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The Role of Pyroptosis in Coronary Heart Disease

ABSTRACT

The incidence and mortality of cardiovascular diseases, of which coronary heart disease (CHD) is a significant cardiovascular burden, are on the rise. Pyroptosis as an incipient programmed cell death mediated by inflammasomes can sense cytoplasmic contamination or interference and is typically marked by intracellular swelling, plasma membrane blistering and intense inflammatory cytokine release. As research on pyroptosis continues to progress, there is mounting evidence that pyroptosis is a vital participant in the pathophysiological basis of CHD. Atherosclerosis is the major pathophysiological basis of CHD and involves pyroptosis of endothelial cells, macrophages, vascular smooth muscle cells, and other immune cells, often in association with the release of pro-inflammatory factors. When cardiomyocytes are damaged, it will eventually lead to heart failure. Previous studies have covered that pyroptosis plays a critical role in CHD. In this review, we describe the properties of pyroptosis, summarize its contribution and related targets to diseases involving angina pectoris, myocardial infarction, myocardial ischemia in perfusion injury and heart failure, and highlight potential drugs for different heart diseases.

Keywords: Pyroptosis, NLRP3, cardiomyocytes, atherosclerosis, therapeutic implication

REVIEW

INTRODUCTION

Although we have observed a dramatic decline in premature mortality worldwide over the last few decades, with more pronounced declines in the more developed countries, the number of deaths from cardiovascular diseases (approximately 31% of global mortality) still exceeds other causes each year.[1] Coronary heart disease (CHD) is considered to be the most prevalent cause of morbidity and mortality globally, primarily due to atherosclerosis (AS) of the coronary arteries. It is a complex molecular and cellular process, mainly vascular wall inflammation. In the process of plaque evolution and growth, the progressive formation of arterial thin cap fibroatheroma containing lipid, inflammatory, and necrotic material is the main pathological feature leading to coronary artery stenosis or occlusion.[2] Several plaque cells like endothelial cells (ECs), vascular smooth muscle cells (VSMCs), immunocytes, inflammatory cells, and stem cells are in direct contact with endogenous danger signals related to metabolites, resulting in pyroptosis and plaque cell dysfunction, which in turn contribute to the evolution of CHD.[3]

Pyroptosis, a well-known inflammation-dependent programmed cell death (PCD), is deemed to be a type of necrotic and lytic cellular self-destruction phenomenon that exist basically as a defense against pathogens by secreting pro-inflammatory cytokines and damage-associated molecular patterns (DAMPs).[4] Inflammasome has become an exciting key mediator in the process of pyroptosis, especially NLRP3 (a receptor like nucleotide-binding oligomerization domain containing pyrin domain 3) inflammasome, mainly composed of the adapter protein apoptosis-associated speck-like protein containing a caspase recruitment domain, and the effector protein pro-caspase-1, and NLRP3 protein, which can trigger inflammatory reactions.[5] Excess inflammasomes can lead to pyroptosis of plaque cells. When CHD is at an advanced stage or is more severe, it tends to cardiomyocyte (CM) dysfunction, regulating CM homeostasis and cardiac fibrosis and inducing heart failure (HF).[6] In summary, no matter how far pyroptosis goes, the above-mentioned various cell activities do not occur independently, and these cells interact with each other through complex signal pathways in the vascular

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microenvironment under the impact of multiple stimulating factors. In this article, we comprehensively summarize the current knowledge of various cells in CHD-related pyroptosis and actively seek some potential targeted therapeutic drugs.

CHARACTERISTICS AND MOLECULAR MECHANISMS OF PYROPTOSIS

The unique morphology of pyroptosis is apparently different from other types of PCD. When cells are subject to pyroptosis, the nucleus undergoes condensation, DNA becomes fragmentation, there is cell swelling, membrane rupture, and ultimately membranous pore formation that maintain the organism homeostasis, with the gasdermin D (GSDMD) of gasdermin family proteins serving as the pivotal downstream effector protein in the formation of specific channels for cytokines release.[7] In the canonical pyroptosis pathway, NLRP3 is activated as a sensor to capture danger signals, generating a series of inflammatory signaling cascades that recruit pro-caspase 1 and form NLRP3 inflammasome. GSDMD is cleaved by functionalized caspase 1 to cause cell lysis, expelling the inhibitory C-terminal structural end from the other end of GSDMD (i.e., GSDMD-N). GSDMD-N relocates to the cytoplasmic membrane and immediately afterwards followed by the formation of pores, triggering lytic death widely recognized as pyroptosis, while trying to convert both pro-IL-1β and pro-IL-18 into the mature forms IL-1β and IL-18, separately.[8,9] In contrast to the canonical pathway, the noncanonical pathway identifies lipopolysaccharides (LPS), an endotoxin produced by gram-negative bacteria, to stimulate human analogues caspase 4/5 and murine caspase 11.[4] Although IL-18 or IL-1β is not directly activated by caspase 4/5/11, both of them initiate the cleavage of GSDMD and the outflow of potassium, which allows them to upregulate NLRP3 and activate caspase 1 (Figure 1).[10] Much attention is now being attracted to other alternative pathways of pyroptosis, which also have an indispensable influence in activating the pyroptosis pathway.

MECHANISMS FOR THE INVOLVEMENT OF PYROPTOSIS IN CORONARY HEART DISEASE

Coronary heart disease is a complex clinical syndrome primarily due to myocardial ischemia and hypoxia. At present, the therapeutic strategies for CHD have expanded from traditional factors such as hyperglycemia, hyperlipidemia, and old age to oxidative stress, lipid disorders, release of inflammation cytokines, endothelial dysfunction, foam cell formation, VSMC activation, and heredity.[11-13] These factors can predispose to and exacerbate vascular and cardiac tissue dysfunction by initiating NLRP3 inflammasome in response to appropriate stimuli and rendering various cells in patients with CHD are more prone to pyroptosis. Conversely, pyroptosis could upregulate the expression of inflammatory mediators in patients' blood with CHD and accelerate the progression of AS to promote plaque rupture, and vascular occlusion, ultimately triggering an acute cardiovascular event.[14] Inhibition of all aspects of the plaque cell pyroptosis pathway effectively restrains inflammatory factors release, delays the progress of AS, reduces the area of myocardial infarction (MI) and improves cardiac function. We cite specific examples of non-CMs and CMs involved in pyroptosis, with a particular focus on cell type-specific features, triggers, and mediators of pyroptosis.

Endothelial Cell Pyroptosis and Coronary Heart Disease

ECs are a thin layer of the metabolically active layer that cover almost all blood vessels surfaces and serve as an interface medium between the circulating blood and the blood vessel wall. Normally, it maintains vascular homeostasis by secreting vasodilators and vasoconstrictors.[15] Under pathological conditions, many factors will lead to EC death, on the contrary, ECs actively participate in the process of cell death. Inappropriate EC pyroptosis, proliferation, invasion, migration, and aberrant expression of adhesion molecule proteins are all hallmarks of EC dysfunction. When the homeostasis is destroyed, many inflammatory diseases, including AS, undergo a series of reactions through the activation of the nicotinamide adenine nucleotide phosphate (NADPH) oxidase system, which generates free radicals like reactive oxygen species (ROS), and sustained ROS stimulation triggered NLRP3 inflammasome activation and EC dysfunction, which could facilitate NLRP3 expression by stimulating the NF-κB pathway.[16] Notably, NLRP3-mediated pyroptosis is central to EC injury, involving membrane rupture and pro-inflammatory factors release. There is a disequilibrium between superfluous ROS and the anti-oxidant defense system, the imbalance of which brings about oxidative stress. Meanwhile, the body's natural LDL is oxidized into oxidized LDL (ox-LDL). Ox-LDL not only promotes cells to produce vasoconstrictors and ROS but also enhances cell adhesion, resulting in EC dysfunction and pyroptosis.[17] EC pyroptosis increases vascular permeability and damages the endothelium with the lapse of time. In turn, endothelial dysfunction has been shown to occur at the onset of AS, giving rise to arterial wall thickening and plaque formation. Studies have demonstrated that the AS property of ox-LDL was endowed with its ability to EC pyroptosis via the miR-125a-5p/TET2 pathway, which further stimulated the upregulation of NLRP3, activation of caspase 1, release of mature IL-1β.[18] Many miRNAs have functions involving the regulation of vascular growth, remodeling and inflammation in the vascular system. miR-223 was an upstream stimulator of pyroptosis in AS, it could be suppressed by lncRNA MEG3

HIGHLIGHTS

- In this review, we underscore the important role endothelial cells, immune cells, vascular smooth muscle cells, and cardiomyocytes play in the development of coronary artery disease.
- We describe the properties of pyroptosis and summarize its contribution and related targets to diseases involving angina pectoris, myocardial infarction, myocardial ischemia in perfusion injury and heart failure.
- We highlight potential anti-pyroptosis drugs for different heart diseases.

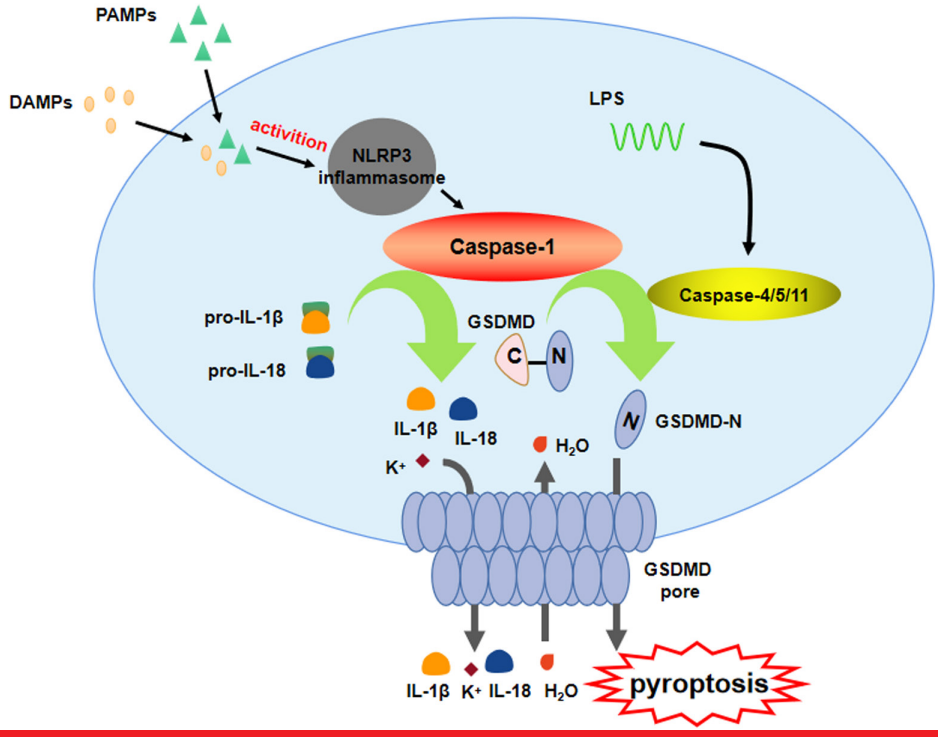

Figure 1. The canonical pathway and the noncanonical pathway of pyroptosis. The classical pathway: When DAMPs and PAMPs are phagocytosed by cells, NLRP3 inflammasomes are stimulated, and active caspase 1 is released. Then caspase 1 hydrolyzes pro-IL-1β and pro-IL-18 precursor cytokines, expelling mature IL-1β and IL-18 to cause inflammation, whereas the activated caspase 1 induces the cleavage of GSDMD to form GSDMD-N, resulting in the formation of pores in the cell membrane, release of inflammatory factors, and efflux of massive K+, which is followed by water entry, causing cell swelling. The nonclassical pathway involves the stimulation of caspase 4/5/11 by LPS, which only recognize GSDMD and do not produce IL-1β or IL-18. However, low levels of IL-1β and IL-18 secretion can be triggered by indirect activation of the NLRP3-ASC-caspase 1 pathway to pyroptosis.

through the sequence complementarity principle, increased the expression of NLRP3 and further enhanced EC pyroptosis.[19] In addition, hyperglycemia caused HUVECs to undergo pyroptosis with subsequent damage to ECs, massive inflammatory secretion, platelet aggregation and thrombosis.[20] Under the action of low shear stress, the activation of NLRP3 and the release of IL-1β in HUVECs were increased, leading to mitochondrial dysfunction and ROS production, and inducing EC pyroptosis via the TET2/SDHB/ROS pathway.[21] Dysfunction of ECs will lead to form vulnerable plaques and compromise vascular homeostasis. When atherosclerotic plaques rupture, platelets gather to form a clot that blocks the coronary artery lumen, eventually causing acute coronary syndrome (ACS). To reduce the area of MI and improve clinical outcomes, patients with acute MI (AMI) are usually managed with revascularization. Paradoxically, however, restoring coronary blood flow also creates additional myocardial injury. Zhang et al[22] found that the microvascular EC pyroptosis triggered by ischemia–reperfusion (I/R) injury aggravated cardiac dysfunction and poor adaptive remodeling, whereas, overexpression of lysine-specific demethylase 3A(KDM3A), a histone demethylase, could significantly ameliorate the potential of I/R injury.

Immune Cell Pyroptosis and Coronary Heart Disease

Macrophages are a vital component of the natural immune system, which can coordinate the preservation of organizational steady state, host defense during pathogen attack and invasion and tissue repair after damage, thus preventing infection.[23] When sensing various organizational sources or environmental stimulus, macrophages attempt to initiate pyroptosis to undertake different pathophysiological changes. NLRP3 inflammasome could be activated by viral pathogens, and some viral surface proteins, including glycoproteins, were necessary to mediate viral entry and fusion and were one of the necessary triggers for THP-1 macrophage pyroptosis.[24] NLRP3 promotes the inflammatory response by activating caspase 1, which is involved in the secretion of IL-1β and IL-18 secreted by pyroptosis. Macrophages are the most affluent hematopoietic cells during the process of vascular plaque formation. Previous studies have demonstrated that the necrotic cell death stimulated the formation of AS though inducing inflammation and expansion of the necrotic nuclei, and the dominant reason for the necrotic core formation and plaque destabilization during the late pathological process was macrophage pyroptosis, followed by the release of some substances such as cell contents, cytokines and proteases.[25] Phorbol myristate acetate (PMA) was applied to encourage THP-1 monocytes isolated from CHD patients to differentiate into macrophages. The NLRP3 inflammasome in macrophages was activated after ATP treatment to potentially promote plaque progression. In the plaque of homocysteine-fed mice, the degree of macrophage death was worsened and more

IL-1β and IL-18 were produced, making the progression of AS more severe.[26] Macrophage pyroptosis in AS lesions is conducive to forming a necrotic core and thinning the fibrous cap, which are important in the ACS pathogenesis. Ye et al[27] found that GSDMD and GSDMD-NT expression levels were markedly upregulated after MI in macrophages infiltrated in the infarcted area. By reducing the release of inflammatory cytokines, GSDMD deficiency could significantly alleviate MI and improve heart function. NR1D1 was a nuclear receptor which relied on the NLRP3 inflammasome to perform a cardiovascular protective role. The absence of NR1D1 would aggravate macrophage infiltration, inflammatory reaction and oxidative stress.[28] Ox-LDL produced during oxidative stress is directly recognized by toll-like receptor 4 (TLR4), can also promote vascular inflammation, induce NLRP3 inflammasome activation, and cause mature and bioactive IL-1β to be released in human macrophages.[29] Wu et al fed NR1D1$^{-/-}$ ApoE$^{-/-}$ mice a high-fat diet and found that the levels of pyroptosis-related genes in macrophages were clearly higher than in the control group, increasing plaque fragility and making plaque rupture.[28] Permanent the left anterior descending artery (LAD) ligation in rats to construct an MI model revealed abundant macrophages infiltrated in the myocardial tissue, and the expressions of NLRP3 inflammasome and IL-1β were greatly increased, which triggered myocardial inflammation in MI, and increased the infarct area and promoted ventricular remodeling (VR).[30]

Besides macrophages, resident immune cells scattered throughout the heart tissue include neutrophils, mast cells, dendritic cells, etc. The heart injury stimulates the immune system, recruits immune cells, secretes pro-inflammatory cytokines, and then recruits various leukocytes from the blood in a cascade reaction that activates inflammation.[31] Nonetheless, there is still a great deal of controversy as to whether neutrophils are involved in pyroptosis, with some studies suggesting that neutrophils could undergo pyroptosis, leading to cytokine release, and others suggesting that neutrophils were capable of activating inflammasomes and releasing cytokines but resisting the progression of GSDMD-dependent pyroptosis cleavage by utilizing a cell-specific mechanism to conditionally participate in pyroptosis while maintaining IL-1β efflux for effective microbial killing.[32-34]

Vascular Smooth Muscle Cell Pyroptosis and Coronary Heart Disease

Vascular smooth muscle cells are the basic constituents of the arterial medial layer, responsible for regulating vascular tension and blood flow. Changes in cardiovascular function can occur when their mechanical and structural properties are altered. A wide variety of factors, including high concentration of calcium, sophisticated phosphate and oxidative stress, can contribute to VSMC injury.[35-37] In the event of vascular injury, VSMCs dedifferentiate and switch from a static "contraction" phenotype to a "pro-inflammatory" phenotype in order to cope with the occurrence of an inflammatory reaction.[29] The dedifferentiated VSMCs release cytokines and contribute to the upregulation of various inflammasome elements.[38] In the initial stage, the accumulation of VSMCs in fibrous caps or intima is traditionally beneficial. The activated VSMCs effectively proliferate and migrate, which is helpful for vascular wall repair. Vascular smooth muscle cells are involved in all stages of AS and produce extracellular matrix such as collagen and elastin in order to form fibrous caps. The thickness of the fibrous cap is a potential indicator of plaque stability.[39] Nonetheless, in the late stage, fatty streaks composed of foam cells gradually develop into AS or even plaques. Recent studies have shown that the treatment of VSMCs with xanthine oxidase increased LOX-1 receptor expression and ROS production, which activated the NLRP3 inflammasome and its subsequent pro-inflammatory signals like caspase 1, IL-1β, and IL-18, and induced foam cell formation to promote accelerated plaque development and instability.[40] Transformation in the VSMC phenotype or the occurrence of pyroptosis leads to the enlargement of necrotic nuclei, the release of large quantities of pro-inflammatory factors and ultimately plaque rupture.[41] GSDMD, as one of the integral prerequisites for pyroptosis of VSMCs, has become attractive research site for host defense, immune disorders, inflammation and other diseases as a central initiator of pyroptosis. Puylaert et al[42] reported that the cleaved GSDMD was found to be expressed among the populated regions of macrophages and VSMCs in human plaques. In addition, they used hybridization technology to generate ApoE$^{-/-}$ GSDMD$^{+/+}$ mice and ApoE$^{-/-}$ GSDMD$^{-/-}$ mice and further revealed a substantial reduction in the size of the brachiocephalic artery plaques in ApoE$^{-/-}$ GSDMD$^{-/-}$ mice in comparison. These results illustrated that targeting GSDMD reduced VSMC pyroptosis and limited the transformation of the vulnerable plaque phenotype to improve plaque stability. miRNAs are short single-stranded noncoding RNAs that negatively regulate the translation or promote the degradation of target genes. The absence in melanoma 2 (AIM2) inflammasome could also recruit ASC adaptor proteins to cleave GSDMD and increase the secretion of inflammatory cytokines, potentially promoting pyroptosis and tissue inflammation. Studies have found that treatment of cultured human aortic SMC with double-stranded DNA could induce AIM2 expression, pro-caspase 1 and GSDMD cleavage, contributing to aortic aneurysm and dissection.[43]

Cardiomyocyte Pyroptosis and Coronary Heart Disease

Essential for maintaining normal heart function, CMs are the key cellular component of the myocardium. CM pyroptosis will result in the loss of CMs and the occurrence of inflammatory responses. Fascinating new literature suggested that inflammasome-induced CM pyroptosis was implicated in the development of CHD and caused end-organ damage. Following a cardiac injury such as ischemia and myocardial inflammation, many CMs are lost and cardiac dysfunction occurs, ultimately contributing to cardiac fibrosis and congestive HF.[44,45] RBP4 was initially identified as an important adipokine, and emerging evidence has discovered that elevated RBP4 was associated with CHD and might have a potential pro-inflammatory effect in heart tissue. Increased RBP4 in CMs were positively associated with IL-1β and IL-18 levels in the serum of MI mice, exacerbating CM dysfunction through the NLRP3-mediated pyroptosis pathway activation. Moreover, the inhibition of RBP4 downgraded the CM

pyroptosis.[46] CM death impairs myocardial contractility and triggers adverse remodeling. Ventricular remodeling is a chronic pathological change. Abundant CM death results in perdurable deprivation of vital function in the infarcted regions and causes myocardial fibrosis and rarefaction of capillaries in the surrounding areas, evoking pathological compensatory hypertrophy of CMs that sustain cardiac output.[47] High levels of pro-caspase 1 exacerbate myocardial hurts and increase infarct size under a VR stress environment. The occurrence of HF is closely associated with VR and is one of the most common end stages of CHD. It is generally characterized by impaired cardiac function and pathological VR.[48] Cardiomyocyte death is a core trait of HF, and inflammation can accelerate and exacerbate HF. Enhanced IL-1β and IL-18 overproduction and inflammasome assembly were documented in cardiac tissues of mice with the preserved ejection fraction (HFpEF) phenotype.[49] Diabetic cardiomyopathy (DCM) is also a leading contributor to HF. Hyperglycemia causes massive ROS production, induces multiple cytokines and inflammatory factors, and promotes the progression of DCM.[50,51] Thioredoxin interacting/inhibiting protein (TXNIP) levels were elevated in hyperglycemic cultured cells and in the peripheral blood and tissues of diabetic animals, and activated AMP-activated protein kinase (AMPK) degraded TXNIP, mediated the anti-pyroptosis pathway via the ROS-AMPK-TXNIP pathway, and inhibited pyroptosis proteins to preserve systolic and diastolic dysfunction in diabetic hearts.[52,53] When CMs undergo molecular biological changes in association with neural and humoral factors, they can also lead to structural and functional disturbances of the heart, compensatory VR disorders, and eventually HF. Tissue protease B (CTSB) is a hydrolase located in the lysosomes of CMs. Stimulated by high glucose, CTSB could bind to NLRP3 and promote the onset of pyroptosis in the classical pathway, exacerbating DCM, worsening cardiac dysfunction, leading to VR, and ultimately evolving into chronic HF.[54]

PYROPTOSIS-RELATED DRUG TARGETS FOR TREATING CORONARY HEART DISEASE

Coronary heart disease is still the most prevalent adverse cardiovascular event today and can be classified into chronic CAD and ACS based on its pathogenetic features. Of these, chronic CAD includes stable angina, occult CAD and ischemic cardiomyopathy. Acute coronary syndrome includes unstable angina, ST-segment elevation myocardial infarction (STEMI), and non-STEMI (NSTEMI).[55] Pyroptosis is recognized as one of the predominant factors contributing to the progression of CAD and has a complex part to play in the development of CHD. For the various causes of heart disease, we have listed below the diverse therapies that target pyroptosis (Table 1).

Angina Pectoris

Angina pectoris is a clinical syndrome with episodes of chest pain or chest discomfort as the main manifestation of transient ischemia and hypoxia of the myocardium due to AS and changes in coronary artery function.[56] In this process, LDL promotes the deposition of cholesterol crystals, and macrophages phagocytose lipoproteins to form foam cells on the one hand and phagocytose-damaged lysosomes on the other hand,[57] releasing ROS and initiating NLRP3-mediated inflammatory pathways through multiple activation and signaling mechanisms. Activated macrophages may produce IL-18 to further damage VSMCs, which is causally related to the pathogenesis of AS.[58] AS triggers plaque rupture and platelet aggregation, which can block part of the arteries leading to an inequality between myocardial oxygen demand and blood supply, causing myocardial ischemia. Statins have long been used in the therapy of CHD and are efficient in lowering blood lipid levels and inhibiting inflammatory responses, thereby stabilizing or reversing atherosclerotic plaque formation. Higher levels of the NLRP3 inflammasome and expression of IL-1β and IL-18 were observed in mononuclear cells from peripheral blood of the stable angina pectoris patients, and expression of NLRP3 and its downstream factors was severely downregulated in a time-dependent manner in response to in vitro interference with rosuvastatin.[14]

Myocardial Infarction

AMI is a sharp reduction in coronary blood flow secondary to coronary AS thrombosis, which gives rise to a sudden decrease in cell energy and subsequent cell necrosis.[59] Diverse types of cell death occur after MI, consisting of pyroptosis. It leads to myocardial perforation and cell membrane rupture when the GSDMD is cut, releasing pro-inflammatory factors. ASC spots were detectable in the myocardium of mice with AMI, suggesting that the NLRP3 inflammasome drove cytokine release and pyroptosis.[60] AMI mice treated with VX-765, a specific caspase-1 inhibitor that is also a pyroptosis inhibitor, was observed to significantly improve left ventricular ejection fraction values and reduce the area of cardiac damage.[61] Additionally, nicorandil has potent anti-inflammatory activity. It can safeguard CMs through the pathway mediated by TLR4/MyD88/NF-κB/NLRP3 and ameliorate MI-induced pyroptosis.[62] Sacubitril/valsartan (LCZ696) is a new type of angiotensin receptor enkephalinase depressor that suppresses inflammation and oxidative stress by reducing aldosterone secretion. The TAK1/JNK signaling pathway has been implicated to be involved in the activation of NLRP3. Overexpression of TAK1 modulated JNK phosphorylation level while activating the NLRP3 inflammasome, which promoted cleavage of the N-terminal end of the GSDMD, thereby facilitating release of IL-1β and IL-18. Notably, LCZ696 suppressed the expression of TAK1 and NLRP3, improved VR, and demonstrated a protective effect on MI hearts.[63] lncRNA H19 overexpression could inhibit cytochrome P450 1B1 (CYP1B1) activity by regulating PBX3, which reduced pyroptosis-related proteins expression and attenuated MI in rat models.[64] miR-378a-3p (an exosomal miRNA) enriched in extracellular vesicles of M2 macrophage origin, effectively blocked the NLRP3/caspase-1/GSDMD pathway activation, reduced the levels of pyroptosis markers, and inhibited pyroptosis in MI mice and hypoxic HL-1 cells.[65] miR-135b has a positive effect on cardiac function. Studies have shown that miR-135b directly targeted caspase 1 to downregulate IL-1β levels, attenuated MI-induced cell swelling and membrane rupture, and protected the heart from MI

Table 1. Summary of Pyroptosis-mediated Treatments of Cardiac Pathologies Inducing Coronary Heart Disease

Disease Pathogenesis	Drug	Experimental Subject	Mechanism of Action	Outcome	Reference
Angina pectoris	Rosuvastatin	In vivo In vitro	NLRP3 inhibition	Attenuated the inflammatory process of AS	DOI: 10.3892/mmr.2019.10382
Myocardial infarction	VX-765	In vivo	Caspase-1 inhibition	Reduced area of cardiac damage and improved cardiac function	DOI: 10.1038/s41419-021-04143-3
	Nicorandil	In vivo	Inhibited TLR4/MyD88/NF-κB/NLRP3 signaling pathway	Protected against myocardial injury	DOI: 10.1177/15353702211013444
	LCZ696	In vivo In vitro	Inhibited TAK1/JNK signaling pathway	Inhibited myocardial fibrosis and improved VR	DOI: 10.3892/mmr.2021.12315
	lncRNA H19	In vivo In vitro	Depended on PBX3/CYP1B1 manner	Promoted cell proliferation rate and attenuated MI progression	DOI: 10.1007/s11010-020-03998-y
	miR-378a-3p	In vivo In vitro	Inhibited NLRP3/caspase-1/GSDMD pathway	Restored cardiac function and reduced myocardial damage	DOI: 10.1038/s41440-022-00851-1
	miR-135b	In vivo In vitro	Inhibited NLRP3/caspase-1/IL-1β pathway	Alleviated MI injury and protected cardiac function	DOI: 10.1016/j.ijcard.2019.09.055
	Mitofilin	In vivo In vitro	Activated PI3K/AKT pathway	Mitigated AMI- induced myocardial injury	DOI: 10.3389/fcvm.2022.823591
	Melatonin	In vivo In vitro	Inhibited TLR4/NF-κB signaling pathway	Improved cardiac dysfunction and reduced cardiomyocyte death	DOI: 10.1155/2021/5387799
	Qishen granules	In vivo In vitro	NLRP3 inhibition	Improved the cardiac function, reduced inflammatory cell infiltration and collagen deposition.	DOI: 10.1016/j.jep.2021.114841
	G-Rh2	In vivo	Inhibited NLRP3/caspase-1/IL-1β pathway	Inhibited the pathological development of AMI	DOI: 10.1155/2022/5194523
Myocardial ischemia–reperfusion injury	miR-320b	In vivo In vitro	Inhibited NLRP3/caspase-1 pathway	Protected the myocardium against I/R injury	DOI: 10.2147/DDDT.S239546
	Iguratimod	In vivo In vitro	Inhibited COX2/NLRP3 pathway	Alleviated myocardial I/R injury	DOI: 10.3389/fcell.2021.746317
	TMZ	In vivo In vitro	Inhibited TLR4/MyD88/NF-κB/NLRP3 pathway	Protected the myocardium against I/R injury	DOI: 10.1007/s00011-021-01530-6
	Insulin	In vivo	Regulated pyruvate dehydrogenase E1 alpha subunit (PDHA1) dephosphorylation to inhibit NLRP3 expression	Improved myocardial energy metabolism and reduced the area of MI	DOI: 10.1177/02676591221099807
	PDA@M	In vivo In vitro	Inhibited NLRP3/caspase-1 pathway	Reduced infarct size and improved cardiac function after MI/RI	DOI: 10.1021/acsami.1c03421
	Curcumin	In vitro	NLRP3 inhibition	Improved endothelial cell dysfunction	DOI: 10.3892/mmr.2022.12730
Heart failure	BAY11-7082	In vivo In vitro	Inhibited NF-κB/NLRP3 pathway	Reduced cardiac remodeling and cardiac dysfunction	DOI: 10.1016/j.intimp.2019.106116
	Anakinra	In vivo	IL-1 inhibition	Inhibited AS and reduced vascular injury	DOI: 10.1016/j.jacbts.2021.08.006
	Canakinumab	In vivo	IL-1β inhibition	Reduced hospitalization rate and mortality rate	DOI: 10.1056/NEJMoa1707914
	MCC950	In vivo	NLRP3 inhibition	Protected against cardiomyocyte injury	DOI: 10.1038/s41419-020-02777-3
	Echinacoside	In vivo In vitro	Suppressed NADPH/ROS/ER stress	Improved cardiac function and prevented HF	DOI: 10.1111/jcmm.17564

damage by preventing pyroptosis.[66] When the researchers used the overexpressed mitofilin in the AMI model, it memorably reduced the indicators related to pyroptosis, showing its inhibitory effect on pyroptosis.[67] As a common endocrine hormone, melatonin reversed elevated TLR4 and NF-κB after MI and inhibited NLRP3 inflammasome-mediated cellular pyroptosis, thereby attenuating CM loss.[68] At present, a number of traditional Chinese herbal medicine preparations broadly applied in clinical practice to treat MI, such as Qishen Granules and Ginsenoside Rh2(G-Rh2), have also been confirmed to inhibit the development of AMI by alleviating CM pyroptosis.[69,70] G-Rh2, a hydrolysate derived from ginsenoside which is the active constituent of ginseng, was recently found to significantly ameliorate the severe damage to CMs and organelles in AMI-modeled rat CMs, with marked inhibition of both NLRP3 and caspase-1 levels.[70]

Myocardial Ischemia and Reperfusion Injury

The sudden recovery of coronary blood flow in the infarct-associated artery itself leads to heart muscle damage and cell death, halving the size of the infarct, known as I/R injury.[71] The elements in relation to this dynamic process of I/R injury are intricate and include principally microvascular obstruction, inflammatory response, oxidative stress and so on.[72-74] Damage to the myocardium evokes a blazing inflammatory response. GSDMD-mediated CM pyroptosis is a serious incident in I/R injury process and releases multifarious DAMPs, combined with the infiltration of pro-inflammatory factors. The NF-κB initiation signal is activated by the TLRs, and ROS is immediately produced, causing NLRP3 inflammasome assembly and caspase-1 activation.[75] Sensitized caspase 1 cleaves GSDMD and splits the precursors of IL-1β and IL-18, triggering pore formation in the plasmalemma, increased cell permeability, and liberation of cell contents (mature IL-1β and IL-18). In the meantime, the alterations in cell permeability will normally cause extracellular fluid elicitation to obtain access to cells, inducing cell lysis. Clinically, GSDMD and IL-18 expressions were higher in STEMI patients than in controls after percutaneous coronary intervention (PCI). It was shown that NLRP3/caspase-1-mediated IL-1β secretion was highly expressed in the pathophysiology of microvascular and I/R injury.[27] The exosome is a multifunctional vesicle that contains a wealth of genetic material with biological activities. Mesenchymal stem cell (MSC)-derived exosomes (MSCs-exos) have been reported to be endowed with the ability to inhibit cell pyroptosis. Tang et al[76] constructed the main model of myocardial I/R injury through the hypoxia/reoxygenation (H/R) injury model on primary CMs cultured in vitro. They found and confirmed that the viability of cells in the H/R model was decreased and pyroptosis was intensified, whereas the MSCs-exos could improve pyroptosis in the H/R model. In terms of mechanism, miR-320b in the H/R cells screened out by PCR was significantly upregulated in MSCs-exos, and MSCs-exos as well facilitated miR-320b in the H/R model. To recap, exosomal miR-320b inhibited I/R injury though repressing the target gene NLRP3 and related protein caspase 1 in pyroptosis. Furthermore, other miRNAs (such as miR-33a-5p, miR-200a-3p, and miR-126) are also able to restrain myocardial pyroptosis through their respective pathways.[77-79] As a burgeoning antirheumatic drug, iguratimod has been widely applied in the therapy of rheumatoid arthritis.[80] It not only selectively inhibits the activity of COX2, but has been suggested to notably improve the undue heart inflammation and CM damage caused by myocardial I/R injury. In particular, COX2 in cardiac fibroblasts increased after I/R injury, which is attributed to NLRP3 inflammasome and caspase-1 level being transferred to a higher extent. Iguratimod inhibits myocardial fibroblast pyroptosis by acting on the COX2/NLRP3 signaling pathway, thus reducing the secretion of inflammatory cytokines and myocardial inflammatory reaction, and ultimately subsiding myocardial I/R injury.[81] Trimetazidine (TMZ) has conventionally been considered as an anti-anginal drug to protect the heart by switching energy from fatty acid oxidation to glucose oxidation.[82] In addition to its cardioprotective capability, the more exhilarating result was that TMZ suppressed GSDMD-mediated pyroptosis, which enhanced CM morphological changes, attenuated inflammatory cell infiltration, and weakened IL-1β in extracellular and intracellular cells. It was pointed out that the inhibitory effect of TMZ on I/R injury was partly fulfilled via the anti-inflammatory effect of TMZ.[83] Insulin lessened NLRP3-induced CM pyroptosis and altered myocardial energy metabolism by regulating PDHA1.[84] The newly established biomimetic nanoplatform (PDA@M) of polydopamine (PDA) effectively alleviated MI/RI-induced oxidative stress, allowing PDA to exert its antioxidant effects after being delivered to the infarct zone with the help of the outer membrane structure and endocytosis by CMs. Cardiac function after MI/RI was improved by restaining the NLRP3/caspase-1 pathway.[85] By the way, some natural substances and their derivatives, such as emodin, piperine, cinnamic aldehyde, curcumin, astragaloside IV (AS-IV), and esculetin, can also reduce the swelling and dissolution of CMs and accompanied by the decline of IL-1β levels, which is in line with the properties of inhibiting pyroptosis and can reduce the area of MI.[86-88] Curcumin has been proven to have the competence to inhibit H2O2-induced HUVEC inflammation and pyroptosis. AS-IV suppressed LPS-activated HUVECs pyroptosis by way of motivating ROS/NLRP3-mediated inflammation.[89]

Heart Failure

Ischemic cardiomyopathy (ICM) is a specific type of CHD or the consequence of advanced progression. ICM occurs primarily as a result of prolonged myocardial ischemia and limited regenerative capacity of cardiac tissue, leading to diffuse myocardial fibrosis and a decrease in cardiac ejection fraction.[90] In response to ischemic injury, CM necrosis evokes innate immune system and inflammatory signal pathways that generally lead to poor cardiac remodeling and progressive HF. Currently, NLRP3-induced pyroptosis has gradually gained widespread attention. Inhibition of pyroptosis reduces the structural dysfunction that leads to HF. Dectin 1, which belongs to the C-type lectin receptor (CLR) family, is an emerging PRR known primarily for its involvement in the coupling of innate and adaptive immunity.[91] Li et al[92] confirmed that cardiac dectin-1 mRNA and protein expression were markedly increased by NF-κB and NLRP3 activation in mice after MI. Silencing of dectin

1 through both in vitro and in vivo experiments dramatically ameliorated cardiac fibrosis in mice. BAY11-7082, an NF-κB inhibitor, markedly inhibited VR and dysfunction to delay the onset of HF. Inhibition of cellular pyroptosis can memorably reduce the structural dysfunction that leads to HF. Endogenous IL-1β and IL-18 also immediately regulate cardiac contractility. Anakinra blocks the activity of IL-1α and IL-1β and is an IL-1 receptor antagonist. Clinical trials have shown that treatment with anabolic acid reduced the N-terminal B-type natriuretic peptide precursor (NT-proBNP) levels in patients, resulting in a lower incidence of hospitalization for HF.[93,94] Alternatively, Canakinumab may also fulfill its therapeutic potential for HF by inhibiting IL-1β.[95,96] Mixed-spectrum kinase 3 (MLK3) is a mitogen-activated protein kinase (MAPK) kinase that provokes the MAPK pathway. MLK3 is closely associated with inflammation and ROS.[97] In a transverse aortic constriction (TAC)-intervened HF mice model, MLK3 depletion inhibited pyroptosis-related GSDMD cleavage and caspase 1 and NLRP3 activation. These levels were partially reduced when MLK3 was inhibited and NLRP3 was inhibited via MCC950.[98] Echinacoside (ECH) is an important active ingredient. Based on previous findings, ECH reversed VR and improved cardiac function by inhibiting mitochondrial ROS.[99] And that in HF, NADPH oxidase (mainly NOX2 and NOX4 subunits) is the primary source of intracellular ROS.[100] Pyroptosis protein markers, NOX2 and NOX4 were significantly upregulated, and ROS and endoplasmic reticulum stress production were increased in isoproterenol (ISO)-treated left ventricular tissues from HF rats, whereas ECH reversed this change and diminished GSDMD-N expression, caspase 1, NLRP3, and IL-1β. In summary, ECH exerted anti-CM pyroptosis and cardioprotective effects via inhibiting NADPH/ROS/ER stress.[101]

CONCLUDING REMARKS AND PERSPECTIVES

Coronary heart disease is still a nonnegligible threat to human life and health. Cardiomyocyte death is a heterogeneous event, containing multiple simultaneous PCDs. Current studies have concentrated on the effects of the classical NLRP3 inflammasome-mediated pyroptosis pathway on CHD, and research on pyroptosis in the treatment of CHD is still lacking. Further studies exploring the mechanisms and pathology of other inflammasomes in CHD are warranted and may provide insight into elucidate the upstream signals and molecules implicated in inflammasome activation and correlation with heart disease. We have therefore undertaken a review to help better understand and manage CHD. We list the research advances and available therapeutic agents for pyroptosis in angina pectoris, MI, myocardial I/R injury, and HF, which are not yet comprehensive despite there have been some key breakthroughs and discoveries in the studies of pyroptosis mechanisms. The potential benefits and side effects of these existing drugs in the clinical setting still require extensive experiments to assess their safety and efficacy, and further studies on pyroptosis are necessary. It is believed that with further research, pyroptosis will provide new strategies for the treatment of CHD.

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REFERENCES

1. Read SH, Wild SH. Prevention of premature cardiovascular death worldwide. *Lancet*. 2020;395(10226):758-760. [CrossRef]
2. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on coronary plaque composition. *J Am Coll Cardiol*. 2018;72(17):2012-2021. [CrossRef]
3. Rayner KJ. Cell death in the vessel wall: the good, the bad, the ugly. *Arterioscler Thromb Vasc Biol*. 2017;37(7):e75-e81. [CrossRef]
4. Loveless R, Bloomquist R, Teng Y. Pyroptosis at the forefront of anticancer immunity. *J Exp Clin Cancer Res*. 2021;40(1):264. [CrossRef]
5. Coll RC, Schroder K, Pelegrín P. NLRP3 and pyroptosis blockers for treating inflammatory diseases. *Trends Pharmacol Sci*. 2022;43(8):653-668. [CrossRef]
6. Lala A, Desai AS. The role of coronary artery disease in heart failure. *Heart Fail Clin*. 2014;10(2):353-365. [CrossRef]
7. Chen X, He WT, Hu L, et al. Pyroptosis is driven by non-selective gasdermin-D pore and its morphology is different from MLKL channel-mediated necroptosis. *Cell Res*. 2016;26(9):1007-1020. [CrossRef]
8. Liu X, Zhang Z, Ruan J, et al. Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. *Nature*. 2016;535(7610):153-158. [CrossRef]
9. Booty LM, Bryant CE. Gasdermin D and beyond - gasdermin-mediated pyroptosis in bacterial infections. *J Mol Biol*. 2022;434(4):167409. [CrossRef]
10. Kayagaki N, Stowe IB, Lee BL, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. *Nature*. 2015;526(7575):666-671. [CrossRef]
11. Vanhoutte PM, Shimokawa H, Tang EH, Feletou M. Endothelial dysfunction and vascular disease. *Acta Physiol (Oxf)*. 2009;196(2):193-222. [CrossRef]
12. Marchio P, Guerra-Ojeda S, Vila JM, Aldasoro M, Victor VM, Mauricio MD. Targeting early atherosclerosis: a focus on oxidative stress and inflammation. *Oxid Med Cell Longev*. 2019;2019:8563845. [CrossRef]
13. He X, Fan X, Bai B, Lu N, Zhang S, Zhang L. Pyroptosis is a critical immune-inflammatory response involved in atherosclerosis. *Pharmacol Res*. 2021;165:105447. [CrossRef]
14. Zhu J, Wu S, Hu S, et al. NLRP3 inflammasome expression in peripheral blood monocytes of coronary heart disease patients and its modulation by rosuvastatin. *Mol Med Rep*. 2019;20(2):1826-1836. [CrossRef]
15. Galley HF, Webster NR. Physiology of the endothelium. *Br J Anaesth*. 2004;93(1):105-113. [CrossRef]
16. Long Y, Liu X, Tan XZ, et al. ROS-induced NLRP3 inflammasome priming and activation mediate PCB 118- induced pyroptosis in

endothelial cells. *Ecotoxicol Environ Saf*. 2020;189:109937. [CrossRef]
17. Kattoor AJ, Goel A, Mehta JL. LOX-1: regulation, signaling and its role in atherosclerosis. *Antioxidants (Basel)*. 2019;8(7). [CrossRef]
18. Zhaolin Z, Jiaojiao C, Peng W, et al. OxLDL induces vascular endothelial cell pyroptosis through miR-125a-5p/TET2 pathway. *J Cell Physiol*. 2019;234(5):7475-7491. [CrossRef]
19. Zhang Y, Liu X, Bai X, et al. Melatonin prevents endothelial cell pyroptosis via regulation of long noncoding RNA MEG3/miR-223/NLRP3 axis. *J Pineal Res*. 2018;64(2). [CrossRef]
20. Wang X, Wang W, Zhang R, et al. Melatonin attenuates high glucoseinduced endothelial cell pyroptosis by activating the Nrf2 pathway to inhibit NLRP3 inflammasome activation. *Mol Med Rep*. 2023;27(3). [CrossRef]
21. Chen J, Zhang J, Wu J, et al. Low shear stress induced vascular endothelial cell pyroptosis by TET2/SDHB/ROS pathway. *Free Radic Biol Med*. 2021;162:582-591. [CrossRef]
22. Zhang B, Liu G, Huang B, et al. KDM3A attenuates myocardial ischemic and reperfusion injury by ameliorating cardiac microvascular endothelial cell pyroptosis. *Oxid Med Cell Longev*. 2022;2022:4622520. [CrossRef]
23. Yan J, Horng T. Lipid metabolism in regulation of macrophage functions. *Trends Cell Biol*. 2020;30(12):979-989. [CrossRef]
24. Eisfeld HS, Simonis A, Winter S, et al. Viral glycoproteins induce NLRP3 inflammasome activation and pyroptosis in macrophages. *Viruses*. 2021;13(10). [CrossRef]
25. Henein MY, Vancheri S, Longo G, Vancheri F. The role of inflammation in cardiovascular disease. *Int J Mol Sci*. 2022;23(21). [CrossRef]
26. Wang R, Wang Y, Mu N, et al. Activation of NLRP3 inflammasomes contributes to hyperhomocysteinemia-aggravated inflammation and atherosclerosis in apoE-deficient mice. *Lab Invest*. 2017;97(8):922-934. [CrossRef]
27. Ye X, Zhang P, Zhang Y, et al. GSDMD contributes to myocardial reperfusion injury by regulating pyroptosis. *Front Immunol*. 2022;13:893914. [CrossRef]
28. Wu Z, Liao F, Luo G, et al. NR1D1 deletion induces rupture-prone vulnerable plaques by regulating macrophage pyroptosis via the NF-kappaB/NLRP3 inflammasome pathway. *Oxid Med Cell Longev*. 2021;2021:5217572. [CrossRef]
29. Liu J, Huang GQ, Ke ZP. Silence of long intergenic noncoding RNA HOTAIR ameliorates oxidative stress and inflammation response in ox-LDL-treated human macrophages by upregulating miR-330-5p. *J Cell Physiol*. 2019;234(4):5134-5142. [CrossRef]
30. Liu W, Sun J, Guo Y, et al. Calhex231 ameliorates myocardial fibrosis post myocardial infarction in rats through the autophagy-NLRP3 inflammasome pathway in macrophages. *J Cell Mol Med*. 2020;24(22):13440-13453. [CrossRef]
31. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. *Circ Res*. 2012;110(1):159-173. [CrossRef]
32. Kambara H, Liu F, Zhang X, et al. Gasdermin D exerts anti-inflammatory effects by promoting neutrophil death. *Cell Rep*. 2018;22(11):2924-2936. [CrossRef]
33. Chauhan D, Demon D, Vande Walle L, et al. GSDMD drives canonical inflammasome-induced neutrophil pyroptosis and is dispensable for NETosis. *EMBO Rep*. 2022;23(10):e54277. [CrossRef]
34. Dubyak GR, Miller BA, Pearlman E. Pyroptosis in neutrophils: multimodal integration of inflammasome and regulated cell death signaling pathways. *Immunol Rev*. 2023;314(1):229-249. [CrossRef]
35. Leopold JA. Vascular calcification: mechanisms of vascular smooth muscle cell calcification. *Trends Cardiovasc Med*. 2015;25(4):267-274. [CrossRef]
36. Montezano AC, Dulak-Lis M, Tsiropoulou S, Harvey A, Briones AM, Touyz RM. Oxidative stress and human hypertension: vascular mechanisms, biomarkers, and novel therapies. *Can J Cardiol*. 2015;31(5):631-641. [CrossRef]
37. Durham AL, Speer MY, Scatena M, Giachelli CM, Shanahan CM. Role of smooth muscle cells in vascular calcification: implications in atherosclerosis and arterial stiffness. *Cardiovasc Res*. 2018;114(4):590-600. [CrossRef]
38. Chistiakov DA, Orekhov AN, Bobryshev YV. Vascular smooth muscle cell in atherosclerosis. *Acta Physiol (Oxf)*. 2015;214(1):33-50. [CrossRef]
39. Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. *Circ Res*. 2016;118(4):692-702. [CrossRef]
40. Dai Y, Cao Y, Zhang Z, Vallurupalli S, Mehta JL. Xanthine oxidase induces foam cell formation through LOX-1 and NLRP3 activation. *Cardiovasc Drugs Ther*. 2017;31(1):19-27. [CrossRef]
41. Badimon L, Vilahur G. Thrombosis formation on atherosclerotic lesions and plaque rupture. *J Intern Med*. 2014;276(6):618-632. [CrossRef]
42. Puylaert P, Van Praet M, Vaes F, et al. Gasdermin D deficiency limits the transition of atherosclerotic plaques to an inflammatory phenotype in ApoE knock-out mice. *Biomedicines*. 2022;10(5). [CrossRef]
43. Ageedi W, Zhang C, Frankel WC, et al. AIM2 inflammasome activation contributes to aortic dissection in a sporadic aortic disease mouse model. *J Surg Res*. 2022;272:105-116. [CrossRef]
44. Payan SM, Hubert F, Rochais F. Cardiomyocyte proliferation, a target for cardiac regeneration. *Biochim Biophys Acta Mol Cell Res*. 2020;1867(3):118461. [CrossRef]
45. Mishra PK, Adameova A, Hill JA, et al. Guidelines for evaluating myocardial cell death. *Am J Physiol Heart Circ Physiol*. 2019;317(5):H891-H922. [CrossRef]
46. Rychter AM, Skrzypczak-Zielińska M, Zielińska A, et al. Is the retinol-binding Protein 4 a possible risk factor for cardiovascular diseases in obesity? *Int J Mol Sci*. 2020;21(15). [CrossRef]
47. De Geest B, Mishra M. Role of high-density lipoproteins in cardioprotection and in reverse remodeling: therapeutic implications. *Biochim Biophys Acta Mol Cell Biol Lipids*. 2021;1866(11):159022. [CrossRef]
48. Hua F, Li JY, Zhang M, et al. Kaempferol-3-O-rutinoside exerts cardioprotective effects through NF-kappaB/NLRP3/Caspase-1 pathway in ventricular remodeling after acute myocardial infarction. *J Food Biochem*. 2022;46(10):e14305. [CrossRef]
49. Xia YY, Shi Y, Li Z, et al. Involvement of pyroptosis pathway in epicardial adipose tissue - myocardium axis in experimental heart failure with preserved ejection fraction. *Biochem Biophys Res Commun*. 2022;636(2):62-70. [CrossRef]
50. Tsai KH, Wang WJ, Lin CW, et al. NADPH oxidase-derived superoxide anion-induced apoptosis is mediated via the JNK-dependent activation of NF-kappaB in cardiomyocytes exposed to high glucose. *J Cell Physiol*. 2012;227(4):1347-1357. [CrossRef]
51. Cai L, Wang Y, Zhou G, et al. Attenuation by metallothionein of early cardiac cell death via suppression of mitochondrial oxidative stress results in a prevention of diabetic cardiomyopathy. *J Am Coll Cardiol*. 2006;48(8):1688-1697. [CrossRef]
52. Wei H, Bu R, Yang Q, et al. Exendin-4 protects against hyperglycemia-induced cardiomyocyte pyroptosis via the AMPK-TXNIP pathway. *J Diabetes Res*. 2019;2019:8905917. [CrossRef]
53. Luo B, Li B, Wang W, et al. NLRP3 gene silencing ameliorates diabetic cardiomyopathy in a type 2 diabetes rat model. *PLoS One*. 2014;9(8):e104771. [CrossRef]
54. Liu C, Yao Q, Hu T, et al. Cathepsin B deteriorates diabetic cardiomyopathy induced by streptozotocin via promoting

NLRP3-mediated pyroptosis. *Mol Ther Nucleic Acids*. 2022;30:198-207. [CrossRef]
55. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. *Eur Heart J*. 2013;34(10):719-728. [CrossRef]
56. Kaski JC, Crea F, Gersh BJ, Camici PG. Reappraisal of ischemic heart disease. *Circulation*. 2018;138(14):1463-1480. [CrossRef]
57. Chuang SY, Yang CH, Chou CC, Chiang YP, Chuang TH, Hsu LC. TLR-induced PAI-2 expression suppresses IL-1beta processing via increasing autophagy and NLRP3 degradation. *Proc Natl Acad Sci U S A*. 2013;110(40):16079-16084. [CrossRef]
58. Ahn H, Kim J, Jeung EB, Lee GS. Dimethyl sulfoxide inhibits NLRP3 inflammasome activation. *Immunobiology*. 2014;219(4): 315-322. [CrossRef]
59. Choudhury T, West NE, El-Omar M. ST elevation myocardial infarction. *Clin Med (Lond)*. 2016;16(3):277-282. [CrossRef]
60. Takahashi M. Cell-specific roles of NLRP3 inflammasome in myocardial infarction. *J Cardiovasc Pharmacol*. 2019;74(3):188-193. [CrossRef]
61. Liu W, Shen J, Li Y, et al. Pyroptosis inhibition improves the symptom of acute myocardial infarction. *Cell Death Dis*. 2021;12(10):852. [CrossRef]
62. Chen F, Chen ZQ, Zhong GL, Zhu JJ. Nicorandil inhibits TLR4/MyD88/NF-kappaB/NLRP3 signaling pathway to reduce pyroptosis in rats with myocardial infarction. *Exp Biol Med (Maywood)*. 2021;246(17):1938-1947. [CrossRef]
63. Shen J, Fan Z, Sun G, Qi G. Sacubitril/valsartan (LCZ696) reduces myocardial injury following myocardial infarction by inhibiting NLRP3induced pyroptosis via the TAK1/JNK signaling pathway. *Mol Med Rep*. 2021;24(3). [CrossRef]
64. Han Y, Dong B, Chen M, Yao C. LncRNA H19 suppresses pyroptosis of cardiomyocytes to attenuate myocardial infarction in a PBX3/CYP1B1-dependent manner. *Mol Cell Biochem*. 2021;476(3):1387-1400. [CrossRef]
65. Yuan W, Liang X, Liu Y, Wang H. Mechanism of miR-378a-3p enriched in M2 macrophage-derived extracellular vesicles in cardiomyocyte pyroptosis after MI. *Hypertens Res*. 2022;45(4):650-664. [CrossRef]
66. Li A, Yu Y, Ding X, et al. MiR-135b protects cardiomyocytes from infarction through restraining the NLRP3/caspase-1/IL-1beta pathway. *Int J Cardiol*. 2020;307:137-145. [CrossRef]
67. Ma M, Liang SC, Diao KY, Wang Q, He Y. Mitofilin mitigates myocardial damage in acute myocardial infarction by regulating pyroptosis of cardiomyocytes. *Front Cardiovasc Med*. 2022;9:823591. [CrossRef]
68. Wen L, Wang M, Luo P, Meng X, Zhao M. Melatonin exerts cardioprotective effects by inhibiting NLRP3 inflammasome-induced pyroptosis in mice following myocardial infarction. *Oxid Med Cell Longev*. 2021;2021:5387799. [CrossRef]
69. Chen X, Li Y, Li J, et al. Qishen granule (QSG) exerts cardioprotective effects by inhibiting NLRP3 inflammasome and pyroptosis in myocardial infarction rats. *J Ethnopharmacol*. 2022;285:114841. [CrossRef]
70. Song W, Dai B, Dai Y. Influence of ginsenoside Rh2 on cardiomyocyte pyroptosis in rats with acute myocardial infarction. *Evid Based Complement Alternat Med*. 2022;2022:5194523. [CrossRef]
71. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. *N Engl J Med*. 2007;357(11):1121-1135. [CrossRef]
72. Heusch G. Myocardial ischaemia-reperfusion injury and cardioprotection in perspective. *Nat Rev Cardiol*. 2020;17(12):773-789. [CrossRef]
73. Li J, Sun D, Li Y. Novel findings and therapeutic targets on cardioprotection of ischemia/ reperfusion injury in STEMI. *Curr Pharm Des*. 2019;25(35):3726-3739. [CrossRef]
74. Hu X, Ma R, Lu J, et al. IL-23 promotes myocardial I/R injury by increasing the inflammatory responses and oxidative stress reactions. *Cell Physiol Biochem*. 2016;38(6):2163-2172. [CrossRef]
75. Zheng Y, Xu X, Chi F, Cong N. Pyroptosis: a newly discovered therapeutic target for ischemia-reperfusion injury. *Biomolecules*. 2022;12(11). [CrossRef]
76. Tang J, Jin L, Liu Y, et al. Exosomes derived from mesenchymal stem cells protect the myocardium against ischemia/reperfusion injury through inhibiting pyroptosis. *Drug Des Devel Ther*. 2020;14:3765-3775. [CrossRef]
77. Ye X, Hang Y, Lu Y, et al. CircRNA circ-NNT mediates myocardial ischemia/reperfusion injury through activating pyroptosis by sponging miR-33a-5p and regulating USP46 expression. *Cell Death Discov*. 2021;7(1):370. [CrossRef]
78. Chen ZQ, Zhou Y, Chen F, et al. miR-200a-3p attenuates coronary microembolization-induced myocardial injury in rats by inhibiting TXNIP/NLRP3-mediated cardiomyocyte pyroptosis. *Front Cardiovasc Med*. 2021;8:693257. [CrossRef]
79. Fei L, Zhang N, Zhang J. Mechanism of miR-126 in hypoxia-re oxygenation-induced cardiomyocyte pyroptosis by regulating HMGB1 and NLRP3 inflammasome. *Immunopharmacol Immunotoxicol*. 2022;44(4):500-509. [CrossRef]
80. Xie S, Li S, Tian J, Li F. Iguratimod as a new drug for rheumatoid arthritis: current landscape. *Front Pharmacol*. 2020;11:73. [CrossRef]
81. Zhang M, Lei YS, Meng XW, et al. Iguratimod alleviates myocardial ischemia/reperfusion injury through inhibiting inflammatory response induced by cardiac fibroblast pyroptosis via COX2/NLRP3 signaling pathway. *Front Cell Dev Biol*. 2021;9:746317. [CrossRef]
82. Heggermont WA, Papageorgiou AP, Heymans S, van Bilsen M. Metabolic support for the heart: complementary therapy for heart failure? *Eur J Heart Fail*. 2016;18(12):1420-1429. [CrossRef]
83. Chen X, Lin S, Dai S, et al. Trimetazidine affects pyroptosis by targeting GSDMD in myocardial ischemia/reperfusion injury. *Inflamm Res*. 2022;71(2):227-241. [CrossRef]
84. Pan SS, Wang F, Hui YP, et al. Insulin reduces pyroptosis-induced inflammation by PDHA1 dephosphorylation-mediated NLRP3 activation during myocardial ischemia-reperfusion injury. *Perfusion*. 2023;38(6):1277-1287. [CrossRef]
85. Wei Y, Zhu M, Li S, et al. Engineered biomimetic nanoplatform protects the myocardium against ischemia/reperfusion injury by inhibiting pyroptosis. *ACS Appl Mater Interfaces*. 2021;13(29):33756-33766. [CrossRef]
86. Ye B, Chen X, Dai S, et al. Emodin alleviates myocardial ischemia/reperfusion injury by inhibiting gasdermin D-mediated pyroptosis in cardiomyocytes. *Drug Des Devel Ther*. 2019;13:975-990. [CrossRef]
87. Guo X, Hu S, Liu JJ, et al. Piperine protects against pyroptosis in myocardial ischaemia/reperfusion injury by regulating the miR-383/RP105/AKT signalling pathway. *J Cell Mol Med*. 2021;25(1):244-258. [CrossRef]
88. Zheng B, Qi J, Yang Y, et al. Mechanisms of cinnamic aldehyde against myocardial ischemia/hypoxia injury in vivo and in vitro: involvement of regulating PI3K/AKT signaling pathway. *Biomed Pharmacother*. 2022;147:112674. [CrossRef]
89. Yuan Y, Zhang C, He Y, et al. Curcumin improves the function of umbilical vein endothelial cells by inhibiting H(2)O(2)induced pyroptosis. *Mol Med Rep*. 2022;25(6). [CrossRef]
90. Del Buono MG, Moroni F, Montone RA, Azzalini L, Sanna T, Abbate A. Ischemic cardiomyopathy and heart failure after acute myocardial infarction. *Curr Cardiol Rep*. 2022;24(10):1505-1515. [CrossRef]

91. Kalia N, Singh J, Kaur M. The role of dectin-1 in health and disease. *Immunobiology*. 2021;226(2):152071. [CrossRef]
92. Li X, Bian Y, Pang P, et al. Inhibition of Dectin-1 in mice ameliorates cardiac remodeling by suppressing NF-kappaB/NLRP3 signaling after myocardial infarction. *Int Immunopharmacol*. 2020;80:106116. [CrossRef]
93. Olsen MB, Gregersen I, Sandanger Ø, et al. Targeting the inflammasome in cardiovascular disease. *JACC Basic Transl Sci*. 2022;7(1):84-98. [CrossRef]
94. Morton AC, Rothman AM, Greenwood JP, et al. The effect of interleukin-1 receptor antagonist therapy on markers of inflammation in non-ST elevation acute coronary syndromes: the MRC-ILA Heart Study. *Eur Heart J*. 2015;36(6):377-384. [CrossRef]
95. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med*. 2017;377(12):1119-1131. [CrossRef]
96. Del Buono MG, Crea F, Versaci F, Biondi-Zoccai G. NLRP3 inflammasome: a new promising therapeutic target to treat heart failure. *J Cardiovasc Pharmacol*. 2021;77(2):159-161. [CrossRef]
97. Lee HS, Hwang CY, Shin SY, Kwon KS, Cho KH. MLK3 is part of a feedback mechanism that regulates different cellular responses to reactive oxygen species. *Sci Signal*. 2014;7(328):ra52. [CrossRef]
98. Wang J, Deng B, Liu Q, et al. Pyroptosis and ferroptosis induced by mixed lineage kinase 3 (MLK3) signaling in cardiomyocytes are essential for myocardial fibrosis in response to pressure overload. *Cell Death Dis*. 2020;11(7):574. [CrossRef]
99. Ni Y, Deng J, Liu X, et al. Echinacoside reverses myocardial remodeling and improves heart function via regulating SIRT1/FOXO3a/MnSOD axis in HF rats induced by isoproterenol. *J Cell Mol Med*. 2021;25(1):203-216. [CrossRef]
100. Chen X, Xu S, Zhao C, Liu B. Role of TLR4/NADPH oxidase 4 pathway in promoting cell death through autophagy and ferroptosis during heart failure. *Biochem Biophys Res Commun*. 2019;516(1):37-43. [CrossRef]
101. Ni Y, Zhang J, Zhu W, Duan Y, Bai H, Luan C. Echinacoside inhibited cardiomyocyte pyroptosis and improved heart function of HF rats induced by isoproterenol via suppressing NADPH/ROS/ER stress. *J Cell Mol Med*. 2022;26(21):5414-5425. [CrossRef]