Reperfusion therapy is the optimal therapy for acute myocardial infarction (AMI), but acute inflammatory injury and chronic heart failure (HF) after myocardial ischemia and reperfusion (MI/R) remain the leading cause of death after AMI. Pyroptosis, a newly discovered form of cell death, has been proven to play a significant role in the acute reperfusion process and the subsequent chronic process of ventricular remodeling. Current research shows that multiple stimuli activate the pyroptotic signaling pathway and contribute to cell death and nonbacterial inflammation after MI/R. These stimuli promote the assembly of the nucleotide-binding and oligomerization-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome by activating NLRP3. The mature NLRP3 inflammasome cleaves procaspase-1 to active caspase-1, which leads to mature processing of interleukin (IL)-18, IL-1β, and gasdermin D (GSDMD) protein. That eventually results in cell lysis and generation of nonbacterial inflammation. The present review summarizes the mechanism of NLRP3 inflammasome activation after MI/R and discusses the role that NLRP3-mediated pyroptosis plays in the pathophysiology of MI/R injury and ventricular remodeling. We also discuss potential mechanisms and targeted therapy for which there is evidence supporting treatment of ischemic heart disease.

Keywords: 
Myocardial Reperfusion Injury • NLRP3 Protein, Human • Pyroptosis • Ventricular Remodeling

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Background

Ischemic heart disease (IHD) is the leading cause of morbidity and mortality worldwide [1]. The leading cause of death from IHD is acute myocardial infarction (AMI). Rupture of the Fibrous cap on the surface of an atherosclerotic plaque on the coronary artery wall is the main cause of AMI, and leads to secondary thrombosis, occlusion of the coronary lumen, blood flow obstruction, and stagnation [2]. All these pathological changes lead to a sharp drop in oxygen and energy available for myocardial tissue supplied by the culprit coronary artery; the result is irreversible necrosis of the myocardium [3]. In essence, AMI is an imbalance in oxygen supply and demand [4]. Thus, the most effective strategy for rescuing the dying cardiomyocytes is immediate reperfusion therapy to restore blood flow [5]. However, a series of studies have demonstrated that although reperfusion treatment minimizes the area of infarction caused by hypoxia in infarcted myocardium, it also provokes a series of events that lead to damage to myocardial function, metabolism, and electrophysiology, which is known as myocardial ischemia/reperfusion (MI/R) injury [6].

Whether patients who experience AMI are treated with reperfusion or not, their damaged myocardium is often unable to contract to complete the heart’s pumping function because of irreversible loss of function and activity [7]. To maintain constant cardiac output, fibroblasts become hyperplastic and healthy cardiomyocytes experience hypertrophy and elongation [8]. The site and extent of AMI are the most crucial predictors of ventricular remodeling [9]. Ventricular remodeling is a chronic pathological alteration that contributes to congestive heart failure (HF), which is the long-term cause of death from AMI [10].

Recently, an increasing number of studies have documented the role of pyroptosis in ischemic cardiomyopathy [11-14]. Pyroptosis is a type of programmed cell death that was first observed in macrophages infected by salmonellla [15]. The process is mainly dependent on the enzymatic activity of the cysteine-dependent aspartate-specific protease family, which can be activated by the nucleotide-binding and oligomerization (NOD)-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome [16]. The NLRP3 inflammasome is one of the most widely studied inflammasomes. NLRP3 can recruit precursors of caspase-1 and apoptosis-associated speck-like protein that contain a caspase-recruiting domain (CARD) (apoptosis speck-like protein; ASC) to form mature NLRP3 inflammasomes [16]. A series of damaging factors, such as complete pathogens, pathogen-related molecular patterns (PAMPs) with diverse structures, host-derived risk signals (danger-related molecular patterns, DAMPs), and environmental stimuli, can activate NLRP3 to recruit procaspase-1 and ASC to construct a mature NLRP3 inflammasome [17]. The NLRP3 inflammasome is involved in the pathogenesis of many diseases [18-20]. Inhibition of NLRP3-mediated pyroptosis may be an important target of therapy for MI/R injury and ventricular remodeling, and it has a significant impact on the development of and prognosis for AMI [21]. In the present review, we systematically summarize the current molecular mechanism of NLRP3-mediated pyroptosis and highlight its role and therapeutic significance in MI/R and later myocardial remodeling. Our aim is to contribute to advancing the concept of the NLRP3 inflammasome-mediated signaling pathway as a future target for treatment of coronary heart disease.

Activation of the NLRP3 Inflammasome

Pattern recognition receptors are an essential component of the innate immune system and they include toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors, and C-type lectin receptors [22]. Unlike the other 3, NLR can recognize PAMPs and DAMPs [23,24]. The NLR family contains a central nucleotide-binding and oligomerization domain, which is often surrounded by leucine-rich repeats (LRRs) and the CARD and pyrin domains (PYD) [25]. However, the construction of NLRP3 contains PYD without CARD. NLRP3 can be activated by endogenous or exogenous signals, such as adenosine triphosphate, potassium, and calcium, reactive oxygen species (ROS), uric acid crystals, glucose, mitochondrial dysfunction, and lysosome rupture. After NLRP3 is activated, it must be bound to ASC and contains PYD and CARD domains. ASC can recruit CARD-carrying procaspase-1 and then assemble it to form a mature NLRP3 inflammasome [26].

The activation process for the NLRP3 inflammasome is known to be mediated by a dual-signal model (Figure 1) [27]. First, various endogenous molecules promote transfer of nuclear factor-kB (NF-kB) into the nucleus, regulate the transcription and translation of the NLRP3 gene in the nucleus, and release it into the cytoplasm [28]. Then, various endogenous or exogenous signals further activate the expressed NLRP3 in the cytoplasm to promote maturation of the NLRP3 inflammasome assembly [29]. This second step is divided into non-canonical caspase-11-mediated and canonical NLRP3 inflammasome-mediated pyroptosis pathways [29,30]. In the non-canonical caspase-11-mediated pyroptosis pathway, the lipid A portion of lipopolysaccharide (LPS) interacts with the CARD of caspase-11 to promote oligomerization of caspase-11, causing potassium efflux and caspase-11-dependent cleavage of the membrane channel pannexin-1 [30]. Subsequent release of adenosine triphosphate (ATP) activates the NLRP3 inflammasome, which in turn activates the purinergic receptor P2X7R and pyroptosis [31]. In the canonical NLRP3 inflammasome-mediated pyroptosis pathway, NLRP3 is directly activated by various stimuli to form inflammasomes. Regardless of which signal activates
NLRP3, the mature NLRP3 recruits ASC and procaspase-1 to form the NLRP3 inflammasome and activate the downstream common signal pathway. Procaspase-1 can be cleaved to active caspase-1 by the NLRP3 inflammasome. The active caspase-1 not only converts pro-interleukin (IL)-1β and pro-IL-18 expressed in the nucleus into the mature inflammatory cytokines IL-1β and IL-18 to cause nonbacterial inflammation, but also leads to the mature processing of the gasdermin D protein (GSDMD), which eventually causes cell lysis and pyroptosis [29].

**Potassium Efflux**

During acute myocardial ischemia, cellular potassium efflux is increased and cellular potassium influx is decreased in cardiomyocytes. An open ATP-sensitive potassium (KATP) channel is the main mechanism of unidirectional potassium efflux in cardiomyocytes that experience acute ischemia and it is beneficial to accumulation of extracellular potassium [32]. Sodium-activated potassium channels and free fatty acid potassium channels have been identified as related to ischemia-induced potassium efflux [33,34]. ATP hydrolyzes the decrease in phosphorylation level during AMI, simultaneously promoting dysfunction in the sodium-potassium pump, lowering cellular potassium influx [35].

Potassium promotion of activation of IL-1β was first observed in intracellular LPS-activated macrophages [36]. Since then, it has been confirmed that stimulation of the NLRP3 inflammasome...
by acute ischemia, ATP, nigericin, and crystalline matter can cause intracellular potassium efflux and subsequently activate the NLRP3 inflammasome [32,37]. It is widely recognized that alteration in potassium concentration gradients in cardiomyocytes contributes to activation of the NLRP3 inflammasome [38].

What remains unclear, however, is the role of potassium efflux in activation of the NLRP3 inflammasome and the relationship between potassium efflux and the NLRP3 inflammasome. This is notwithstanding the variation in potassium concentration gradients caused by potassium efflux, which is a consideration as the upstream signal for the NLRP3 inflammasome. Successful assembly of the NLRP3 inflammasome has been observed without the outflow of potassium [39]. Stimuli such as GB111-NH2 and CL097 promote activation of the NLRP3 inflammasome, which is not accompanied by potassium efflux [40]. This finding suggests that another signal cascade downstream from the potassium efflux and other parallel-signaling pathways independent of potassium efflux can regulate activation of the NLRP3 inflammasome. A recent study revealed that release of IL-1β decreases when the intracellular potassium outflow is stopped [41]. When the potassium outflow increases, it directly increases activation of caspase-1, expression of NIMA-related kinase 7 (NEK7), and formation of the NLRP3 inflammasome.
Researchers have observed that with the rise in calcium concentration in the cytoplasm, the level of mature NLRP3 increases [48]. Therefore, the hypothesis is that the NLRP3 inflammasome is activated directly by calcium overload. Meanwhile, calcium flows into the mitochondria through mitochondrial calcium channels and voltage-dependent anion-selective channels, causing mitochondrial instability [52-54]. Cardiolipin and mitochondrial DNA (mtDNA) are released from the mitochondria to activate NLRP3 and promote maturation of caspase-1 and inflammatory factors [55-57]. Another study found that activation of the NLRP3 inflammasome and secretion of IL-1β were significantly inhibited after a calcium chelator was applied [58]. ATP and Leu-Leu-Ome, 2 stimuli of NLRP3, regulate the NLRP3 inflammasome without causing fluctuations in the concentration of calcium in the cytoplasm [59]. That finding indicates that although calcium overload plays an important role in activating the NLRP3 inflammasome, the inflammasome can be activated in a calcium overload-independent manner (Figure 2).

**Reactive Oxygen Species**

ROS are the most common second messengers of oxidative stress inside and outside the cell. They participate in a series of regulatory mechanisms inherent in growth and development of cells in the body. An excess of ROS, however, promotes oxidative stress and damages the mitochondria, DNA, and proteins, leading to cell dysfunction [60]. AMI leads to inhibition of activity in the mitochondrial electron transport chain complex and leakage of electrons. Complexes I and III have been regarded as the primary source of ROS [61,62]. An accumulation of redundant succinic acid in cardiomyocytes during hypoxia promotes reverse electron transport, producing ROS throughout the complex I [63]. After myocardial reperfusion, the opening of the mitochondrial permeability transition pore (MPTP) increases the level of ROS, which in turn increases the number of openings in the MPTP, creating a vicious cycle [64]. In addition, nicotinamide adenine dinucleotide phosphate oxidase has been shown to play an important role in ROS production in MI/R. Braunerreuther et al found that after MI/R, mice with specific knockouts for NOX1 and NOX2 had significantly fewer areas of MI than wild-type mice [65]. Matsushima et al. found that in mice, MI/R treatment after knockout of myocardial-specific NOX4 reduced ROS production and MI area [66].

Although ROS are not essential to the cascade for activation of the NLRP3 inflammasomes, they are a crucial upstream signal for activation of the inflammasomes [60,67]. It is worth noting that the process of NLRP3 activation by various NLRP3 stimuli is accompanied by production of ROS [68,69]. ROS can regulate apoptosis through NF-κB signaling [70]. The level of activation of the NLRP3 inflammasome increases in proportion to increases in the NF-κB level. To confirm that ROS triggers...
activation of the NLRP3 inflammasomes by regulating NF-κB, researchers tested various antioxidants and eventually demonstrated that NF-κB and NLRP3 activation were positively correlated during oxidation or anti-oxidation [71].

However, ROS does not always stimulate an increase in NF-κB. It has been reported that slight increases in ROS are conducive to activation of NF-κB, but excessive accumulation of ROS prevents activation of NF-κB. These results may indicate that NF-κB is not the only signal downstream of ROS that plays a role in activation and assembly of the NLRP3 inflammasomes [72].

Thioredoxin-interacting protein (TXNIP) is the ligand of NLRP3 in the cytoplasm [73]. Under normal physiological conditions, thioredoxin (TRX) inhibits the activity of TXNIP by binding to TXNIP [74]. Transient increases in intracellular ROS levels promote a dissociation between TRX and TXNIP and activation of the NLRP3 inflammasome through increased binding of TXNIP and NLRP3 [75,76]. In the non-canonical caspase-11-mediated signaling pathway, ROS activates NLRP3 by promoting the expression and activation of caspase-11. However, the mechanism of ROS that regulates caspase-11 needs to be further explored (Figure 2) [77].

**Mitochondrial Dysfunction**

During ischemia, the opening of MPTP causes water and cytoplasm to penetrate the mitochondria, resulting in swelling and rupture of the outer mitochondrial membrane and leading to loss of factors and induction of apoptosis in cytochromes. The degree to which MPTP is open can be further aggravated during reperfusion. Some studies have found that inhibiting the opening of MPTP can reduce damage to and death of myocardial cells [78]. The mitochondria are the most important source of ROS in cells and the most crucial organelle for oxidative stress. The mitochondria produce ROS through the oxidative respiratory chain [79]. Electron transport of the mitochondria is continuously damaged during MI. The damage progresses from the distal end of complex I, leading first to a reduction in oxidation of glutamate and succinic acid, which are the substrate of complex I and the donor of complex II, respectively. As the ischemia worsens, complex III and the phosphorylation device, including complex IV and the adenine nucleotide transporters, are damaged, too [80-82]. Rotenone, a mitochondrial complex I inhibitor, can cause loss of mitochondrial membrane potential and a high level of ROS after it is added to the cell [83,84]. A similar but slight effect can be observed in the cell when antymycin A acts on mitochondrial complex II and 2-thenoyltrifluoroacetone acts on complex III [85,86]. These findings indicate that complex I may be the principal site of production of ROS by the mitochondria.

Abnormal calcium mobilization induces mitochondrial dysfunction and can activate the NLRP3 inflammasome [87]. Transport of calcium into the mitochondria can lead to loss of the membrane’s potential to activate the NLRP3 inflammasome [88,89]. NLRP3 stimuli such as ATP, urea microcrystals, and nigericin reportedly can cause the loss of potential in the mitochondrial membrane. ROS-induced release of oxidized mtDNA from the mitochondria can interact with and activate the NLRP3 inflammasome [90,91]. Diphosphatidylglycerol exists on the inner membrane of mitochondria. Damage to the cell can result in transfer of diphosphatidylglycerol from the inner membrane to the outer membrane and binding to the free NLRP3 LRRs in the cytoplasm, promoting activation of NLRP3 (Figure 2) [92].

**Lysosomal Damage**

Lysosomes are the organelles that hydrolyze proteins, nucleic acids, polysaccharides, and other macromolecules. Lysosomal damage is widely believed to be related to myocardial ischemia. In the last century, Acosta et al. have found that myocardial ischemia increases the instability of lysosomal membranes, releasing powerful hydrolases into the cytoplasm and causing damage to intracellular organelles and important submicroscopic structures [93]. Lysosomes contain multiple types of hydrolase, including cathepsin B. Not only does the lysosome cause decomposition of damaging factors that can permeate the cell, it also swallows internal impaired organelles and useless substances. Particulate foreign substances, such as alum, silica, asbestos, amyloid-beta protein, cholesterol crystals, and calcium crystals, can hurt the lysosome membrane and promote the release of cathepsin B [94]. The amount of cathepsin B released into the cytoplasm is positively correlated with activation of NLRP3 [95,96]. In one study, after CA-074-Me was applied to inhibit cathepsin B, the level of NLRP3 activation decreased and a similar decrease was seen in the cathepsin B level [97]. This experiment indicated that cathepsin B is an upstream signal for NLRP3 and that inhibition of it suppresses NLRP3 activation. However, studies have found that in cathepsin-deficient macrophages, NLRP3 inflammasomes can be activated by particulate matter, which indicates that cathepsin B is one of the signals that activate NLRP3, but not the only one (Figure 2) [98,99].

**NLRP3-Mediated Pyroptosis**

When cells are subjected to harmful stimuli or under stress, NLRP3 activation accompanies the exposure of the N-terminal thermoprotein region, which can bind to ASC [100,101]. Another terminus of ASC contains the recruitment domain CARD, which recruits caspase-1 precursors to assemble the mature NLRP3 inflammasomes [102,103]. Procaspase-1 is cleaved by the NLRP3 inflammasome to become an activated form of caspase-1 [104]. The latter cleaves the pro-GSDMD and the proinflammatory factors IL-1β and IL-18, transforming them into a mature state. Mature GSDMD has pore-forming properties, forming cavities in the cell membrane to cause cell cytoplasmatic
exudation and changes in osmotic pressure. IL-18 and IL-1β flow out of the cytoplasm from the pores made by the GSDMD, leading to sterile inflammation [105].

Morphologic Alterations of Pyroptosis

Both pyroptosis and apoptosis are programmed cell death, but there are considerable differences between them. Morphologically, apoptotic cells have chromatin condensation (pyknosis), DNA fragmentation, plasma membrane blebbing, and they shed apoptotic bodies [106]. Because apoptosis is an innate cellular mechanism of programmed suicide, it does not cause cytosolic contents to be released into the extracellular environment, which would not lead to an inflammatory response. Pyroptotic cell changes are characterized by cellular swelling and formation of numerous bubble-like protrusions visible under light microscopy [107]. When pyroptotic cell walls begin to swell, chromatin condensation and DNA fragmentation is visible on electron microscopy [108]. With the formation of pores in a pyroptotic cell, the cell ruptures and the outflow of its intracellular contents is accompanied by inflammation.

NLRP3-Mediated Pyroptosis and MI/R Injury

Early positive revascularization therapy has been shown to vastly decrease the size of AMI-associated MIs and to improve prognosis. However, persistent reperfusion therapy can induce an extensive range of inflammatory damage, affecting up to 50% of the area of an infarct. In the acute phase following reperfusion, the myocardial tissue exposed to sublethal ischemic insults (the infarct area) and the tissue exposed to lethal damage are areas beside the necrotic tissue which are at risk. Activation of the NLRP3 inflammasome in damaged cardiomyocytes is associated with cell death and inflammatory injury, further aggravating myocardial injury [109]. Studies have demonstrated that pyroptosis is significantly associated with MI/R injury [110-112]. Pyroptosis can lead to overwhelming production of inflammatory mediators and cardiomyocyte death. Our previous research has demonstrated that NLRP3 inflammasome-mediated caspase-1 signaling pathway-induced pyroptosis plays a vital role in MI/R injury [113]. Our previous study confirmed that uric acid worsens MI/R damage in the NLRP3 inflammasome-mediated pyroptosis signaling pathway by stimulating ROS generation. Inhibiting ROS production and activation of calpain can alleviate the MI/R injury by inhibiting NLRP3 inflammasome-mediated pyroptosis. Huairui et al found that GSDMD deficiency in cardiomyocytes significantly reduced myocardial infarct size. GSDMD gene deletion also blocked H/R-induced cardiomyocyte pyroptosis and IL-18 release [114].

Studies have shown that myocardial damage in diabetic rats is more considerable than in normal rats treated with the same surgery, and it is accompanied by a higher level of pyroptosis [12,115]. This finding indicates that NLRP3 inflamasomes are activated during MI/R, which is demonstrated by NLRP3 activation and release of inflammatory factors mediated by downstream caspase-1. In vitro, the application of NLRP3 inflammasome inhibitors and caspase-1 inhibitors significantly reduced the occurrence of cell inflammatory damage and pyroptosis [116,117]. Another study showed that silencing the NLRP3 gene can inhibit formation of the NLRP3 inflammasomes and limit MI size [118,119]. Therefore, NLRP3 and caspase-1 may be potential future targets for reducing MI/R injury.

NLRP3-Mediated Pyroptosis and Ventricular Remodeling

Immediate reperfusion therapy reduces mortality in the acute phase of AMI and ventricular remodeling and mortality in the later phase. However, rehospitalization and mortality rates in the terminal stage were higher in patients with previous AMI who had no HF [120]. Massive cardiomyocyte death leads to permanent loss of function in cardiomyocytes in the infarcted area and causes compensated hypertrophy of cardiomyocytes in surrounding regions that typically maintain cardiac output, which is known as ventricular remodeling [121]. Ventricular remodeling caused by MI is one of the most common clinical causes of terminal HF [122,123]. Cardiac ventricular remodeling, which involves exaggerated inflammatory responses and neurohumoral mechanisms, is the compensatory repair process for local and global cardiac structure and function [124,125].

Researchers have dynamically detected changes in mouse cardiac function and death rates and found that NLRP3-deficient animals had higher survival rates and better heart function [126]. The authors have pointed out that the early nociceptive/inflammatory phase is the most critical window for the effect of NLRP3 on poor myocardial healing, adverse structural remodeling, left ventricular dysfunction, and dilation. After MI/R, mice were treated with an NLRP3 inflammasome inhibitor for 2 successive weeks. One month later, the level of myocardial fibrosis and the NLRP3-mediated pyroptotic signal were visibly reduced in the mice treated with MCC950 [127]. MCC950 also increased the ejection fraction and decreased the left ventricular end-systolic volume (LVESV) in the mice that underwent a surgical procedure for MI/R. Silencing P2X7 inhibited the activation of caspase-1 in AMI and alleviated ventricular remodeling on the 7th day, which was characterized by slight ventricular dilation and dysfunction [128]. That finding indicates that NLRP3 inflammasome-mediated pyroptosis participates in ventricular remodeling after AMI. When NLRP3 is inhibited, the rate of HF caused by ventricular remodeling is further reduced.

Beyond NLRP3, inflammatory cytokines such as tumor necrosis factor (TNF)-α [129], IL-1 [130], IL-6 [131], and C-reactive protein (CRP) [132] clearly are increased in ventricular remodeling.
These inflammatory cytokines are considered to be associated with regulation of ventricular remodeling, cardiac hypertrophy, cardiac fibrosis, and decreased cardiac contractility. Left ventricular end-diastolic volume and LVEFSV, measured by trans-thoracic echocardiography, were significantly reduced after IL-1β was inhibited. Left ventricular ejection fraction and left ventricular fractional shortening (LVFSV) also were increased [133]. These findings indicate that NLRP3 inflammasome-mediated pyroptosis may be an important target of pharmacological treatment for ventricular remodeling.

**Treatment for NLRP3-Mediated Pyroptosis**

**Impact on MI/R Injury and Ventricular Remodeling**

Even though the specific molecular mechanisms involved need to be explored in more depth, the critical role of NLRP3-mediated pyroptosis in MI/R injury and subsequent ventricular remodeling has been widely confirmed. However, in multiple studies, inhibition of NLRP3 has been shown to reduce myocardial damage and inhibit ventricular remodeling after ischemia [134-136]. To assess the effect of inhibiting NLRP3 on cardiac function during MI/R, Marchetti et al established experimental MI/R and permanent ischemia mouse models using coronary artery occlusion [137]. NLRP3 inflammasome inhibitors were administered to the mice at reperfusion. Treatment with an NLRP3 inflammasome inhibitor significantly reduced infarct size and troponin I serum levels in mouse 24 h after creation of MI/R. After 7 days, the NLRP3 inflammasome inhibitor significantly alleviated the left ventricular systolic dysfunction (LVSD) in the MI/R mice. A significant increase in left ventricular end-diastolic dimension and LVESD evidenced by left ventricle dilatation, and a decrease in LVFS evidenced by systolic dysfunction, were observed in a mouse with permanent ischemia after 7 days. The NLRP3 inflammasome inhibitor obviously reversed the changes described after MI/R. Similar studies have proven the protective effect of an NLRP3 inflammasome inhibitor on cardiac function [134]. Following is a summary of information on some inhibitors of NLRP3-mediated pyroptosis.

**NLRP3 Inhibitors**

**Colchicine**

Colchicine, a tricyclic alkaloid, was developed initially for the treatment of gout. The drug was not regarded as an NLRP3 inhibitor until 2009, when it was found to inhibit the assembly and activation of NLRP3. Microtubules, essential components for intracytoplasmic localization and assembly of the NLRP3 inflammasome, are a subcellular channel for transporting NLRP3, pro-caspase-1, and ASC [138,139]. Colchicine can irreversibly combine with microtubule protein to inhibit microtubule formation and elongation and promote microtubule depolymerization [140]. Studies have shown that administration of colchicine can block the subsequent inflammatory response mediated by NLRP3 in monocytes that secrete IL-18 and IL-1β and positively correlate with inflammasome activation [134]. In a mouse model of AMI, treatment with oral colchicine (0.1 mg/kg/d for 7 consecutive days) significantly reduced activation of the NLRP3 inflammasome and expression of downstream pyroptosis-related proteins of NLRP3 after 24 h. After 7 days of treatment, oral colchicine dramatically reduced the scar area in the infarct zone and ventricular remodeling of the left ventricular infarction area and improved the survival rate [134]. In another mouse MI/R model, coronary artery ligation was performed for 45 min and then 400 μg/kg of colchicine was administered intraperitoneally 25 min before reperfusion. After 24 h, colchicine significantly reduced the area of MI, while levels of troponin T and verification markers were significantly reduced [141]. After 10 weeks, the degree of myocardial fibrosis in the mice in the colchicine group also was significantly reduced. These results indicate that colchicine inhibits the inflammatory response and ventricular remodeling after AMI by inhibiting NLRP3-mediated pyroptosis. Given the progress with colchicine in basic research, some clinical studies have been done showing that the drug decreases the infarct area and myocardial damage [142,143].

**Glibenclamide and 16673-34-0**

Glibenclamide, a sulfonylurea hypoglycemic agent, lowers blood sugar mainly by inhibiting hepatic gluconeogenesis. In macrophages incubated with glibenclamide after being treated with NLRP3 stimuli, the drug was found to inhibit activation of the NLRP3 inflammasome and release of IL-1β in a dose-dependent manner [144]. The role of glibenclamide in inhibition of NLRP3-mediated pyroptosis has been proven in vivo and in vitro, but the doses of glibenclamide in vitro must be 100-fold higher than those used for clinical treatment of diabetes, which inevitably causes fatal hypoglycemia [144]. To eliminate that adverse effect, an intermediate of glibenclamide, 16673-34-0, has been designed to inhibit the NLRP3 inflammasome [135]. Zymosan A-induced peritonitis in mice, which is entirely dependent on assembly and activation of the NLRP3 inflammasome, is mediated by the pyroptotic signaling pathway [135]. The action of 16673-34-0 in alleviating the severity of peritonitis and inhibiting activation and formation of the NLRP3 inflammasome is dose-dependent. In a study of 16673-34-0, mice were subjected to 30-min myocardial ischemia followed by 24-h reperfusion to establish an MI/R model. They were given 16673-34-0 30 min before ischemia was induced and immediately on reperfusion, and then it was administered 3 times more over a 6-h period [135]. The 16673-34-0 significantly limited the expansion of infarcts and downregulated the troponin T level and expression of the NLRP3 inflammasome.
These data suggest that 16673-34-0 alleviates MI/R injury by inhibiting NLRP3 inflammasome-mediated pyroptosis [135].

**MCC950**

MCC950 reversibly inhibits the NLRP3 inflammasome by changing the conformation of NLRP3, inhibiting activation of the NLRP3 inflammasome. NLRP3 undergoes a structural rearrangement during the process of activation. MCC950 can non-covalently bind to the Walker B motif of the region in the vicinity of the Walker B motif to convert NLRP3 to an inactive and closed conformation, which inhibits activation of the NLRP3 inflammasome [145]. In one study, female Landrace pigs were treated with 60-min balloon occlusion of the left anterior descending artery followed by 7 days of reperfusion to establish a MI/R model. MCC950 was found to decrease the infarct size and the level of IL-18 and IL-1β when it was injected intravenously 30 min before reperfusion into the pigs that had undergone MI/R [136].

**Caspase-1 Inhibitors**

**VX-765**

VX-765 is a highly selective inhibitor of caspase-1 function that acts by covalently modifying cysteine residues. In one study, rats were subjected to 1-h myocardial ischemia to imitate MI, followed by 2-h reperfusion to establish a MI/R model after separate i.v. injection of VX765, cangrelor, and VX765 combined with cangrelor. The combination of antiplatelet drugs and VX765 provided an extra protective effect in the rats, reducing the MI/R injury [146]. However, because the inhibitory effects were reversible, no further exploration was planned about the protective effect of VX765 in rats with MI/R injury. The experiments were repeated by Jonathan, with extension of reperfusion over 3 days. VX765 was found to decrease the infarct size in a time-dependent manner, and with the myocardial damage alleviated, caspase-1 and the downstream inflammatory factor were downregulated. VX765 has been studied in combination with antiplatelet drugs [147].

**α1-Antitrypsin**

α1-antitrypsin (A1AT) is an acute-phase glycoprotein secreted and synthesized by hepatocytes that increased in acute inflammation-related diseases [148,149]. A1AT downregulates the production of IL-1β, chemokine, and interferon after being added to human monocytes [150]. An increase in A1AT levels in the plasma of patients with AML suggests that A1AT could protect against myocardial damage. In one study, mice with myocardial ischemia were treated with an intraperitoneal injection of 60 mg/kg of A1AT at reperfusion. A1AT significantly minimized infarct size and LVSD during the initial 24 h and 7 days after reperfusion. A1AT also downregulated the expression of caspase-1 but did not influence the degree of leukocyte infiltration near the infarct region [151]. A1AT inhibited activation of caspase-1 and ventricular remodeling after myocardial infarction in mice that had undergone permanent ligation of the left anterior descending coronary artery.

**IL-1 Inhibitor**

Anakinra, an exogenous recombinant human IL-1 receptor antagonist (IL-1ra), has been used to treat rheumatoid arthritis and cryopyrin-associated periodic syndrome by interfering with IL-1β binding to IL-1 reporter I [152,153]. In vivo, anakinra alleviates myocardial remodeling and left ventricular dysfunction in mice that have been subject to acute MI and reperfusion. IL-1ra inhibits IL-1 by interacting with IL-1, competing with the IL-1 reporter I and protecting the heart from inflammatory injury [154,155]. In rats with MI, overexpression of IL-1ra has been found to diminish infarct size by 50% [156]. In recent clinical experiments, anakinra has been used to treat patients with non-ST-segment-elevation acute coronary syndrome, resulting in fewer hospitalizations for HF and less worsening of the condition than in the placebo group [157]. Even though a reduction in hsCRP values was observed in the MRC-ILA Heart clinical trial, there was late recurrence of ischemic events in patients who had received anakinra once daily for 14 days [158]. There was no clear explanation for those events, but they may be associated with a rebound inflammatory mechanism. A similar phenomenon has not been observed in another clinical experiment. However, the safety and efficacy of anakinra treatment in patients with myocardial infarction needs to be further explored in clinical experiments with a large sample size.

**Clinical Application and Perspectives**

Reperfusion is recognized as the most effective treatment for MI. However, myocardial injury and ventricular remodeling after reperfusion are still urgent clinical problems that need to be resolved. The NLRP3 inflammasome is a form of inflammatory cell death closely related to the occurrence and development of cardiovascular disease. Exploring the activation and mechanism of NLRP3 under ischemic conditions is crucial to understanding the pathophysiological mechanism of MI/R injury and myocardial remodeling. It also provides new directions for exploring and researching new pathological mechanisms and treatment strategies for MI/R injury and ventricular remodeling after ischemia. We have described the NLRP3-mediated pyroptosis-related pathway inflammation inhibitors that have been widely studied and used in clinical practice. The clinical trial data on targeting of inhibition of NLRP3-mediated pyroptosis as a way to reduce MI/R injury and myocardial remodeling provide a theoretical and practical basis for further extensive
research and clinical practice. In theory, NLRP3 inflammasome inhibitors should have pharmacological characteristics, such as fast onset, long duration of therapeutic effect, reasonable specificity, and high safety to reduce short-term and long-term damage caused by acute MI. In a previous large-scale phase III multicenter clinical study, canakinumab significantly reduced acute inflammatory response and risk of coronary restenosis in patients with AMI [159]. Therefore, we need more research to discover more specific, safe, and effective NLRP3 inflammasome inhibitors, as well as large-scale clinical trials to corroborate their clinical safety and effectiveness.

Conclusions

NLRP3 has been identified as essential in relieving MI/R injury and easing post-MI ventricular remodeling that are activated by specific stimuli. Many inhibitors of NLRP3-mediated signaling pyroptosis have been shown to vastly reduce post-MI myocardium injury, providing additional targets for alleviating MI/R injury and ventricular remodeling. Whether inhibition of NLRP3-mediated pyroptosis is associated with other adverse effects, however, requires further exploration.

Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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