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Research advances in understanding the role and mechanism of pyroptosis in myocardial ischemia-reperfusion injury

Ziyue Li[1], Bailong Hu[2], Xiaohua Zou[2]

[1]College of Anesthesiology, Guizhou Medical University, Guizhou 550004, China. [2]Department of Anesthesiology, the Affiliated Hospital of Guizhou Medical University, Guizhou 550004, China.

Corresponding authors: Bailong Hu and Xiaohua Zou.

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Highlights

Currently, ischemic heart disease ranks as the most prevalent form of primary heart disease. The risk of myocardial ischemia-reperfusion injury, along with its associated mortality, is notably rising among perioperative patients. Recognizing the underlying mechanisms of myocardial ischemia-reperfusion injury and identifying suitable treatments are crucial. Inhibitors targeting the key molecules involved in pyroptosis hold promise as potential therapeutic options for managing myocardial ischemia-reperfusion injury.

Abstract

Myocardial ischemia-reperfusion injury (MIRI) emerges when the restoration of blood flow fails to recover myocardial function following transient ischemia, marking a significant pathological challenge that adversely affects revascularization outcomes and patient mortality. This condition often occurs post-cardiac procedures, including cardiopulmonary bypass, angioplasty, primary percutaneous coronary intervention, and thrombolytic therapy. Over the last decade, researches have been pivotal in deciphering the pathophysiological underpinnings of MIRI, aiming to identify viable targets and therapeutics for mitigation. Among these, pyroptosis, a form of inflammatory, programmed cell death, has been recognized for its integral role in MIRI, interacting with various other mechanisms such as oxidative stress, calcium dysregulation, autophagy, ferroptosis, and apoptosis. This review delves into the mechanisms by which pyroptosis influences MIRI, discusses its impact on both cardiomyocytes and non-cardiomyocytes in MIRI, and highlights recent advancements in the development of inhibitors targeting key molecules involved in pyroptosis such as Nod-like receptor protein 3 inhibitors, Caspase-1 inhibitors, and traditional Chinese medicines.

Keywords: Myocardial ischemia-reperfusion injury, pyroptosis, Nod-like receptor protein 3

Introduction

Acute myocardial infarction (AMI) is characterized by acute myocardial necrosis resulting from various pathogenic factors, including coronary stenosis, coronary plaque rupture, and atherosclerosis. Due to its rapid progression, AMI can lead to a high incidence of severe complications and morbidity if not addressed promptly, making it a leading cause of death among patients with coronary artery disease globally [1-3]. Coronary artery disease ranks as the third leading cause of death worldwide, contributing to approximately 17.8 million fatalities each year [4]. Early coronary artery revascularization is crucial in treating AMI and

Address correspondence to: Bailong Hu, Department of Anesthesiology, the Affiliated Hospital of Guizhou Medical University, NO. 28 Guiyi Street, Guiyang 550004, Guizhou, China. Phone number: +86-15185184309; E-mail: hubailong@gmc.edu.cn. **Xiaohua Zou,** Department of Anesthesiology, the Affiliated Hospital of Guizhou Medical University, NO. 28 Guiyi Street, Guiyang 550004, Guizhou, China. Tel: +86-13809416036; Fax: +86-851-86771013; E-mail: zouxiaohuazxh@gmc.edu.cn.

minimizing infarct size. The main treatment strategies include percutaneous coronary intervention (PCI) and coronary artery bypass Grafting for managing ST-segment elevation AMI [5-7].

Nonetheless, a pathological condition known as myocardial ischemia-reperfusion Injury (MIRI) can occur, where, paradoxically, myocardial function fails to improve or even worsens after reperfusion, further aggravating the injury [8, 9]. MIRI often manifests immediately to within two hours post-PCI in myocardial infarction patients, with a marked decrease in postoperative diastolic function compared to pre-operative levels [10]. Factors such as the short duration between AMI onset and infarct-related artery revascularization, infarction in the inferior wall, reduced forward blood flow in the infarct-related artery (less than TIMI grade 1), multivessel lesions, and renal insufficiency heighten the risk of MIRI following primary PCI.

Conversely, pre-infarction angina might serve as a cardioprotective factor, mitigating the severity of MIRI [11]. MIRI is characterized by high morbidity and mortality and can lead to numerous complications, including myocardial stunning, the no-reflow phenomenon, and reperfusion arrhythmias [12-14]. MIRI significantly influences the efficacy of revascularization and the mortality among these patients. The currently acknowledged pathogenic mechanisms of MIRI encompass several theories and processes, including the leukocyte theory, calcium overload, elevated reactive oxygen species (ROS), endoplasmic reticulum stress, autophagy, and apoptosis [15]. However, the complete understanding of MIRI's mechanisms remains elusive, attributed to the myriad of contributing factors and the complexity of its underlying mechanisms.

Pyroptosis, a proinflammatory type of programmed cell death, has gained substantial interest in recent times. This process is triggered by inflammasomes and members of the cysteinyl aspartate-specific proteinase (caspase) family. It is marked by the rupture of the cell membrane and the consequent release of inflammatory factors, which intensify the inflammatory cascade. Pyroptosis accelerates many cardiovascular diseases, such as atherosclerosis, heart failure, myocardial infarction, and other disease processes [16, 17]. Therefore, elucidating the mechanism of pyroptosis may help alleviate MIRI by targeting this pathway.

Overview of pyroptosis

History of pyroptosis

Friedlander AM first documented that treating mouse macrophages with anthrax lethal toxin resulted in cell death accompanied by the release of cellular contents [18]. Following this discovery, Zychlinsky et al. observed that Shigella flexneri induced death in mouse macrophages through a mechanism akin to apoptosis [19]. Both studies highlighted a novel mechanism of cell death, distinct from traditional apoptosis, characterized by the secretion of cellular contents.

In 2001, D'Souza et al. introduced the term "pyroptosis", deriving from Greek roots to describe this phenomenon. Pyroptosis involves the rupture of the cell membrane and the release of inflammatory factors, intensifying the surrounding inflammatory response. This process visually resembles burning, hence the name "pyroptosis" [20]. As researches evolved, pyroptosis came to be defined as a form of proinflammatory cell death mediated by cysteine-aspartate-specific proteinase-1 (caspase-1), marking a significant advancement in our understanding of cell death mechanisms [21].

Following initial discoveries, subsequent researches identified that gasdermin protein D (GSDMD) serves as the ultimate substrate for caspase-1 and caspase-11/4/5, establishing pyroptosis as a form of programmed cell death predominantly triggered by the activation of GSDMD by the caspase family [22]. GSDMD acts as an executor, breaching the cell membrane to facilitate the release of inflammatory factors [16, 23]. In 2018, the Nomenclature Committee for Cell Death formally recognized pyroptosis as a type of regulatory programmed cell death. This process is characterized by the involvement of gasdermin protein family members, which perforate the cell membrane, leading to cell swelling and eventual rupture. This event is typically accompanied by caspase family activation and the consequent leakage of inflammatory factors, further elucidating the intricate mechanisms underlying pyroptosis [24].

Key molecules involved in apoptosis

Pyroptosis is orchestrated through the formation of inflammasomes, which trigger the cleavage and perforation of GSDMD and result in the proinflammatory cell death characterized by the release of interleukin-1β (IL-1β) and interleukin-18 (IL-18). The principal

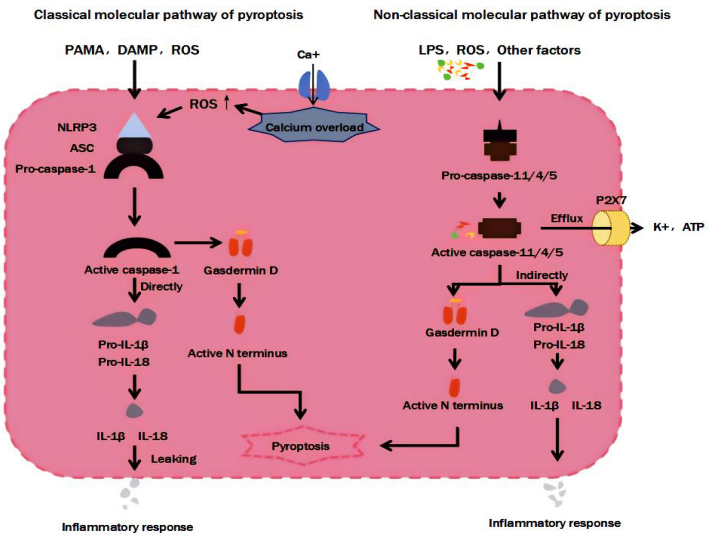

Figure 1. The process of pyroptosis. PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; ROS, reactive oxygen species; LPS, lipopolysaccharide; ASC, apoptosis-associated speck-like protein; IL, interleukin; ATP, adenosine triphosphate.

proteins and molecules implicated in pyroptosis encompass the Nod-like receptor protein 3 (NLRP3) inflammasome, caspase-1, and GSDMD [25, 26].

Inflammasomes are multi-molecular complexes that are activated by various physical and chemical stimulus, such as pathogen-associated molecular patterns, ROS, and damage-associated molecular patterns [27, 28]. Activation occurs when such stimulus engages pattern recognition receptor on the cell surface, initiating a cascade of cell signaling events. This process leads to the activation of the inflammasome, which then orchestrates the assembly and activation of downstream signaling pathways, culminating in the release of inflammatory cytokines [29]. Inflammasomes encompass a variety of components, including CARD-domain containing 4, absent in melanoma 2, the Nod-like receptor (NLR) family pyrin domain containing NLRP1, NLRP3, and pyrin, among which NLRP3 is the most common.

The NLRP3 inflammasome is composed of three key elements: (1) the NLRP3 sensor molecule, (2) an apoptosis-associated speck-like protein (ASC) that includes a caspase-recruitment domain, and (3) the precursor form of cysteine aspartate-specific proteinase-1 (pro-caspase-1) [30]. NLRP3 facilitates the conversion of pro-caspase-1 into its active form, caspase-1, which plays a pivotal role in generating IL-18 and IL-1β and in cleaving the GSDMD protein [31, 32]. GSDMD, a member of the gasdermin protein family, is expressed across various cells and tissues in the cytoplasm. In its inactive state, GSDMD's N-terminus is bound to its C-terminal domain. Upon cleavage by caspase-1, the N-terminal fragment of GSDMD (GSDMD-N) separates and attaches to phosphoinositides on the cell membrane, subsequently perforating the membrane [33].

Classical molecular pathway of pyroptosis

The classical pathway of pyroptosis is orche-strated by Caspase-1 (See **Figure 1**). Upon exposure of pattern recognition receptors to pathogen-associated or damage-associated molecular patterns, NLRP3 becomes activated, facilitating the transformation of pro-caspase-1 into its active form, caspase-1. As previously discussed, GSDMD is subsequently cleaved by activated caspase-1 into two fragments: GSDMD-N and GSDMD-C. GSDMD-N forms pores ranging from 10–15 nm within the cell membrane's lipid layer, enhancing cell permeability. This increase in permeability leads to the leakage of intracellular inflammatory substances, amplifying the inflammatory response. Concurrently, the influx of extracellular fluid into the cells results in cell swelling, rupture and eventual lysis [34, 35]. Moreover, caspase-1 also cleaves pro-IL-1β and pro-IL-18, activating them into IL-1β and IL-18, respectively. These cytokines then escape through the pores formed by GSDMD-N, further propagating the inflammatory response in the surrounding tissue [36-38].

Non-classical molecular pathway of pyroptosis

The non-classical pathway of pyroptosis represents a divergence from the traditional caspase-1-mediated mechanism, relying instead on the activation of caspase-11/4/5 (See **Figure 1**). This pathway is triggered by bacterial lipopolysaccharide (LPS), ROS, and a variety of physical, chemical, and biological stimulus acting on caspase-11/4/5 [39]. Similar to caspase-1, activated caspase-11/4/5 can cleave GSDMD and facilitate the release of IL-1 and IL-18, contributing to the process of pyroptosis [40]. Additionally, caspase-11/4/5 plays a role in modulating the efflux of potassium (K^+) and adenosine triphosphate via the P2X7 membrane channel, thereby

mediating pyroptosis in target cells [41]. It is important to note that while caspase-11/4/5 does not directly target pro-IL-1β and pro-IL-18 for activation, it can indirectly influence and promote the release of these cytokines, further amplifying the inflammatory response associated with pyroptosis [42].

Other pathways of pyroptosis

Proteins within the gasdermin family exhibit highly conserved structural features, including C- and N-terminal domains, with the N-terminal domain acting as the functional executor responsible for inducing pyroptosis in target cells [43]. Traditionally, caspase-3/8 were not considered to impact GSDMD or to induce pyroptosis. However, current studies have revealed that certain molecular agents, such as chemotherapeutic drugs, can "trick" caspase-3 into cleaving Gasdermin E (GSDME), allowing the GSDME-N to perforate the cell membrane and effectively trigger pyroptosis in the target cell [33, 34].

Additionally, caspase-8, when influenced by factors like tumor necrosis factor-alpha, can cleave Gasdermin C (GSDMC) into GSDMC-N, which then perforates the cell membrane and mediates pyroptosis [44]. Liu et al. have also demonstrated that chimeric antigen receptor T cells can activate caspase-3 within target cells, leading to pyroptosis through the caspase-3/GSDME pathway [45]. Furthermore, the activation of the Gasdermin B (GSDMB) pathway has been shown to induce pyroptosis [46]. These novel mechanisms significantly broaden the understanding of pyroptosis, highlighting its complexity and the diverse roles of caspases and gasdermin proteins in cell death.

Role of pyroptosis in MIRI

Pyroptosis occurs in both cardiomyocytes and non-cardiomyocytes, significantly contributing to the progression of MIRI. During MIRI, the pyroptosis of various cell types, such as cardiomyocytes, fibroblasts, vascular endothelial cells, and macrophages, is triggered by mechanisms such as increased ROS, calcium overload, and an inflammatory response. This process intensifies the development of MIRI through multiple regulatory mechanisms, including mitochondrial dysfunction, altered energy metabolism, and oxidative stress. Pyroptosis interacts with MIRI and affect each other.

Xu et al. demonstrated that, in comparison to normal rats, the MIRI model group exhibited a higher rate of myocardial cell pyroptosis, an enlarged area of myocardial infarction, and an intensified inflammatory response. However, the use of NLRP3 inhibitors or the genetic knockdown of NLRP3 was shown to mitigate myocardial pyroptosis, reduce infarct size, and lessen the inflammatory response [47]. Similarly, Sandanger et al. found that, during myocardial MIRI, the combined effects of ROS and potassium (K^+) efflux could activate the NLRP3 inflammasome in cardiac fibroblasts, leading to the secretion of IL-1β and the subsequent pyroptosis of these cells [48].

Furthermore, Zhang et al. reported that the surge of ROS during MIRI stimulates the NLRP3 inflammasome in myocardial microvascular endothelial cells, inducing pyroptosis and thereby aggravating inflammation and myocardial damage in the affected area [49]. Moreover, Dai et al. demonstrated that microRNA-2a, carried by exosomes derived from M2 macrophages (M2D-exos), can mitigate MIRI by targeting the TXNIP and TLR4/NF-κB/NLRP3 signaling pathways [50]. In a related vein, Wang et al. observed that hypoxia/reoxygenation treatment prompts macrophages to adopt the M1 phenotype, which in turn mediates cardiomyocyte pyroptosis through miR-1a carried by exosomes [51]. Further research by Wang et al. uncovered that an increase in hypoxia-inducible factor-1 alpha can diminish MIRI by lowering mitochondrial ROS production and minimizing mitochondrial damage [52]. Additionally, Tian et al. found that preconditioning with isoflurane, especially when combined with captopril treatment over three days (as opposed to just one hour), significantly reduces MIRI by lessening oxidative stress and inflammation [53].

These findings collectively underscore the critical role of pyroptosis in both myocardial and non-myocardial cells, such as fibroblasts, vascular endothelial cells, and macrophages, is inextricably linked to MIRI. Thus, targeting pyroptosis across various cellular components emerges as a pivotal approach in the prevention and treatment of MIRI.

Relationship between pyroptosis and other MIRI-related mechanisms

Pyroptosis and oxidative stress

During MIRI, a significant increase in ROS occurs, especially in the early phases of reperfusion. These excessive ROS levels can lead to lipid peroxidation in cell membranes or trigger inflammatory responses, causing

cellular damage [54, 55]. Moreover, the surge in ROS amplifies oxidative stress, promotes apoptosis, and intensifies the severity of MIRI [56, 57]. Beyond contributing to oxidative stress, ROS also play a pivotal role in pyroptosis during MIRI. Shen et al. discovered that ROS could directly activate the NLRP3 inflammasome, thereby inducing pyroptosis [58]. Furthermore, ROS facilitates the activation and production of IL-18, which in turn promotes tissue inflammation and aggravates MIRI [59]. Pyroptosis itself can enhance ROS production through various mechanisms, including the disruption and impairment of mitochondrial function. Consequently, the interplay between pyroptosis and oxidative stress significantly contributes to the onset and progression of MIRI.

Pyroptosis and calcium overload

Calcium overload, often triggered by sodium pump dysfunction and an increase in ROS, is both a common cause and consequence of MIRI. This condition can disrupt the oxidative phosphorylation cycle and mitochondrial membrane potential, a well-acknowledged pathogenic mechanism in MIRI [60]. Researches have established a close link between calcium overload and pyroptosis. For instance, Wang et al. discovered in a rat MIRI model that calcium overload could initiate cardiomyocyte pyroptosis via the NLRP3/caspase-1 pathway. The application of ginsenoside, targeting the retinoblastoma susceptibility gene (Rb1) to mitigate calcium overload, was found to decrease myocardial pyroptosis and cellular damage [61]. Similarly, Zhou et al. demonstrated that inhibiting calcium overload could lessen pyroptosis in glioblastoma cells [62]. While the precise mechanism through which calcium overload directly influences pyroptosis remains unclear, there is an undeniable link between the two in the context of MIRI. Future research should delve into the reciprocal regulatory mechanisms between calcium overload and pyroptosis.

Pyroptosis, apoptosis, and programmed necrosis

The pathogenesis of MIRI is multifaceted, with apoptosis, pyroptosis, and programmed necrosis playing significant roles in its development [63]. Numerous studies have highlighted how these distinct forms of cell death may interact and impact one another, suggesting the presence of "crosstalk" between pyroptosis, apoptosis, and programmed necrosis, wherein caspase-8 plays a pivotal role [64-67]. As a protease, caspase-8 primarily governs apoptosis but is also known to mediate programmed necrosis [68, 69]. This dual function raises questions about the multifaceted roles caspase-8 may play in cell death processes. Recent research has further elucidated caspase-8's critical role in the non-classical pathway of pyroptosis. Upregulation of caspase-8 can suppress the expression of GSDMD by inhibiting the formation of ASC and pyroptosis [70]. These findings underscore the complex interplay between pyroptosis, apoptosis, and programmed necrosis, indicating that their interactions may significantly contribute to the progression of MIRI. Future research should delve into the potential crossover, superposition, or feedback mechanisms among these modes of cell death, aiming to better understand their collective impact on the onset and evolution of MIRI.

Drugs for targeted inhibition of cell death and amelioration of MIRI

NLRP3 inhibitors

MCC950 is a small molecule known for its selective inhibition of the NLRP3 inflammasome, effectively preventing the activation conformation of NLRP3 and, consequently, inhibiting both NLRP3 activation and pyroptosis [71, 72]. In a porcine model of MIRI, various doses of MCC950 significantly reduced both the area of myocardial infarction and the inflammatory response [73].

Colchicine, traditionally used in the clinical management of gout, has recently been identified as an effective NLRP3 inhibitor, showing promise in the prevention and treatment of MIRI [74, 75]. Colchicine targets tubulin which is crucial for the localization and assembly of the NLRP3 inflammasome, by irreversibly binding to it, thereby inhibiting microtubule formation and NLRP3 activation [76-79]. Studies in an AMI rat model demonstrated that nanoparticles loaded with colchicine markedly decreased NLRP3 and pyroptosis-related protein expression, reducing infarct size [80].

Metformin, a primary medication for type 2 diabetes, has also shown efficacy beyond diabetes, particularly in ischemia-reperfusion injuries affecting cardiovascular, liver, and kidney tissues [81-83]. Research by Zhang et al. revealed that metformin mitigates the inflammatory response in MIRI by activating AMP-activated protein kinase (AMPK) and suppressing NLRP3 inflammasome activation,

thereby offering cardioprotective benefits [84]. Additionally, metformin postconditioning in isolated rat heart perfusion and neonatal rat MIRI models inhibited NLRP3 inflammasome activation and reduced the expression of inflammatory markers such as tumor necrosis factor-alpha, IL-6, and IL-1β, subsequently decreasing the area of myocardial infarction [81].

INF4E (ethyl 2-((2-chlorophenyl)hydroxyl) methyl) acrylate), another effective NLRP3 inflammasome inhibitor, has been shown to reduce the activity of caspase-1 and NLRP3-ATPase [85, 86]. Mastrocola et al. demonstrated that pretreatment with INF4E diminished myocardial infarct size, improved myocardial contractility, and downregulated the expression of the NLRP3 inflammasome and GSDMD via the reperfusion injury salvage kinase pathway, thereby alleviating MIRI [85].

These findings underscore the potential of targeting NLRP3 inhibition as a key strategy for preventing and treating MIRI. However, further research is necessary to develop more specific, safer, and efficacious NLRP3 inflammasome inhibitors, alongside large-scale clinical trials to verify their clinical safety and effectiveness.

GSDMD inhibitors

GSDMD serves as the executor and pivotal effector molecule in pyroptosis, playing a crucial role in the release of downstream inflammatory factors such as IL-18 and IL-1β [87]. Consequently, compounds that target GSDMD have been developed, demonstrating potential therapeutic value across various disease models. Necrosulfonamide (NSA) is one such GSDMD inhibitor that binds directly to the C191 site of GSDMD, preventing its oligomerization and inhibiting its expression [88]. He et al. demonstrated that NSA treatment could suppress GSDMD expression and pyroptosis, thereby ameliorating cardiac dysfunction following ischemia/reperfusion injury in rats [89].

Another GSDMD inhibitor, dimethyl fumarate (DMF), acts by succinylating the C191 site of GSDMD, which also prevents its oligomerization [90]. Shi et al. found that DMF could diminish NLRP3 inflammasome activation and GSDMD expression through the regulation of protein kinase A signaling, reducing pyroptosis and the inflammatory response and offering relief in mouse models of autoimmune hepatitis [91]. While DMF's anti-inflammatory properties have been documented in various conditions, including LPS-induced sepsis, familial Mediterranean fever, and autoimmune encephalitis, its effects on MIRI have yet to be explored [92].

Trimetazidine, a known inhibitor of free fatty acid oxidation, offers myocardial protection in patients with diabetes, angina, and those undergoing PCI [93, 94]. A recent study suggests that trimetazidine can also target GSDMD to modulate pyroptosis. It plays a significant role in regulating the expression of the TLR4/Myd88/NF-κB pathway and the NLRP3 inflammasome [95].

Given GSDMD's central role in controlling the release of inflammatory factors during pyroptosis, targeting this molecule presents a promising approach to inhibit pyroptosis.

Caspase-1 inhibitors

Intriguingly, a clinical trial demonstrated that colchicine significantly dampens the activity of caspase-1 in monocytes and diminishes the secretion of IL-1β by these cells, thereby delivering cardioprotective benefits [75]. VX-765, a highly selective inhibitor of caspase-1, has shown promise in a mouse model of MIRI [96, 97]. The concurrent use of VX-765 with antiplatelet medications markedly decreased myocardial infarct size and enhanced cardiac systolic function [98].

Further researches have revealed that VX-765 not only reduces the secretion of IL-1β but also inhibits the release of lactate dehydrogenase, thereby mitigating MIRI [98, 99]. Carmo et al. discovered that VX-765 also shields isolated rat hearts via the reperfusion injury salvage kinase pathway [100, 101]. Additionally, α-1 antitrypsin (A1AT), another caspase-1 inhibitor, has been observed to downregulate caspase-1 expression upon intraperitoneal injection in a mouse MIRI model, significantly shrinking the area of myocardial infarction and enhancing ventricular remodeling [102-104].

These findings underscore that with a deeper understanding of the pyroptosis mechanism and the ongoing development of novel small-molecule drugs, a new generation of compounds targeting pyroptosis-specific mechanisms and MIRI is on the horizon. The advent of small-molecule compounds adept at specifically inhibiting pyroptosis holds substantial promise for the prevention and treatment of MIRI, heralding a significant advancement in cardiovascular disease management.

TCM compounds and monomers

Due to its holistic approach, encompassing multiple components, pathways, and targets, traditional Chinese medicine offers distinctive advantages in treating cardiovascular and cerebrovascular diseases, especially myocardial ischemia-reperfusion injury. Emodin, known for its anti-inflammatory and antioxidant properties, also inhibits GSDMD-mediated pyroptosis via the TLR4/MyD88/NF-κB/NLRP3 inflammasome pathway, thereby reducing myocardial cell damage in MIRI [104, 105]. Researches have highlighted that naringin and β-asarone can diminish pyroptosis by suppressing the expression of ASC, caspase-1, NLRP3, and GSDMD, consequently reducing infarct size in rat models of MIRI [106, 107]. Similarly, the cinnamoyl ethyl acetate extract offers protection against MIRI damage in rats by inhibiting the activation of the NLRP3 inflammasome and pyroptosis [108]. Li et al. demonstrated that apigenin treatment lowers the expression of caspase-1, NLRP3, and GSDMD in cardiomyocytes subjected to hypoxia/reoxygenation (H/R), decreasing pyroptosis incidence and providing myocardial protection [109]. Sun et al. found that pre-treatment with gastrodin in cardiac microvascular endothelial cells can obstruct pyroptosis via the classical pathway, alleviate inflammation, and reduce myocardial cell damage [110].

These studies illustrate that Chinese medicines and their monomers possess significant potential in combating cell pyroptosis and MIRI due to their pharmacological actions. Nonetheless, future efforts should aim at a more thorough investigation and translational research on the modulation of pyroptosis and the protective effects of traditional Chinese medicine against MIRI, paving the way for their early clinical adoption.

Anesthetic

In recent years, the cardioprotective effects of anesthetics on cardiovascular and cerebrovascular diseases have garnered increasing attention from researchers globally. Both intravenous and inhalational anesthetics have been shown to offer myocardial protection [111, 112]. Sevoflurane, a widely used inhalational anesthetic in clinical settings, has been recognized for its cardioprotective properties in various studies [110].

Dharmalingam et al. reported that pre-treatment with volatile anesthetics, including isoflurane and sevoflurane, can suppress ROS, thereby preventing oxidative stress during coronary artery bypass grafting [113]. Additional researches indicate that sevoflurane can also block the P2X7 ion channel on mitochondrial membranes, decrease the expression of NLRP3, ASC, caspase-1, and GSDMD, and reduce myocardial enzyme release, thereby playing a role in mitigating MIRI [114-116]. Deng et al. further revealed that sevoflurane can modulate autophagy via the AMPK/ULK1 pathway and inhibit NLRP3-mediated pyroptosis in cardiomyocytes, thus improving myocardial ischemia/reperfusion injury [117].

Dexmedetomidine, a highly selective α-2 adrenergic receptor agonist commonly utilized for perioperative sedation, has been found to protect against ischemia-reperfusion injury by enhancing myocardial function [118-120]. Zhong et al. and Wang et al. discovered that dexmedetomidine could mitigate MIRI in a rat model by downregulating miR-29b, activating FoxO3a, and reducing pyroptosis [121, 122]. While there is significant evidence to suggest that both inhaled and intravenous anesthetics have profound effects on the prevention and treatment of MIRI, there remains a scarcity of studies and mechanistic insights into how anesthetics improve MIRI by regulating pyroptosis [114, 123]. Further investigations into the specific targets and mechanisms by which anesthesia influences MIRI are crucial for advancing our understanding and therapeutic approaches.

Summary and outlook

MIRI is a multifaceted pathophysiological phenomenon influenced by numerous genes, molecules, cells, and tissues across different signaling pathways. This review delves into the role and mechanisms of pyroptosis in MIRI, summarizing the impact of various drug categories, including NLRP3 inhibitors, GSDMD inhibitors, caspase-1 inhibitors, anesthetics, and traditional Chinese medicines, on both MIRI and pyroptosis. Key pathogenic mechanisms of MIRI, such as calcium overload, disturbances in energy metabolism, oxidative stress, and autophagy, have been thoroughly investigated, highlighting their importance in modulating the onset and progression of MIRI. The contribution of pyroptosis to MIRI, especially the interactions between pyroptosis, MIRI mechanisms, and associated signaling pathways, remains a critical area for further research.

Most existing research on pyroptosis and MIRI concentrates on mitigating pyroptosis and improving MIRI outcomes by targeting the NLRP3 inflammasome, caspase family proteins, and key GSDMD targets. While the use of pyroptosis inhibitors in animal models of MIRI has shown promising results in reducing myocardial infarct size and enhancing cardiac function, the majority of these studies are confined to preclinical settings. The clinical application of drugs that inhibit pyroptosis-related proteins for MIRI treatment is limited, which restricts our comprehensive understanding of these inhibitors' effects in human clinical trials. Consequently, there is a pressing need for more clinical trials to corroborate the findings from basic research.

Based on current studies and available evidence, NLRP3 inhibitors, caspase-1 inhibitors, and traditional Chinese medicines emerge as potential therapeutic avenues for MIRI treatment. However, given the intricate nature of pyroptosis and MIRI, a singular focus on targeting either pyroptosis or MIRI may not suffice for effective prevention and treatment strategies. Instead, a multi-targeted and multi-mechanism approach to combination therapy may offer a more effective treatment paradigm for MIRI.

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