosis and IRI to indicating the GPX4 ubiquitination status meaningfully [15]. Likewise, USP38 associates with iron regulatory protein 2 (IRP2) and takes away its K48-linked polyubiquitin chains. This causes iron overload and the accumulation of lipid peroxidation, which ultimately trigger ferroptosis. As a result, USP38 and IRP2 activity may be useful biomarkers of iron burden and ferroptotic risk [16].

Various forms of programmed cell death such as pyroptosis are induced in cardiomyocytes by ROS. The presence of excess iron is a process linked to dysregulation of iron metabolism, affecting cell death and CVDs. The specific mechanisms are illustrated in **Figure 1**. In short, core iron metabolism enzymes including GPX4, SLC7A11, FTH1, HO-1, and IRP2 are critical in ferroptosis and inflammation-related cardiovascular injury [17]. Regulators such as FUNDC2, circRNA FEACR, NAD^+, and METTL3 can control the expression or stability of these enzymes, and indirectly participate in ferroptotic processes. Detection of these molecules reflects ferroptotic status while also enabling investigation of the relationship between pyroptosis, inflammation and CVD which help develop new therapeutic intervention strategies.

Expression analysis of pyroptosis-related genes

Pyroptosis as well as ferroptosis jointly contribute to two newly recognized forms of programmed cell death in inflammation and metabolic disorder in CVDs lead to tissue injury. The activation of genes that encode the gasdermin family, caspases, and components of inflammasomes is sufficient to drive pyroptosis. GSDMD causes pore formation in the membrane that lead to cell lysis when cleaved by either caspase-1. Alternatively, gasdermin E (GSDME) activates caspase-3 which converts apoptosis into pyroptosis for amplifying the inflammatory response. In conditions like AS, MI, and HF, NLRP3, AIM2, and NLRC4 are persistently upregulated. These structures activate downstream caspase-1, which cleaves GSDMD and causes excessive maturation and expression of IL-1β and IL-18, leading to inflammation of the vascular wall and fibrosis of the myocardium.

Ferroptosis is characterized by iron accumulation and lipid peroxidation. Importantly, the critical regulators GPX4, SLC7A11, and ACSL4 are essential for myocardial IRI and infarction. OTUD5 prevents dietary GPX4 degradation to combat ferroptosis and myocardial injury [15]. Bioactive agents and herbal constituents interfere with ferroptosis by three pathways-an Nrf2/GPX4 pathway, a System xc-/GPX4 pathway and a HIF-1α/SLC7A11/GPX4 pathway. Solanine (LQF), naringenin (NAR), galangin

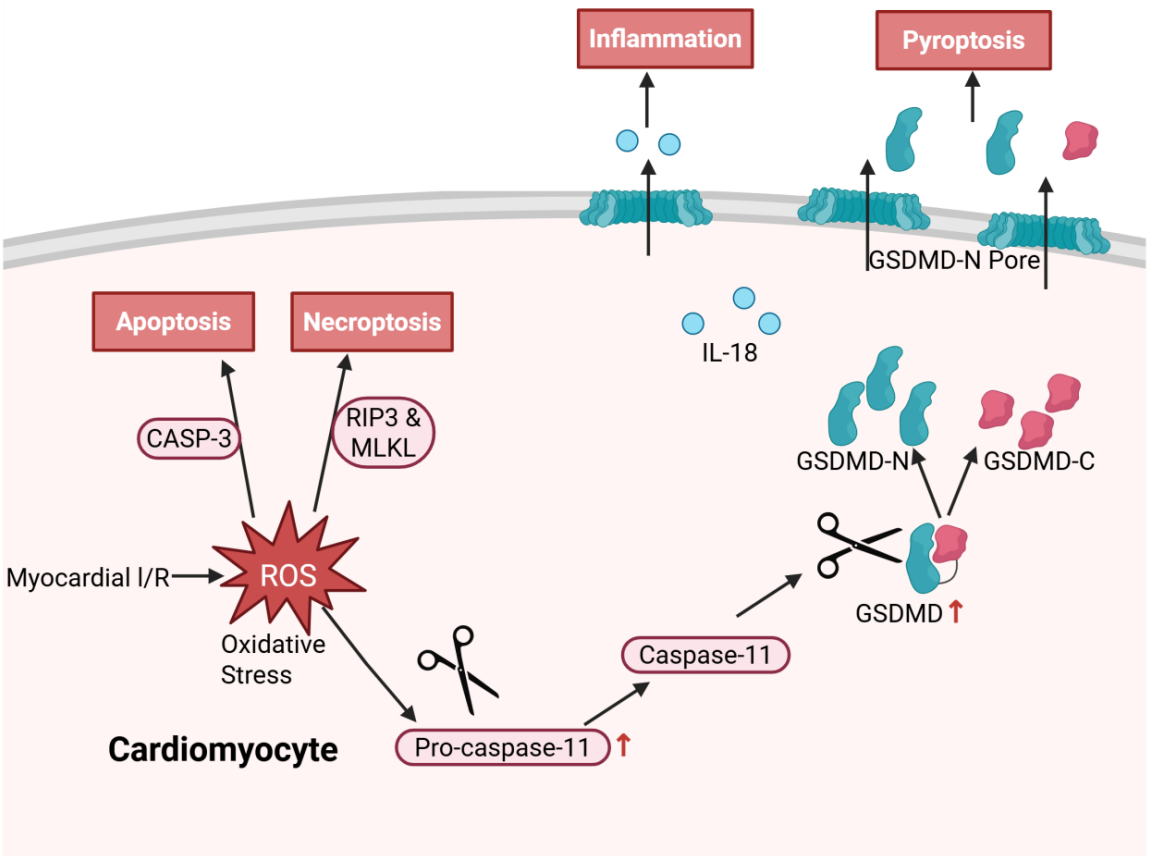

Figure 1. The relationship between ROS-mediated cell death pathways and iron metabolism imbalance in myocardial IRI: during myocardial IRI, ROS serve as triggers for the cell death response that occurs in various programmed cell death pathways, especially pyroptosis, as shown in the figure. Oxygen radicals activate the NLRP3 inflammasome, which in turn activates GSDMD by cleaving caspase-1 to form membrane pores and release IL-1β and IL-18, contributing to myocardial injury and inflammation. When there is a disruption in iron metabolism, it leads to excessive iron loading (high expression of TFR1) and downregulation of iron storage proteins (FTH1, FTL), thereby increasing pyroptosis in cardiomyocytes and accelerating CVDs.

(Gal), danshensu (DS), and hydroxysafflor yellow A (HSYA) have been shown to attenuate myocardial injury [12, 18-21]. Quercetin (QUE) can inhibit ferroptosis via inhibiting SIRT1/p53/SLC7A11 signaling [22], epigallocatechin gallate (EGCG) regulates miR-450b-5p/ACSL4 signaling pathway [23], while Parkin exerts an important protective function through promoting the ubiquitination of ACSL4 [24]. Multicomponent traditional Chinese medicine (TCM) formula LGZGD can inhibit lipid peroxidation and ROS accumulation through upregulating PLIN5 and GPX4 [25]. PV can downregulate NRF2/GPX4 signaling pathway against oxidative damage [26], and SAB enhances the stability of GPX4 and inhibits ROS and apoptosis-related signaling pathways to preserve myocardial function [27].

Expressions of pyroptosis and ferroptosis genes show the crosstalk of inflammatory and metabolism-mediated cell death in CVDs. The gasdermin family, caspase effectors, inflammasome components, and ferroptosis regulators, which include GPX4, SLC7A11, and ACSL4, may be examined at multiple levels to build up a complete molecular picture. It can help us explain how cardiovascular injury occurs and can help target therapies for these injuries.

Mechanisms of inflammation and its impact on cardiovascular health

Cardiovascular effects of inflammatory cytokines

The increase and progression of CVDs are significantly affected by inflammatory cytokines.

IL-6 and TNF-α are the most representative cytokines. IL-6 causes inflammatory reactions and acts through three pathways: JAK/STAT3, MAPK, and PI3K/Akt signaling pathways. Higher amounts of IL-6 not only enhance the liver's production of C-reactive protein (CRP), which can worsen inflammation in the endothelium and damage blood vessels. They also enhance adhesion and infiltration of monocytes and cause migration and proliferation of smooth muscle cells. Finally, it can enhance the formation of atherosclerotic plaques. In HF, IL-6 promotes myocardial hypertrophy and fibrosis, leading to altered calcium homeostasis and energy metabolism, which subsequently impair cardiac function. Mettl14 is capable of aggravating AS by inhibiting macrophage inflammation via the NF-κB/IL-6 pathway [28]; CCN3 levels correlate positively with CAD and IL-6/TNF-α, showing its close association with systemic inflammation [29]; High levels of IL-36 in the serum correlate TNF-α and IL-6 levels with arterial clotting in CAD, causing oxidative stress [30]. The inflammatory cytokine IL-6 may be a potential biomarker for high-risk acute coronary syndrome (ACS) patients, as its levels correlate with disease severity [31]. The prognostic role of IL-6 is further confirmed in high-altitude AMI-VSR patients [32, 33]. In addition, blocking IL-6 signaling can reduce cardiovascular events, with therapeutic efficacy strongly related to CRP reduction [34]. Anti-inflammatory therapy targeting the NLRP3/IL-1β/IL-6/CRP axis has shown favorable safety and efficacy in the secondary prevention of CAD [35].

According to a study, TNF-α is another major pro-inflammatory cytokine. Its receptors TNFR1 and TNFR2 signal to activate the NF-κB, MAPK, and apoptotic pathways. In fact, TNF-α causes a pro-inflammatory and pro-apoptotic effect in AS, IRI, and HF. It has been found in clinical studies that high levels of TNF-α and IL-6 predict recurrent atrial arrhythmias in patients following the implantation of a coronary stent due to a disturbed balance between pro-inflammatory and anti-inflammatory cytokines [36]. Myocardial tissues in HF patients show higher expression of ZBP1, RIPK3, NLRP3, IL-1β, and IL-6, which relate chronic inflammation to progressive cardiac dysfunctions [37]. In addition, QT interval prolongation has been linked to increased IL-6 trans-signaling [38]; Chronic overexpression caused cardiac sympathetic remodeling via STAT3/G protein signaling and enhanced the rate of arrhythmogenicity [39]. The expression of IL-6 and IL-33, as well as subsequent vascular calcification, is stimulated by enzymatically modified low-density lipoprotein (eLDL) in AS [40]. Cadherin-11 causes cardiac fibroblasts to secrete IL-6, a consequence that exacerbates myocardial remodeling in pressure-overload-induced ventricular hypertrophy [41].

IL-6 and TNF-α promote CVDs by amplifying inflammatory cascades, aggravating endothelial injury, modulating immune cells, and altering cardiac electrophysiological stability [42]. CVD-related inflammation biomarkers are not only important but also potential therapeutic targets that can provide insight into the relationship between inflammation and cardiovascular events, helping to personalize treatment plans.

The relationship between inflammation and endothelial dysfunction

The vascular endothelium is an essential barrier to maintain cardiovascular homeostasis. The dysfunction of the vascular endothelium is an early event in the development of AS, HF and IRI. This process is centrally regulated by inflammation. Cytokines that are pro-inflammatory such as IL-6, TNF-α, and IL-1β increase the adhesion molecules such as VCAM-1, ICAM-1, and E-selectin that can enhance the adhesion and transendothelial migration of leukocytes. The endothelial barrier collapses, vascular permeability rises, and the formation of atherosclerotic plaques occurs, worsening vascular disease. Cytokines simultaneously suppress the expression or activity of endothelial nitric oxide synthase (eNOS) while abnormally inducing inducible nitric oxide synthase (iNOS), causing impaired production of nitric oxide (NO) and excess accumulation of ROS. These species of ROS not only deplete peroxynitrite but also react with peroxynitrite, which causes damage to proteins and DNA. Additionally, it interferes with the functioning of endothelial cells by activating apoptotic or pyroptotic pathways.

BACH1 plays an important role in AS as it is related to proinflammatory and adhesive molecules. It was found that the BACH1-YAP axis collateralize and link with the proinflammatory genes and adhesion molecule growth factor genes [43]. PHACTR1 deficiency significantly

reduces endothelial activation caused by disturbed flow. On the other hand, PHACTR1 enhances inflammatory responses and reduces NO bioavailability, contributing to endothelial dysfunction [44, 45]. In hypertension models, deleting NLRP3 effectively lowers blood pressure and restores p-eNOS-Ser1177 expression. These results indicate a contribution of inflammasomes to Ang II-induced endothelial damage [46].

Based on clinical and experimental observations, inflammation and endothelial dysfunction are closely linked. The raised levels of IL-6 and TNF-α are highly correlated with impaired flow-mediated dilation, and patients suffering from ACS or HF exhibit significantly reduced endothelium-dependent vasodilation. Recent investigations showed that Ang II leads to endothelial dysfunction in hypertension through YAP nuclear translocation and Gal-3 upregulation, while YAP targeting ameliorates inflammation and slows AS progression [47, 48]. Taken together, the data indicate that inflammatory cytokines create a pathological milieu of endothelial injury by interacting with molecular networks, including BACH1-YAP, PHACTR1, and NLRP3, leading to vascular dysfunction and CVD.

The impact of inflammation on cardiac remodeling

The development of CVDs involves the remodeling of the cardiac tissues. An important regulator of remodeling is inflammation. Following acute myocardial injury, a large number of inflammatory cells infiltrate the area of injury and release largely overproduced proinflammatory cytokines, namely TNF-α, IL-1β, IL-6. Mediators trigger the NF-κB and MAPK signaling pathways. They cause heart cells to undergo apoptosis or necrosis. Imbalance of oxidative stress and calcium homeostasis also occur during this process. This further worsens heart function [49]. The heightened production of ROS and mitochondrial dysfunction causes metabolic abnormalities in cardiomyocytes. The protein IL-34 leads cells to inflammation, aggravating the situation post-stroke and heart attack [50]. In contrast, ZBP1 functions as an endogenous barrier to inflammation induced by mitochondrial DNA (mtDNA), while also offering protection from heart remodeling [37]. Hematopoietic cells secrete IL-6 and TNF-α, which signal at different levels and affect the proliferation of cardiac fibroblasts and activation of cardiac macrophages. In addition, IL-6 signaling drives the production of cardiac myofibroblasts. The TGF-β/Smad3 signaling cascade is triggered by the S1P/S1PR3 pathway and propels cardiac fibrosis and remodeling linked with inflammation [51]. Studies using CD11b-deficient mice show that CD11b deficiency limits Ang II-induced macrophage adhesion, M1 polarization, myocardial hypertrophy, and myocardial fibrosis [52].

At the molecular level, miR-30d accumulates selectively in cardiomyocytes under hypoxia stress and targeting MAP4K4 controls apoptosis. During acute phases, miR-30d suppresses fibroblast activation and confers protection from remodeling via paracrine signaling [53]. Following a MI, the primary producers of IL-6 are activated fibroblasts and T cell-derived adenosine regulates their production [54]. CaMKIIδ inhibition of natural products augments inflammation through NF-κB and NLRP3 in TAC and Ang II models [55]. YAP and TAZ play a role in driving inflammation and fibrosis through IL-6 and repulsive Arg1-related reparative pathway. Their deficiency improves cardiac function post-infarction [56]. In mice with HFpEF, deleting CXCR4 in myeloid cells reduced inflammatory activity and macrophage infiltration. Additionally, it reduces hardening and improves heart muscle relaxation [57]. The lack of NLRC5 makes IL-6 secreted more, resulting in cardiomyocyte hypertrophy and activated fibroblast [58]. Evidence shows that inhibition of IFI-16/IFI-204 significantly dampens the release of inflammatory cytokines and cardiac remodeling after infarction [59].

It is remarkable that bioactive substances from natural origin and certain molecular targets may have therapeutic power to influence the inflammatory-remodeling axis. Ginsenoside Rg1 has the ability to prevent the polarization of M1 macrophages. It may be able to reduce cardiac fibrosis while preserving structure and function [60]. On the contrary, deficiency of Neo1 worsens inflammation and left ventricular remodeling by the JAK1-STAT1 pathway [61]. CVDs are associated with IL-1β, IL-18 and other cytokines. The local inflammatory responses are generated by them and cause, instead of

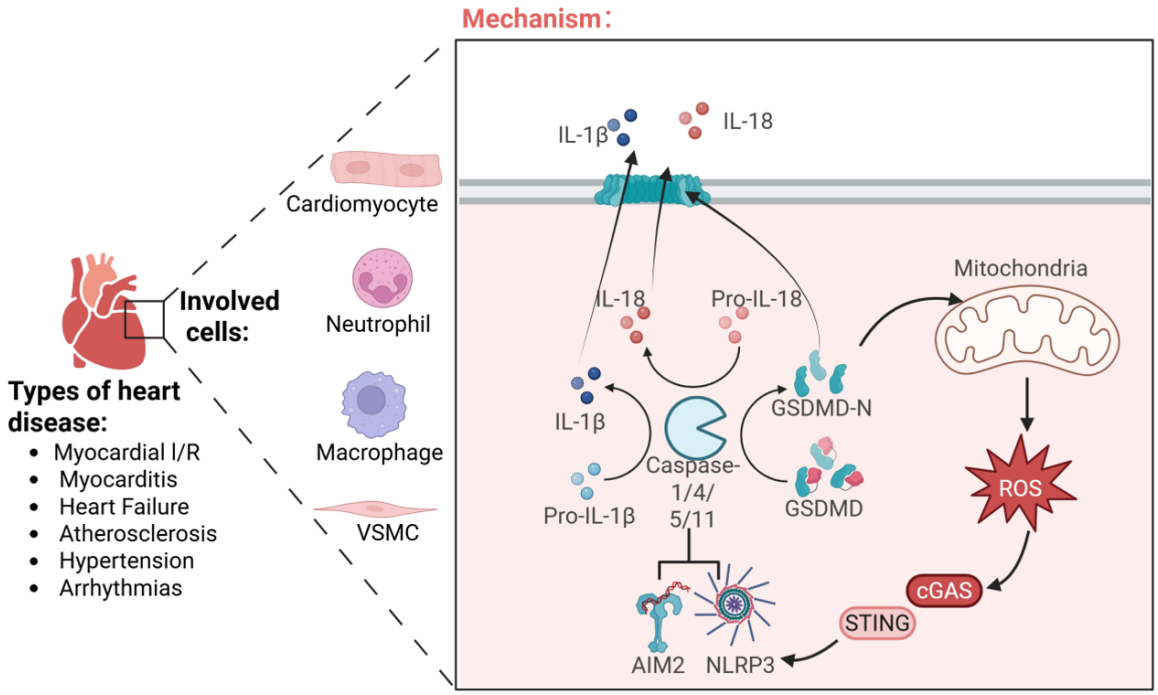

Figure 2. The interaction mechanism between pyroptosis and inflammation in CVDs: this figure depicts how pyroptosis interacts with inflammation in CVDs. Pyroptosis is activated by inflammasomes (NLRP3, AIM2), whereby cleavage of GSDMD by Caspase-1/4/5/11 occurs, mediating the creation of membrane pores and the release of pro-inflammatory cytokines (IL-1β and IL-18), intensifying local and systemic inflammatory responses. The cGAS-STING pathway and mitochondrial pathways, further activated by ROS, amplify the inflammation associated with CVD and also drive cell death.

the release of pyroptotic cells, the stimulation of pathways such as the NLRP3-inflammasome which may give rise to tissue damage. The cycle whereby pyroptosis causes inflammation, and subsequently, inflammation causes further pyroptosis, predicts injury in the heart and blood vessels. According to the mechanisms shown in **Figure 2**, inflammation has a 'double-edged sword' effect on cardiac remodeling. Moderate acute inflammation facilitates necrotic cell clearance and angiogenesis. Nonetheless, prolonged or excessive inflammation causes more loss of cardiomyocytes, deposition of fibrosis and loss of function. By deciphering how inflammation alters the heart and developing drugs to specifically block molecular switches or groups of immune cells, we may improve heart health.

The relationship between pyroptosis and CVDs

The role of pyroptosis in AS

Being the main pathological basis implicated in CVDs, a hallmark of inflammation is evident in the initiation as well as progression of CVDs. In the last few years, accumulating evidence has demonstrated that an inflammasome-dependent programmed cell death, pyroptosis accelerates the development of AS. The cleavage of gasdermin D is facilitated by caspase-1 through the classical process or caspase-4/5/11 through the non-classical process. The N-terminus of GSDMD builds pores on the plasma membrane to lyse the cell and release proinflammatory cytokines like IL-1β and IL-18, which intensify local inflammation and hasten plaque destabilisation. At the early stage of AS, pyroptosis of endothelial cells leads to injury of vascular barrier, increased permeability, and upregulation of adhesion molecules, thereby promoting monocyte adhesion and infiltration. As an illustration, NEAT1, a lncRNA, can activate NLRP3 transcription through binding to KLF4, thus resulting in endothelial pyroptosis. Exercise intervention effectively inhibits this process and prevents AS progression [62]. In addition, the ROS/NLRP3 signaling axis mediates the effect of oxidized low-density lipoprotein (Ox-LDL), hyperglyce-

mia, nicotine, and inflammatory extracellular vesicles (EVs) to promote endothelial pyroptosis, further aggravating lesions [63-65].

As AS reaches the intermediate and late stage, macrophage pyroptosis becomes more pronounced, with macrophages laden with lipids becoming foam cells, and their pyroptosis not only releases a large number of inflammatory mediators but also releases intracellular lipids and necrotic material into the plaque core, thereby enlarging the necrotic core and significantly enhancing plaque vulnerability. Through endoplasmic reticulum (ER) stress, ER-mitochondria coupling damage, and calcium imbalance, homocysteine (Hcy) speeds up the progression of AS by inducing macrophage pyroptosis [66, 67]. In contrast, the pharmacological intervention of GZTLT can suppress macrophage pyroptosis through the Piezo1/NLRP3 pathway, thus delaying plaque formation and progression [6]. The increased production of chemokines (such as HCC-1) augments the recruitment and infiltration of monocytes. Consequently, this recruits pro-inflammatory M1 macrophages and promotes pyroptosis. The net result is exacerbation of the AS burden. Notably, HCC-1 may serve as an early biomarker reflecting the severity of AS [68]. Moreover, in response to inflammatory cytokines and metabolic stress, pyroptosis of VSMCs results in thinning of the fibrous cap and less collagen deposition, which causes plaque destabilization.

The theory is well-supported by both clinical and experimental evidence. High serum levels of IL-1β are linked to plaque instability in patients with AS, while deletion of NLRP3 and caspase-1 in murine models significantly reduces plaque burden and instability. According to pharmacology studies, statins, colchicine, and the new NLRP3 inhibitors have at least partially anti-atherosclerotic action through pyroptosis suppression [69]. As such, pyroptosis is an important pathogenic mechanism of AS, which plays a vital role in the initiation and progression of disease by regulating the inflammation and death process of endothelial cells, macrophages, and VSMC. The specific mechanisms and Signaling pathways of pyroptosis in the initiation and progression of AS are summarized in **Table 1**. Future study should clarify the molecular mechanism of the Inflammasome-pyroptosis axis in detail, and targeted inhibitors and interventions should be further studied to provide new theoretical basis and therapeutic strategies for precision diagnosis and individualized treatment of AS.

Mechanisms of pyroptosis in HF

HF is a final state of a number of CVDs, which is characterized pathologically by ventricular remodeling and impaired contractile function. According to recent evidence, pyroptosis plays a critical role in heart failure initiation and progression. Pyroptosis involves cell death that is dependent on the inflammasome. The hallmark caspases involved are caspase-1 or caspases-4/5/11, which then lead to the cleavage of GSDMD. This ultimately leads to the formation of pores in the cell membrane, which results in rupture of the cell. This process results in the secretion of proinflammatory cytokines like IL-1β and IL-18, which further amplify inflammatory processes and contribute to the acceleration of myocardial injury and functional deterioration. A consistent rise in oxidative stress and pyroptosis-related proteins can negatively impact heart contraction. Toll-like receptor 4 (TLR4) is a significant biomarker and potential therapeutic target in doxorubicin (DOX)-induced HF [70].

At the onset of HF, modulating risk signals activate the TLR-NLRP3-NF-κB axis to cause cardiomyocyte pyroptosis, which includes IRI, mechanical overload, and accumulation of ROS. As a result, inflammatory mediators are released, and immune cells are recruited. This leads to a vicious cycle of 'cell death-inflammation amplification-myocardial injury'. Concurrently, DUOX1-derived genotoxic stress drives HF progression through the interplay of oxidative stress and pyroptotic pathways [4]. Echinacoside (ECH) inhibits the expression of NOX2 and NOX4, decreases ROS levels, and blocks the NADPH/ROS/ER stress signaling pathway. Thus significantly suppressing cardiomyocyte pyroptosis and improving cardiac function both in vivo and in vitro [71].

In addition to cardiomyocytes, HF pathogenesis is also critically influenced by the pyroptosis of fibroblasts and ECs. Myocardial fibrosis and ventricular compliance reduction are caused by pyroptosis-induced fibroblast-ECM metabolism alteration. The microvascular balance is

Table 1. Mechanisms and signaling pathways of pyroptosis in the initiation and progression of AS

Study Subjects/Models	Key Inducers	Pyroptosis-Related Signaling Pathways	Major Cell Types	Pathological Implications	Potential Therapeutic Targets	References
Human umbilical vein endothelial cells (HUVECs)	Ox-LDL	NLRP3/caspase-1 pathway	Vascular endothelial cells	Endothelial injury and pyroptosis	SIRT1/Nrf2 signaling axis	[116]
Hyperlipidemic apolipoprotein E-/- (ApoE-/-) mice; human/mouse macrophages, endothelial cells, and smooth muscle cells	HFD; in vivo activation of the NLRP3 inflammasome	NLRP3 inflammasome activation → GSDMD -mediated pyroptosis → IL-1β release	Macrophages, endothelial cells, and smooth muscle cells	Atherosclerotic lesion formation; expansion of necrotic core regions; inflammatory response	Disulfiram (a GsdmD inhibitor)	[117]
ApoE-/- mice treated with MCC950	NLRP3 activation	NLRP3 inhibition attenuates pyroptosis	Macrophages	Reduced plaque burden	MCC950 (an NLRP3 inhibitor)	[118]
ApoE-/- mice treated with VX-765	Caspase-1 activation	Caspase-1 inhibition reduces pyroptosis	Macrophages	Attenuation of vascular lesions	VX-765 (a Caspase-1 inhibitor)	[119]
THP-1-derived macrophages (in vitro)/ ApoE-/- mice (in vivo)	Elevated Hcy	NOX-ROS-NLRP3 inflammasome pathway	Macrophages	Acceleration of AS	Lipid rafts; acid sphingomyelinase (ASM)	[67]
THP-1-derived macrophages	Ox-LDL	Autophagy blockade enhances pyroptosis via the p62/Nrf2/ARE axis	Macrophages	Increased foam cell formation and cell death	Promotion of autophagy/inhibition of the p62/Nrf2 pathway	[120]
Human monocyte-derived differentiation model	Ox-LDL; Ox-LDL combined with PAG; Ox-LDL combined with NaHS; Ox-LDL combined with DTT	Activation and cleavage of NLRP3, caspase-1, and GSDMD	Macrophages	Vascular inflammation and AS	Caspase-1 S-sulfhydration	[121]
Clinical cohorts and NEAT1$^{-/-}$ mice	NEAT1 overexpression/ physical inactivity	METTL14 (m^6A modification) → NEAT1 → KLF4 → NLRP3	Endothelial cells	AS	NEAT1; METTL14	[62]
Mouse and cell experiments (CTSB study)	CTSB upregulation	CTSB → NF-κB → NLRP3	VSMCs	Enhanced inflammation and pyroptosis	Inhibition of CTSB/ NF-κB	[122]
ApoE$^{-/-}$ mouse model/THP-1-derived macrophages	Elevated Hcy	Endoplasmic reticulum stress → calcium dysregulation → mitochondrial dysfunction → ROS → NLRP3 inflammasome → Caspase-1	Macrophages	Enlargement of atherosclerotic plaques and increased secretion of inflammatory cytokines	Caspase-1 inhibitors, 4PBA, BAPTA, 2-APB	[66]
ApoE$^{-/-}$ mice (HFD model)	HFD-induced AS	NLRP3 inflammasome → Caspase-1	Macrophages	Atherosclerotic plaque formation	Polydatin, MCC950	[123]
HUVECs; ApoE-/- mice	Ox-LDL; HFD	miR-302c-3p directly targets and suppresses NLRP3 expression	Endothelial cells	Reduced endothelial pyroptosis; alleviated AS	miR-302c-3p mimics; agomir	[124]
ApoE-/- mice and HAECs (human aortic endothelial cells(HAECs))	HFD and Ox-LDL	Keap1/Nrf2 and NLRP3 pathways	HAECs	Atherosclerotic plaque formation	Nrf2 transcription factor	[125]

ApoE$^{-/-}$ mice (HFD)/in vitro co-culture system	HFD; iron overload (ferric ammonium citrate); Ox-LDL	M1 microglial phenotype → neuronal pyroptosis	Microglia and neurons	Brain injury and learning-memory impairment	Quercetin	[126]
ApoE$^{-/-}$ mouse model; patient serum and tissue samples; in vitro cell model	HCC-1 overexpression	HCC-1 → inflammation and pyroptosis	Endothelial cells and macrophages	Reduced plaque stability and accelerated atherosclerotic burden	HCC-1	[68]
ApoE-/- mice fed a HFD	HFD (12 weeks)	GI-Y2 directly interacts with the Arg10 residue of GSDMD, reducing membrane binding of GSDMD-N	Macrophages	Inhibition of pyroptosis and macrophage infiltration; reduced atherosclerotic plaque formation	GI-Y2 (a small-molecule GSDMD inhibitor); macrophage membrane-encapsulated GI-Y2 nanoparticles	[127]
HFD mice/in vitro (cyclodextrin study)	HFD/cholesterol crystals	TLR4/NF-κB → NLRP3 → GSDMD	Macrophages/ smooth muscle cells	Plaque formation associated with pyroptosis	Cyclodextrin reduces cholesterol crystals	[128]
ApoE-/- mice and Gsdme-/-/ApoE-/- mice (in vivo); HUVECs (human umbilical vein endothelial cells) (in vitro)	Western diet (WD); Ox-LDL	GSDME activation → mitochondrial membrane localization causing mitochondrial damage → mtDNA release into the cytoplasm → mtDNA acts as endogenous DNA to activate the STING pathway → induction of inflammatory response	Endothelial cells	Promotes atherosclerotic plaque formation; increases macrophage infiltration (F4/80^{+}); upregulates vascular inflammatory markers (ICAM-1, VCAM-1, MCP-1); enhances monocyte-endothelial adhesion	Inhibition of GSDME; inhibition of the STING pathway	[129]
ApoE-/- and Ldlr-/- mice	LPS and cholesterol crystals	NLRP3 inflammasome activation → caspase-1 → IL-1β	Bone marrow-derived macrophages and dendritic cells	Progression of atherosclerotic lesions (increased maximal stenosis, mean plaque size, and plaque volume); increased macrophage content in plaques; elevated VCAM-1 and ICAM-1 mRNA expression	MCC950 (a specific NLRP3 inflammasome inhibitor)	[130]
HUVECs (in vitro model)	Ox-LDL	NLRP3/caspase-1/IL-1β	Endothelial cells	Mitochondrial dysfunction and oxidative stress	Melatonin/TET2/ UQCRC1	[131]
J774A.1 rho0 macrophages	Ox-LDL	Reduced activation of NLRP3 inflammasome/caspase-1	Macrophages	Attenuated pyroptosis; potential increase in plaque stability	mtDNA, ROS production	[132]
RAW264.7/THP-1 cell lines	Ox-LDL/LPS stimulation	NLRP3/caspase-1 pathway	Macrophages	Foam cell formation and plaque instability	TLR4/NF-κB and NLRP3 inflammasome pathways	[133]
Jak2VF mice and chimeric mice	Jak2VF mutation-induced replicative stress and oxidative DNA damage	AIM2 inflammasome - caspase-1/11 - GSDMD	Macrophages	Increased macrophage proliferation, necrotic core formation, and plaque instability	IL-1β, Gsdmd, Aim2	[134]

disturbed by pyroptosis of endothelial cells that impairs myocardial perfusion, resulting in worsened ischemia as well as functional deterioration. Many traditional Chinese medicine (TCM) formulations can modulate pyroptosis. For example, LGZGD can reduce HF-related renal damage and the level of pyroptosis by inhibiting the TLR4/NF-κB/IRE1 pathway [72]. Another example is FXD, which improves congestive HF by inhibiting the NLRP3/caspase-1/GSDMD axis [73]. At the molecular level, Smurf1 promotes the degradation of TRIB2, which activates NF-κB signaling and induces cardiomyocyte pyroptosis. In contrast, TRIB2 overexpression prevents this pathway activation, which subsequently inhibits pyroptosis and alleviates myocardial injury, leading to a delay in HF progression [74]. Pyroptosis collectively worsens HF by aggravating cardiomyocyte loss, enhancing myocardial fibrosis, and disrupting the cardiac microenvironment. **Table 2** summarizes the key mechanisms of pyroptosis in HF and potential therapeutic targets. Moreover, both clinical and experimental evidence indicate that the precise regulation of the inflammasome-pyroptosis axis by either small-molecule inhibitors or TCM formulations might provide a novel strategy for HF prevention and treatment.

Pyroptosis in the recovery process after MI

The repair and remodeling process that takes place after acute coronary artery occlusion, governs the clinical end result. Recent research shows that pyroptosis is a programmed cell death depends on the inflammasome. Pyroptosis is a key player in the acute injury and repair of MI. Ischemia-reperfusion (I/R) triggers excessive accumulation of ROS and mitochondrial dysfunction, thereby activating the NLRP3 inflammasome, which in turn promotes caspase-1-dependent GSDMD cleavage and the release of IL-1β and IL-18. While this process facilitates the clearance of necrotic cells, excessive activation can lead to a cytokine storm and exacerbate myocardial damage.

At the mechanistic level, the HIF-1α/TUG1/FUS axis aggravates mitochondrial injury and promotes cardiomyocyte pyroptosis, accelerating MI progression [3]. On the other hand, MARCH2-mediated ubiquitination inhibits the PGAM5/MAVS/NLRP3 pathway and alleviates IRI, showing that the protein degradation system regulates pyroptosis. The study demonstrates that tanshinone IIA may alleviate myocardial damage after acute MI and potentially facilitate the translation of research into clinical application. At the ncRNA level, miR-654-3p deficiency aggravates MI-induced fibrosis and dysfunction via enhanced pyroptosis. Its overexpression effectively reverses this pathology [75]. Exosomes from hMSCs that contain lncRNA KLF3-AS1 can regulate the miR-138-5p/Sirt1 axis as a competing endogenous RNA (ceRNA), demonstrating anti-pyroptotic effects and slowing MI progression [76].

Pyroptosis is chiefly induced by oxidative stress. Research shows that uric acid enhances NLRP3 inflammasome activation and pyroptosis during myocardial IRI by promoting ROS production, while ROS scavengers fully reverse the damage [77]. Numerous pharmaceuticals and natural substances show cardioprotective effects due to the suppression of pyroptosis. For instance, kaempferol inhibits hypoxia/reoxygenation-induced pyroptosis by promoting OGT-dependent GSDME O-GlcNAcylation. Similarly, colchicine suppresses pyroptosis through the ESR1-PI3K-Akt-NF-κB pathway [78]; and geniposide as well as QSG alleviate IRI by inhibiting inflammasome activation via the AMPK/TXNIP/NLRP3 axis [79, 80]. In contrast, the transcription factor IRF2 enhances the disease by mediating GSDMD activation and pyroptosis [81]. Natural compounds such as ginsenoside Rh2 and GP attenuate pyroptosis through TXNIP/NLRP3 pathway modulation and ameliorate cardiac structure and function [82, 83]. KDM3A activates the PI3K/Akt pathway, relieving microvascular endothelial IRI and inhibiting pyroptosis, suggesting its cardioprotective value from an epigenetic perspective [84]. Pyroptosis and its mechanisms in post-MI recovery are outlined in **Table 3**.

Potential therapeutic strategies for regulating pyroptosis

Application of antioxidants in pyroptosis

Pyroptosis is an inflammatory cell death pathway caused by inflammasome activation. It proceeds through the formation of gasdermin pores and is often associated with excess ROS. The NLRP3 inflammasome must be activated

Table 2. Key mechanisms and potential therapeutic targets of pyroptosis in HF

Mechanism/Pathway	Key players	Molecular mechanisms	Affected cells	Experimental models/ Clinical data	Potential therapeutic targets	References
ROS/NLRP3/Caspase-1	NLRP3, Caspase-1, GSDMD	ROS-mediated NLRP3 inflammasome activation induces pyroptosis	Cardiac myocytes	In vivo mouse model; in vitro cardiomyocyte model	si-NLRP3, VX-765	[135]
TLR4/NF-κB p65 Signaling Pathway	TLR4, NF-κB p65, NLRP3, Caspase-1, GSDMD-N	Inhibition of the TLR4/NF-κB p65 axis reduces expression of inflammatory mediators and pyroptosis-executing proteins	Cardiac myocytes	Rat HF model (AMI-induced)/ H9C2 cardiomyocytes H/R model	TLR4/NF-κB p65 signaling pathway	[136]
ER stress-CHOP signaling axis	GSDMD, CHOP, ODC1	GSDMD enhances CHOP signaling and promotes ODC1 expression	VSMCs	Ang II-induced AAA mouse model/ApoE$^{-/-}$ mice/Human plasma cohorts	ODC1 inhibition	[137]
Mitochondrial HDAC3/ HADHA-NLRP3 axis	ALDH2, HDAC3, HADHA, NLRP3, Caspase-1	ALDH2 inhibits HDAC3 mitochondrial translocation, sustains HADHA acetylation,reduces mtROS/ ox-mtDNA, and blocks NLRP3 inflammasome activation	Cardiomyocytes	LPS-induced septic shock mouse model	ALDH2	[138]
TXNIP/NLRP3 Inflammasome Signaling Axis	Txnip, ASC, NLRP3, Caspase-1, GSDMD-N	Inhibition of inflammasome assembly and subsequent activation	Cardiomyocytes	db/db mice/Primary neonatal mouse cardiomyocytes	piR112710	[139]
miR-223-3p/NLRP3 Inflammasome Signaling Axis	miR-223-3p, NLRP3, Caspase-1, GSDMD, IL-1β, ROS	MSCs promote miR-223-3p expression, inhibiting NLRP3 inflammasome activation	Cardiomyocytes	Streptozotocin-induced diabetic cardiomyopathy (DCM) mouse model	Therapeutic agents: Mesenchymal stem cells (MSCs)/miR-223-3p mimics	[140]
TLR4/CaMKII/NLRP3 Inflammasome Signaling Axis	TLR4, CaMKII, NLRP3, GSDMD, ASC, Caspase-1	TAK-242-mediated TLR4 blockade suppresses inflammasome activation and pyroptosis	Cardiomyocytes	Streptozotocin (STZ)-induced diabetic rats/High glucose (30 mM)-treated cells	Therapeutic agent: TAK-242 (TLR4-specific inhibitor, phase II trial NCT03401432)	[141]
Ghrelin-PI3K/AKT-mediated Regulation of ER Stress and NLRP3 Inflammasome	Ghrelin, PI3K, AKT, NLRP3	Exogenous Ghrelin activates PI3K/AKT signaling, antagonizing ER stress and subsequent pyroptosis	H9c2 rat embryonic cardiomyocytes	STZ-induced diabetic rats; H9c2 rat cardiomyoblast cell line	Ghrelin	[142]
SIRT1/NLRP3-mediated pyroptosis pathway in ER stress	SIRT1, NLRP3, GSDMD, ER	Inhibits NLRP3 inflammasome activation and pro-inflammatory cytokine (IL-1β/IL-18) release	Cardiomyocytes	Cecal ligation and puncture (CLP) murine model/LPS-stimulated cardiomyocytes	ER/SIRT1/NLRP3/ GSDMD pathway	[143]
MAPK/NF-κB/NLRP3 pathways	Sema4D,MAPK, NF-κB, NLRP3, Caspase-1, ASC	Sema4D/MAPK-mediated pyroptosis axis	Cardiomyocytes	TAC mouse model, Ang II-induced cardiomyocytes	Sema4D	[144]
GSDMD/TGF-β1/Smads	GSDMD, caspase-1, TGF-β1	GSDMD-dependent pyroptosis triggers TGF-β1/Smad3 signaling cascade via DAMPs	Cardiomyocytes/ Activated human CD8^{+} T cells	Focal cardiac irradiation murine model	GSDMD, caspase-1	[145]

Functional NLRP3 inflammasome assembly and activation	LncMEG3, miR-223, NLRP3	LncMEG3 acts as ceRNA to sponge miR-223-3p	Cardiomyocytes	Streptozotocin-induced type 1 diabetic murine model	LncMEG3, miR-223	[146]
NLRP3/Caspase-1/GSDMD Pathway	IP3R2, Ca^{2+}, NLRP3, Caspase-1, GSDMD	IP3R2-mediated calcium release activates pyroptosis	Neonatal rat cardiomyocytes	LPS-induced rat model; neonatal rat cardiomyocytes	IP3R2 inhibition or NLRP3 blockade	[147]
Nrf2-SLC7A11/GPX4 Antioxidant Pathway	Nrf2, Nlrp3	Nrf2 upregulates antioxidant enzymes to suppress ferroptosis and pyroptosis	Cardiomyocytes	Murine I/R model; H/R-treated cardiomyocytes	Nrf2 activator CBR-470-1	[148]
GSDMD-mediated pyroptosis pathway	GSDMD	Inhibiting GSDMD-mediated pyroptosis alleviates mitochondrial damage	Macrophages, cardiomyocytes	Murine sepsis models (LPS-induced or CLP)	GI-Y2, GI-Y2@MM-NPs	[149]
SIRT1-NF-κB p65 signaling pathway	SIRT1, NF-κB p65	SIRT1 upregulation inhibits NF-κB-mediated pyroptosis	Cardiomyocytes, coronary artery endothelial cells	Kawasaki disease murine model and cell model	Forsythoside B (FTS-B), SIRT1	[150]
NLRP3/NF-κB signaling pathway	MG53, NLRP3, NF-κB, IL-1β/18	MG53 inhibits NF-κB activation and blocks pyroptosis	Cardiomyocytes (HL-1 cell line)	CVB3-infected murine model; HL-1 cell viral model	MG53	[151]
METTL14-miR-221-3p-LncRNA FTX-SESN2 axis	METTL14, miR-221-3p, LncRNA FTX, SESN2	m6A modification promotes pyroptosis	Cardiomyocytes	DOX-induced murine model and cellular model	METTL14	[152]
CCR2-NF-κB-NLRP3 signaling pathway	CCR2, NLRP3 inflammasome	CCR2 inhibition suppresses NF-κB activation and blocks pyroptosis	Cardiomyocytes	Rat myocardial I/R model	CCR2	[153]
AMPK/TXNIP/NLRP3 signaling pathway	AMPK, TXNIP, NLRP3 inflammasome	AMPK activation inhibits NLRP3-mediated pyroptosis	Cardiomyocytes	CME rat model; H9c2 cell model	AMPK/TXNIP	[154]
miR-214-3p/Caspase-1 pathway	lncRNA KCNQ1OT1, miR-214-3p, Caspase-1	KCNQ1OT1 targets miR-214-3p to regulate caspase-1-mediated pyroptosis	Cardiomyocytes	STZ-induced diabetic murine model; patient data from diabetic individuals	lncRNA KCNQ1OT1	[155]
NLRP3 inflammasome activation pathway	NLRP3, GSDMD	Emodin inhibits NLRP3 inflammasome activation	Cardiomyocytes	LPS-induced murine model; in vitro cardiomyocyte model	Emodin	[156]
AMPK-TXNIP signaling pathway	AMPK, TXNIP	Exendin-4 activates pAMPK to promote TXNIP degradation	Cardiomyocytes	HFD rat model; high-glucose-treated cardiomyocyte model	Exendin-4	[157]
PI3K/AKT signaling pathway	Mitofilin (mitochondrial inner membrane protein)	Activation of the PI3K/AKT pathway inhibits pyroptosis	Cardiomyocytes	Murine AMI model; H/R-treated cardiomyocytes	Mitofilin	[158]
TLR4/NLRP3/caspase-1 signaling pathway	Tenascin-C, NLRP3, caspase-1	TNC activates the TLR4/NF-κB/NLRP3 pathway	Cardiomyocytes	Murine MI model	Tenascin-C	[159]
PGAM5/MAVS/NLRP3 axis	MARCH2, PGAM5, MAVS, NLRP3	MARCH2 ubiquitinates and degrades PGAM5 to inhibit NLRP3 inflammasome activation	Cardiomyocytes	Human cardiac samples; murine I/R model	MARCH2	[160]
GSDMD-mediated pyroptosis	GSDMD	GI-Y1 inhibits GSDMD activation, thereby blocking pyroptosis	Cardiomyocytes, macrophages	LPS/CLP-induced septic murine model	GSDMD, GI-Y1	[161]
NR4A1/NLRP3 inflammasome pathway	NR4A1, NLRP3, GSDMD	NR4A1 activates the NLRP3 inflammasome, leading to GSDMD cleavage and triggering pyroptosis	Cardiomyocytes	DOX-induced murine model; in vitro cellular model	NR4A1	[162]

circRbms1/miR-142-3p/MST1	circRbms1, miR-142-3p, MST1	circRbms1 sequesters miR-142-3p to stabilize MST1, thereby regulating pyroptosis	Cardiomyocytes	Murine myocardial I/R model; in vitro human cardiomyocytes (HCMs)	circRbms1	[163]
NLRP3 inflammasome-mediated pyroptosis	NLRP3, Caspase-1, NOX1/4, Drp1	Mitochondrial fission activates Caspase-1	Cardiomyocytes	Dox-induced murine model; DCM patients	NOX1/NOX4 and Drp1 inhibition	[164]

Table 3. Role and mechanisms of pyroptosis in the post-MI recovery process: an overview

Pyroptosis Mechanism	Pyroptosis-Mediated Cellular Processes	Associated Molecules/Pathways	Time Window of Action	Impact on Myocardial Recovery	Affected Cardiac Tissues	References
GSDMD-mediated pyroptosis activation	Neutrophil generation and early mobilization	GSDMD-IL-1β pathway	Within 24 hours post-AMI (early phase)	Expands infarct area and impairs cardiac function	Infarcted myocardial tissue	[165]
ROS/Caspase-1/GSDMD-mediated pyroptosis	Macrophage pyroptosis	ROS/Caspase-1/GSDMD signaling pathway	Post-MI repair phase	Attenuates myocardial fibrosis and adverse cardiac remodeling	Infarct and peri-infarct myocardial tissues	[166]
NLRP3/caspase-1/GSDMD-mediated pyroptosis	Release of inflammatory cytokines IL-1β/IL-18 and programmed cell death	NLRP3/ASC/caspase-1/GSDMD pathway	Starting from 2 weeks post-AMI (repair phase)	Promotes adverse ventricular remodeling	Left ventricular myocardial tissue	[167]
Programmed cardiomyocyte death driving immune-inflammatory responses	Cardiomyocyte programmed death and release of inflammatory factors (e.g., IL-1β)	NLRP3/Caspase-1/GSDMD pathway; AMPK signaling pathway	Exacerbates injury, whereas inhibition attenuates inflammation and promotes repair	Reduces infarct size and enhances cardiac repair	Myocardial tissue in the infarct zone	[168]
NLRP3 inflammasome activation via the S100A8/A9-TLR4 pathway	Promotion of IL-1β secretion	S100A8/A9, TLR4, NLRP3, IL-1β	Acute inflammatoryphase post-MI	Excessive inflammation impedes recovery and reduces cardiac function	Infarct zone	[169]
Transcriptional upregulation of CEBPB and impaired degradation by USP14 inhibition synergistically activate NLRP3	Impairs the vascular repair function of endothelial progenitor cells (EPCs)	NLRP3, CEBPB, USP14, PI3K/Akt/mTOR	Post-MI (particularly under diabetic conditions)	Impairs angiogenesis and functional recovery; genetic ablation improves outcomes	Myocardial infarct zone	[170]
HDAC6 activates Wnt3a/GSK3β signaling, inducing mitochondrial oxidative stress	Promotes mitochondrial dysfunction and ROS production, exacerbating atrial cardiomyocyte pyroptosis, fibrosis, and inflammation	HDAC6, Wnt3a, GSK3β, mitochondrial ROS	At post-MI week 2 in murine models (coinciding with left atrial HDAC6 upregulation)	Promotes atrial maladaptive remodeling; its inhibition ameliorates the phenotype	Left atrium	[171]
NLRP3 inflammasome activation-mediated pyroptosis	Cardiomyocyte death and inflammatory factor release	NLRP3/ASC/Caspase-1/GSDMD, miR-202-5p/TRAF3IP2/JNK	Post-MI (effects persist for 4 weeks post-intervention)	Inhibiting pyroptosis ameliorates cardiac function	Cardiomyocytes (infarct and peri-infarct zones)	[172]
Assembly and activation of NLRP3 inflammasome	Induces inflammatory response and pyroptosis in cardiomyocytes	ERRγ, GBP5, NLRP3 inflammasome	Post-MI (ischemic injury phase)	Promotes cardiac injury; its inhibition ameliorates cardiac function	Cardiomyocytes (ischemic zone)	[173]
O-GlcNAcylated GSDME-mediated pyroptosis	Inflammatory programmed cell death with IL-1β/IL-18 release	NLRP3/Caspase-1/GSDME; OGT/OGA-mediated O-GlcNAcylation	Post-AMI	Promotes myocardial injury; its inhibition alleviates tissue damage	Cardiomyocytes (infarct and H/R zones)	[174]

NLRP3 inflammasome activation and caspase-1 overactivation	Cardiomyocyte death and IL-1β/IL-18 secretion	NLRP3-caspase-1-IL-1β/IL-18 pathway	6 weeks post-MI	Exacerbates ventricular dilation and functional deterioration, impedes recovery	Cardiomyocytes	[175]
Oxidative stress-activated pyroptosis	Inflammatory cell infiltration and cardiomyocyte death	Oxidative stress markers (ROS/MDA/8-OHdG) and pyroptosis-related proteins	Acute phase of AMI (intervention within 24 hours post-infarction)	Impedes recovery; inhibition improves cardiac function	Cardiomyocytes	[176]
NLRP3 inflammasome activation	Lactate dehydrogenase and inflammatory factor release	Nat10-ac4C-Nek7-NLRP3 axis	During reperfusion	Exacerbates injury; inhibition ameliorates myocardial damage	Myocardial tissue	[177]
CASP4-dependent non-canonical inflammasome pathway	Cell death and inflammatory factor release	S100A12/CASP4 signaling axis	During H/R-induced cardiomyocyte injury	Exacerbates injury and impedes functional recovery	Cardiomyocytes (AC16 cell line)	[178]
CXCR4/NF-κB pathway activation of NLRP3 and GSDMD	Pyroptosis with IL-1β and IL-18 release, triggering severe inflammation	CXCR4/NF-κB/NLRP3/Caspase-1/GSDMD pathway	Persistently highly expressed post-MI	Exacerbates inflammatory injury; inhibition ameliorates cardiac function and structure	Cardiomyocytes in the myocardial infarct border zone	[179]
miR-155/SHP2 axis regulates ERK/NLRP3 pathway to activate GSDMD	Myocardial necrosis, fibrosis, and apoptosis post-MI I/R	NLRP3, GSDMD, caspase-3/4/11, ERK1/2 pathway	During myocardial I/R	Exacerbates myocardial injury and impedes cardiac functional recovery	Left ventricular myocardial tissue	[180]
NLRP3 inflammasome activation-mediated pyroptosis	Programmed cell death and inflammatory factor IL-1β release	NLRP3/ASC/caspase-1/GSDMD/IL-1β pathway	During myocardial I/R	Exacerbates cardiac injury; inhibition of pyroptosis ameliorates cardiac function and promotes recovery	Myocardial tissue in the I/R area	[181]
NLRP3/Caspase-1/GSDMD signaling pathway activation	Cardiomyocyte programmed inflammatory cell death	TLR4/MyD88/NF-κB and NLRP3/caspase-1/GSDMD pathways	Acute phase of MI	Exacerbates injury; inhibition ameliorates cardiac function	Myocardial tissue in the ischemic area	[182]
GSDMD-N terminal-mediated pyroptosis	Cardiomyocyte inflammatory lysis with release of IL-1β, IL-18 and other factors	SIRT3/NLRP3 inflammasome signaling pathway	Post-myocardial I/R	Exacerbates injury and impedes functional recovery	Cardiomyocytes	[183]
Autophagic flux blockade and ROS accumulation activate NLRP3 inflammasome-mediated pyroptosis	Macrophage pyroptosis releases IL-1β, thereby inducing cardiomyocyte apoptosis	p62-mediated autophagy pathway; NLRP3; ROS	During myocardial I/R	Exacerbates injury; inhibition of pyroptosis attenuates injury and promotes functional recovery	Myocardial tissue (macrophage-mediated)	[184]
NLRP3/caspase-1/GSDMD pathway activation	Cell swelling and rupture, with release of inflammatory cytokines IL-1β/IL-18	NLRP3, caspase-1, GSDMD, IL-1β, IL-18	Early stage after reperfusion	Aggravates myocardial damage, expanding infarct size	Cardiomyocytes	[185]
ALKBH5 mediates NLRP3 inflammasome activation via Notch1 signaling	Cardiac fibroblasts undergo inflammatory programmed cell death	ALKBH5/Notch1/NLRP3 signaling pathway	Post-MI	Promotes pyroptosis and exacerbates cardiac fibrotic injury	Cardiac fibroblasts	[186]
NLRP3 inflammasome activation drives pyroptosis	Cell death and release of inflammatory factors (e.g., IL-1β)	NLRP3, caspase-1, GSDMD, IL-1β	During H/R	Promotes injury with no protective effect	Cardiomyocytes	[187]
CCR2 regulates NLRP3-dependent cardiomyocyte pyroptosis via NF-κB	Cardiomyocyte death and inflammatory factor (IL-1β/IL-18) release	NLRP3/GSDMD/Caspase-1 and NF-κB pathways	Early reperfusion phase	Promotes injury; inhibition ameliorates function and reduces infarct size	Cardiomyocytes	[153]

by ROS that enhances mitochondrial dysfunction and lipid peroxidation, resulting in sustained pyroptosis mediated by NLRP3. In CVDs such as AS, MI, and HF, oxidative stress causes ROS damage in EC, CM, and macrophage pyroptosis through various mechanisms. Hence, antioxidants that scavenge ROS or enhance mitochondrial functionality can be useful to regulate pyroptosis, control the inflammatory response and alleviate tissue injury.

Current evidence indicates that various antioxidants can effectively suppress pyroptosis through distinct molecular targets, thereby exerting cardioprotective effects. Molecular hydrogen (H_2) significantly reduces oxidative stress and inhibits NLRP3 inflammasome activation, resulting in improved cardiac function in acute AMI and IRI [85]. Melatonin, an endogenous antioxidant, not only blocks inflammasome activation by inhibiting the TLR4/NF-κB pathway but also alleviates oxidative stress and pyroptosis in anthracycline-induced cardiomyopathy via activation of the Sirt1/Nrf2 pathway [86, 87]. Subsequent studies demonstrate that melatonin inhibits pyroptosis in cardiomyocytes and endothelial cells via the SIRT3/FOXO3α/ROS axis and the RORα/miR-223/STAT3 pathway, thereby mitigating AS-related cardiovascular harm [88, 89]. Also, melatonin can downregulate the inflammatory and pyroptotic mediators related to NF-κB, including iNOS, COX-2, NLRP3, caspase-1, and GSDMD, thereby improving LPS induced myocardial injury dramatically [90]. MitoQ, a new antioxidant, targets mitochondria and reduces production of ROS. It inhibits excess activation of NLRP3 inflammasome that blocks both pyroptosis and ferroptosis in cardiomyocytes. With this, MitoQ inhibits myocardial injury under hyperglycemic conditions [91].

Antioxidants can regulate pyroptosis not only through direct ROS scavenging, but also by restoring the intracellular redox balance and breaking the 'oxidative stress-inflammasome activation-pyroptosis' vicious cycle. While clinical translation remains limited due to low bioavailability and patient heterogeneity, novel strategies such as nanodelivery systems, structural modification and combination therapy may considerably improve their specificity and durability. When viewed in their totality, these approaches confirm the effectiveness of antioxidants to mitigate pyroptosis in CVD pathology.

Therapeutic potential of combination strategies with inflammation modulators

There is considerable potential to develop inflammation modulators into effective therapeutics in interventional studies of pyroptosis-related CVDs, in which the combined application of simultaneous coverage of multiple key signaling pathways has been shown to be effective. According to an article published in the Nature Reviews Immunology journal, pyroptosis, or programmed cell death, depends on the presence of inflammasomes and gasdermin. It is marked by the massive release of IL-1β and IL-18. However, the process also triggers the formation of pores in the plasma membrane, which further heightens the inflammatory response. A repetitive 'pyroptosis-inflammation-injury' harmful cycle is driven by this process. While single-target inhibition strategies often prove insufficient in disrupting this cascade, combination approaches may yield more pronounced therapeutic benefits. Evidence from both animal models and clinical studies indicates that polyethylene glycol-20k (PEG-20k), combined with the NLRP3 inflammasome inhibitor MCC950, significantly improves myocardial function and sublingual microcirculation after resuscitation. The mechanism involves the upregulation of SIRT1/PGC1-α and suppression of NLRP3 inflammasome activation [92]. Likewise, combinations of IL-1β or IL-18 antagonists and NLRP3 inhibitors have complementary effects. Importantly, IL-1β monoclonal antibodies, including canakinumab, have already been validated in large-scale clinical trials for reducing cardiovascular event risk. The further induction of NLRP3 inhibitors with monoclonal antibodies may mitigate vascular injury and myocardial remodeling [92].

The combined effects of inflammation modulators and standard cardioprotective agents should not be underestimated. Statins can indirectly inhibit the activation of the NLRP3 inflammasome by reducing ROS levels. Although the immunosuppressive and anti-inflammatory effects of glucocorticoids are manifested quite rapidly, long-term application is limited by their undesirable effects. On the flip side, a combination of selective pyroptosis regulators (e.g.,

caspase-1 or GSDMD inhibitors) with conventional medications could safely and tolerably increase efficacy. Combining aspirin with gastrodin has shown promising cardioprotective effects after myocardial IRI [93]. Also, metabolic factors are essential for the disease progression driven by pyroptosis. Hcy, for example, promotes macrophage pyroptosis by inducing ER stress and disrupting calcium homeostasis, as well as ER-mitochondria coupling, thereby accelerating AS development. This suggests that combining inflammation and metabolic interventions in a high-risk group may provide better clinical benefits [66]. Recent advances in potential therapeutic strategies targeting pyroptosis in CVDs are summarized in **Table 4**.

Future research directions

Prospects of personalized medicine in CVDs

With the rapid development of precision medicine, opportunities have emerged for the prevention and treatment of CVDs. The form of programmed cell death in which the cell undergoes lysis and results in the release of IL-18 and IL-1β is called pyroptosis. It acts via inflammasome and gasdermin-mediated pathways. CVDs like AS, MI and HF engage pyroptosis in the initiation and progression of the disease process. Clinical studies show that CVD patients have significantly higher expression of NLRP3 inflammasome-related genes and pyroptosis rates in PBMCs. ASC specks and IL-1β, IL-6 and IL-18 levels are significantly greater in the serum. Circulating ASC specks, which are novel inflammatory biomarkers, have been put forward for identifying patients with high inflammatory burden, thus providing a substantial basis for precision medical treatment and risk stratification [94].

In terms of therapeutic exploration, the sodium-glucose cotransporter 2 (SGLT2) inhibitor empagliflozin (EMPA) has been shown to reduce oxidative stress and suppress the IFNγ-STAT1-STING inflammatory signaling pathway, significantly improving cardiac function in a murine HFpEF model. Emerging evidence also suggests that SGLT2 inhibitors can ameliorate pulmonary vascular cell function and arterial remodeling [95]. These findings suggest that inhibition of the STAT1-STING axis may represent a promising therapeutic strategy against aging- and inflammation-associated HF, offering new clinical benefits for patients with diabetes or age-related comorbidities [96]. At the same time, clonal hematopoiesis of indeterminate potential (CHIP) studies have discovered new targets for individualized therapy. The association between JAK2 mutations and increased atherothrombotic cardiovascular risk has been linked to a genetic reduction of AIM2 in zebrafish. Additional functional tests show that AIM2 rise and drop can alter ASXL1-related heart disease risk, findings validated in animal models. These findings suggest that CHIP genotypes may help tailor cardiovascular interventions [97].

Through dynamic monitoring and stratified screening of inflammatory biomarkers, targeted modulation of critical signaling pathways, and mechanistic dissection of genetic variants, a solid foundation has been laid for the precision diagnosis and treatment of pyroptosis-related CVDs. These advancements greatly validate their practical use in personalized medicine and provide a path toward more sophisticated preventative and therapeutic strategies for CVDs.

The relationship between pyroptosis and lifestyle factors

The link between lifestyle-related factors (dietary habits, physical activity, etc.) and CVDs is well-established. Recently, a study suggested that part of this link might be through pyroptotic pathways. Inflammatory cell death is known as pyroptosis. It results from excess activation of inflammasomes. This leads to Caspase-1-dependent cleavage of GSDMD and the release of proinflammatory cytokines. The importance of pyroptosis to cardiovascular disease has been recognized. A novel study assesses how this process may affect a variety of lifestyle habits and cardiovascular risk. This section summarizes the compelling findings.

Pyroptosis can be influenced by various dietary factors. High-fat and high-sugar diets are characterized by excessive fat and sugar content, which leads to lipid peroxidation and accumulation of ROS. They cause the hyperactivation of NLRP3 inflammasome, which further boosts endothelial and cardiomyocyte pyroptosis. This process accelerates AS. Conversely, dietary patterns high in fiber, unsaturated fatty acids, and polyphenols, such as Mediterranean or

Table 4. Advances in potential therapeutic strategies targeting pyroptosis in CVDs

Intervention/ Drug	Primary Target	Regulatory Mechanism	Action Stage	Potential Cardiovascular Effect	Current Research Progress	References
Melatonin	NLRP3 inflammasome	Inhibits pyroptosis via suppression of the TLR4/NF-κB signaling pathway	Pyroptosis	Improves cardiac function and reduces cardiomyocyte death	MI mouse model and H9C2 cell model	[86]
Disulfiram	GSDMD Cys192	Antagonizes GSDMD Cys192 palmitoylation to inhibit its membrane localization	Pyroptosis	Reduces infarct size and improves cardiac function	AMI mouse model	[188]
Atorvastatin	lncRNA NEXN-AS1-NEXN pathway	Inhibits pyroptosis by upregulating the NEXN-AS1-NEXN pathway	Pyroptosis	Anti-atherosclerotic effect	Human vascular endothelial cell study	[189]
MCC950	NLRP3 inflammasome	Inhibits NLRP3 inflammasome-mediated pyroptosis	Pyroptosis	Attenuates myocardial injury, oxidative stress, and inflammation	Mouse AMI model and hypoxic cardiomyocyte model	[190]
VX-765	Caspase-1	Inhibits pyroptosis	caspase-1↓	Anti-inflammatory protection	AMI and hypoxia models	[190]
NSA	GSDMD/MLKL	Inhibits pyroptosis/necrosis	Suppresses inflammation and oxidative stress	Alleviates DOX-induced cardiotoxicity	DOX-induced cardiotoxicity mouse model	[191]
Resveratrol	TLR4/MyD88/ NF-κB, NLRP3	Inhibits pyroptosis	Blocks the TLR4/MyD88/NF-κB signaling pathway and suppresses NLRP3 inflammasome activation	Attenuates myocardial injury and improves cardiac function	Rat model of coronary microembolization	[192]
Colchicine	AMPK/SIRT1/ NLRP3	Inhibits pyroptosis	AMPK↑/NLRP3↓	Improves cardiac function and reduces myocardial injury	Coronary microembolization model	[193]
Oridonin	NF-κB/NLRP3	Inhibits pyroptosis	NF-κB/NLRP3↓	Reduces infarct size and enhances cell survival	Mouse I/R model and H/R cell model	[194]
Dapagliflozin	NLRP3 inflammasome	Inhibits pyroptosis	TLR4/p38/NLRP3↓	Improves cardiac function and suppresses inflammation	DOX-induced DCM model	[195]
Liraglutide	SIRT1/NOX4/ ROS	Activates SIRT1 and inhibits the NOX4/ROS pathway, reducing NLRP3 inflammasome activation	Suppresses caspase-1 and GSDMD activation, thereby reducing pyroptosis	Cardioprotective effect	H9c2 cell model	[196]
Triptolide	NLRP3/TGF-β1	Inhibits NLRP3 inflammasome and downstream inflammatory mediators, and suppresses the TGF-β1 pro-fibrotic pathway	Reduces inflammatory mediator release and macrophage infiltration, thereby attenuating myocardial fibrosis	Improves cardiac function and counteracts myocardial remodeling	TAC-induced pressure overload mouse model	[197]
Curcumin	Akt/mTOR	Activation of the mTOR signaling pathway to suppress excessive autophagy and pyroptosis	Downregulation of NLRP3/Caspase-1 to reduce oxidative stress	Alleviation of DOX-induced cardiac dysfunction and oxidative injury	Mouse model and H9c2 cardiomyoblasts	[198]
DEX	miR-29b/ FoxO3a/ARC	Downregulation of miR-29b and activation of the FoxO3a/ARC signaling axis	Inhibition of NLRP3 inflammasome activation and attenuation of inflammatory responses	Mitigation of myocardial IRI and reduction of infarct size	Myocardial ischemia-reperfusion (MIR) rat model and H/R cell model	[199]

NaHS	ROS/NLRP3	Inhibition of cardiomyocyte pyroptosis via the ROS/NLRP3 signaling pathway	ROS↓/NLRP3↓	Improvement of cardiac function and suppression of myocardial fibrosis	STZ-induced diabetic rat and cell models	[200]
Astragaloside IV	Nrf-2/HO-1	Activation of the Nrf2/HO-1 signaling pathway to inhibit pyroptosis	Nrf2↑/HO-1↑, with reduced release of inflammatory mediators	Improvement of cardiac function, with reduced myocardial injury and fibrosis	DOX-induced mouse model of myocardial injury	[201]
Vitamin D3	NOX4/NLRP3	Inhibition of the NOX4/NLRP3 inflammasome pathway	NOX4↓/NLRP3↓, leading to reduced release of inflammatory mediators	Improvement of cardiac function, attenuation of myocardial hypertrophy, and amelioration of metabolic disorders	db/db mouse model and H9c2 cardiomyoblast model	[202]
ESC-Exo	TLR4/NLRP3	Suppression of the TLR4/NLRP3 inflammasome via anti-inflammatory cytokines	Inhibition of caspase-1/GSDMD activation and reduction of pro-inflammatory cytokine release	Attenuation of DOX-induced cardiotoxicity	DOX-treated H9c2 cardiomyoblast model	[203]
EMPA	NF-κB/NLRP3	Inhibition of NF-κB/NLRP3 pathway activation	Suppression of NF-κB nuclear translocation and reduction of pyroptosis	Improvement of cardiac function and attenuation of myocardial inflammation	Experimental autoimmune myocarditis (EAM) mouse model and H9c2 cardiomyoblasts	[204]
Methyl-β-cyclodextrin (Mβ-CD)	TLR4/NF-κB/NLRP3	Inhibition of TLR4/NF-κB/NLRP3 pathway activation	Reduction of GSDMD-NT formation and decreased release of inflammatory cytokines	Reduction of atherosclerotic plaque formation and improvement of lipid metabolism	ApoE$^{-/-}$ mouse model and VSMC model	[128]
GI-Y2	GSDMD	Targeting the GSDMD Arg10 residue to inhibit its membrane binding	Blocking GSDMD-N pore formation to reduce pyroptosis	Reduction of atherosclerotic plaque size and suppression of macrophage infiltration	ApoE$^{-/-}$ mouse model with macrophage-targeted nanoparticles	[127]
Tanshinone IIA	TLR4/NF-κB/NLRP3	Inhibition of TLR4/NF-κB signaling pathway activation	Suppression of NF-κB nuclear translocation and downregulation of pyroptosis-related proteins such as GSDMD-N	Improvement of cardiac function and attenuation of myocardial injury and fibrosis	Rat MI-induced HF model and H9c2 cell H/R model	[136]
H_2 inhalation	NLRP3 inflammasome	Inhibition of oxidative stress and NLRP3-mediated pyroptosis	Reduction of ROS levels and decreased expression of pyroptosis-related proteins	Alleviation of reperfusion injury and improvement of the no-reflow phenomenon	Rat myocardial I/R model	[85]
Quercetin	Nrf2 pathway	Promotion of Nrf2 nuclear translocation and enhancement of antioxidant protein expression	Reduction of ROS accumulation and inhibition of cellular pyroptosis	Attenuation of myocardial fibrosis and improvement of cardiac function	Diabetic rat model and H9c2 cardiomyoblasts	[136]
Taohong Siwu Decoction (THSWD)	Autophagy/NLRP3	Promotion of autophagy and inhibition of NLRP3 inflammasome activation	Increase of LC3 expression and reduction of pyroptosis-related proteins such as GSDMD-N	Alleviation of reperfusion injury and reduction of MI	Mouse I/R model	[205]
Ginsenoside Rh2	HMGB1/NLRP3	Targeting HMGB1 to inhibit NLRP3 inflammasome activation	Downregulation of caspase-1 and GSDMD-N expression	Attenuation of cardiomyocyte injury and suppression of inflammatory responses	H9c2 cell oxygen-glucose deprivation (OGD) model	[206]
Candesartan	NF-κB/MAPK/Autophagy	Multi-pathway inhibition of NLRP3 inflammasome activation	Suppression of NF-κB and reduction of mitochondrial damage	Broad-spectrum anti-inflammatory effects and alleviation of cardiovascular complications	Macrophage and uric acid crystal-induced mouse model	[207]

DASH-type patterns, downregulate NF-κB and NLRP3 signaling, thereby reducing inflammation and pyroptosis. As a result, modifying diet could be an effective option to suppress pyroptosis to improve cardiovascular outcome. Yet, evidence is experimental and observational in large measures, with a general lack of clinical validation so far.

Numerous studies provide substantial evidence that exercise modulates pyroptosis. Preclinical and animal studies show that aerobic exercise suppresses pyroptosis and has multiple mechanisms of cardiovascular protection. After 8 weeks of aerobic training, the inflammation and pyroptosis inhibition, along with PI3K pathway suppression, were observed to attenuate obesity-associated cardiac remodeling and dysfunctions [98]. In AMI and I/R models, exercise alleviates GSDME-dependent pyroptosis via upregulation of IGFBP2, thereby exerting cardioprotective effects [99]. Moderate-intensity aerobic training also reduces inflammation and limits pyroptosis during IRI, providing intrinsic myocardial protection [100]. Exercise further suppresses NLRP3 inflammasome activation to prevent DOX-induced cardiotoxicity [101]; exercise reduces leukocyte infiltration, inhibits pyroptosis and necroptosis-related signaling, and alleviates fibrosis in isoproterenol (ISO)-induced cardiac injury [102]; and exercise activates H_2S signaling, suppressing pyroptosis and preventing disease progression in high-fat diet (HFD)-induced metabolic cardiomyopathy [103]. Collectively, these findings highlight the molecular targets and mechanistic basis by which exercise mitigates cardiovascular pathology through pyroptosis inhibition.

On the other hand, although the associations of pyroptosis with smoking, drinking, and psychological stress are less certain, they could matter. Tobacco or nicotine-derived oxidants can damage endothelial cells and promote pyroptosis, which causes acceleration of vascular stiffening. Long-term alcohol consumption can lead to the hyperactivation of inflammasomes in cardiomyocytes, which may contribute to alcoholic cardiomyopathy. Psychological stress can induce injury to the heart and blood vessels. Stress permanently increases glucocorticoid levels and maintains activation of the sympathetic drive. Stress causes the NLRP3 and caspase-11 pathways to activate aberrantly, leading to further inflammatory injury to the heart and blood vessels. Although biologically plausible, these findings lack systematic clinical validation.

Future research should integrate mechanistic studies, preclinical animal models, and clinical epidemiology to clarify the causal relationship between lifestyle factors and pyroptosis. Key priorities include determining whether dietary and exercise interventions can stably modulate pyroptosis through specific molecular targets and whether such modulation translates into long-term clinical benefits in CVD patients. Advancing this line of research will not only elucidate the pathophysiological chain linking "lifestyle-pyroptosis-CVD" but also provide novel theoretical foundations and practical approaches for precision prevention and individualized therapy.

Discussion

The increasing attention drawn to pyroptosis, a type of programmed cell death activated by the inflammasome and characterized by plasma membrane pore formation, is this type's use in cardiovascular research. Cell death, unlike apoptosis and necrosis, can also amplify the immune response by releasing inflammatory cytokines such as IL-1β and IL-18. Pyroptosis contributes to an imbalance of injury and repair in cardiovascular diseases, thus aggravating their pathology. Over several cardiovascular models activation of inflammasomes and downstream effectors has been demonstrated repeatedly. For example, eliminating STING reduces lipopolysaccharide (LPS)-caused SIC in mice, indicating that targeting cardiomyocyte STING may be a potential approach to prevent SIC [104]. In like manner, SerpinB1 interacts with caspase-1 to block its activation, causing the inhibition of cardiomyocyte pyroptosis, which alleviates pathological hypertrophy and remodeling, opening a new molecular target for cardiac remodeling intervention [105]. The kind of blockage of inflammasome or any compound that can block molecules related to pyroptosis can actually reduce the IRI and dysfunction of the heart. Regarding regulated cell death involving IRI and cardiac injury, new insight has been provided.

Pyroptosis and inflammation create a cycle that keeps getting worse. Caspase-8 and other similar molecular players might function as important switches in the network of cell death, regulating pyroptosis, apoptosis and necroptosis, thus aggravating the vicious cycle [106]. Macrophages and T cells are recruited and attracted to the site of pyroptotic cells through IL-1β, IL-18, and DAMPs. Inflammatory agents like reactive oxygen species and free fatty acids activate the NLRP3 inflammasome, causing ongoing pyroptosis. The macrophage efferocytosis is disturbed and the plaque instability and rupture occur in AS. Chronic HF promotes sustained pyroptosis resulting in fibrosis and ventricular remodeling due to the inflammatory environment. In those metabolic diseases such as diabetes and hypertension, the NLRP3-caspase-1-mediated pyroptosis aggravates insulin resistance and endothelial dysfunction which link metabolism disturbances with cardiovascular injury. Increased levels of MALT1 in the circulation are associated with an imbalance in $CD4^+$ T-cells, increased inflammation, and coronary stenosis, and MALT1 has been proposed as a possible biomarker to predict major adverse cardiovascular event (MACE) in CAD [107]. In conclusion, the pyroptosis-inflammation feedback loop is conservatively functional across a variety of cardiovascular conditions.

Pyroptosis-related molecules are of increasing interest as diagnostic and therapeutic biomarkers. Biomarkers of state of disease and prognosis may be serum IL-1β, IL-18 and cleaved GSDMD fragments. NLRP3 inhibitors, IL-1β antagonists, and small molecules targeting GSDMD all show therapeutic promise. By way of illustration, inhibition of IL-1β diminished MACE occurrence in high-risk atherosclerotic patients with chronic kidney disease (CKD), with benefits most notable in those showing robust initial anti-inflammatory response [108]. These findings indirectly prove the clinical applicability of the pyroptosis-inflammation axis in treatment. Despite these advances, there are still issues with specificity, side effects and long-term safety. For future studies, it would be good to combine new technical approaches, particularly single-cell multi-omics and multimodal imaging, to characterize the dynamic characteristics of pyroptosis in distinct cells and stages of diseases, clarify its crosstalk with other cell deaths and design more selective and controllable therapeutic strategies. As investigation continues, the actions and clinical value of pyroptosis in heart disease are confirmed progressively.

Although this study explores the critical role of pyroptosis in CVDs from multiple perspectives, the existing evidence is still limited by the research models and experimental conditions, and there remains a gap compared to the actual human pathological state [109]. The interactions between pyroptosis, apoptosis, ferroptosis, ATP-induced cell death [110] and inflammatory pathways are complicated and the hierarchy and details of these connections are still unclear. At present, drug ingredients targeting pyroptosis pathways are mostly under study, on the animal and the cellular level. In contrast, there is little clinical evidence, especially from large-scale randomised controlled trials [111]. Future studies using single-cell genomics, multi-omics analysis and real-world clinical data is needed to better clarify the temporal characteristics and population differences of pyroptosis. The clinical validation of pyroptosis targets should also be encouraged, and strategies that combine the regulation of cell death and inflammation should be investigated for the precise prevention and treatment of CVDs [112].

Conclusion

Cell demise due to pyroptosis is an intensively regulated event and plays a vital role in the initiation and development of several CVDs, such as AS, HF, and MI [3, 113, 114]. The activation of inflammasomes and cleavage of GSDMD can elicit the release of pro-inflammatory factors (such as IL-1β and IL-18), resulting in macrophage pyroptosis and inflammatory responses, which further demonstrate the core role of pyroptosis in the pathological mechanism of cardiovascular diseases [115]. Despite considerable progress in identifying pyroptosis-related biomarkers and viable therapeutic targets, currently, there is not enough clinical evidence to support these in practical application. Future research must integrate multi-omics technologies, precise subtyping, and clinical validation to further elucidate the dynamic characteristics of pyroptosis at different disease stages and advance intervention strategies targeting

pyroptosis pathways toward clinical application, providing new directions and possibilities for the precise treatment of CVDs [112].

Acknowledgements

This work was supported by Science and Technology Department of Yunnan Province-Kunming Medical University, Kunming Medical joint special project-surface project, China, No. 202401AY070001-164; and Yunnan Provincial Department of Science and Technology Science and Technology Plan Project-Major Science and Technology Special Projects, China, No. 202405AJ310003; and the Yunnan Pan Xiangbin Expert Workstation under the Yunnan Provincial Project for Scientific and Technological Talents and Platforms Project, No. 202305AF150069.

Disclosure of conflict of interest

None.

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