Myocardial ischemia/reperfusion injury: Mechanisms of injury and implications for management (Review)

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Abstract. Myocardial infarction is one of the primary causes of mortality in patients with coronary heart disease worldwide. Early treatment of acute myocardial infarction restores blood supply of ischemic myocardium and decreases the mortality risk. However, when the interrupted myocardial blood supply is recovered within a certain period of time, it causes more serious damage to the original ischemic myocardium; this is known as myocardial ischemia/reperfusion injury (MIRI). The pathophysiological mechanisms leading to MIRI are associated with oxidative stress, intracellular calcium overload, energy metabolism disorder, apoptosis, endoplasmic reticulum stress, autophagy, pyroptosis, necroptosis and ferroptosis. These interplay with one another and directly or indirectly lead to aggravation of the effect. In the past, apoptosis and autophagy have attracted more attention but necroptosis and ferroptosis also serve key roles. However, the mechanism of MIRI has not been fully elucidated. The present study reviews the mechanisms underlying MIRI. Based on current understanding of the pathophysiological mechanisms of MIRI, the association between cell death-associated signaling pathways were elaborated, providing direction for investigation of novel targets in clinical treatment.

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Contents

1. Introduction

Coronary heart disease (CHD) is one of the primary causes of mortality and disability worldwide. For instance, according to the data obtained through the Unified Health System database from the Ministry of Health of Brazil, the average mortality rate for CHD increased to 78.75 during 2016-2018 in Brazil (1). Timely restoration of blood flow to ischemic myocardium in the early stage effectively limits infarct size and is therefore standard treatment to prevent death of cardiomyocytes at risk (2,3). Evidence has indicated that during myocardial ischemia/reperfusion (MIR), both ischemia and reperfusion cause injury to the ischemic myocardium (4,5). Therefore, myocardial reperfusion may further aggravate death of ischemic cardiomyocytes in patients with myocardial infarction (MI); this is known as MIR injury (MIRI) (3,4).

MIRI, first reported by Jennings *et al* in 1960 (6), causes four types of injury including myocardial stunning (7), the no-reflow phenomenon (8), reperfusion arrhythmia (9) and lethal reperfusion injury (10). The first two forms are reversible while the others are irreversible (11). Clinically, percutaneous coronary intervention (PCI) (12), antiplatelet (13) and anticoagulant (14) therapy are primarily used for patients exposed to the latter two types of injury to maintain coronary artery patency. During myocardial reperfusion, timely and effective restoration of blood flow cannot effectively prevent MIRI.

Numerous studies have researched mechanisms underlying MIRI; the pathophysiological mechanisms of MIRI are associated with oxidative stress, intracellular calcium overload,

energy metabolism disorder, apoptosis, endoplasmic reticulum stress (ERS), autophagy, pyroptosis, ferroptosis and necroptosis (15,16). Furthermore, these mechanisms are interrelated and may directly or indirectly lead to the aggravation of cell death. The present review summarizes research on the pathophysiological mechanisms underlying MIRI.

2. Pathophysiological mechanisms of MIRI

Oxidative stress. Reactive oxygen species (ROS), including superoxide, hydrogen peroxide (H_2O_2), singlet oxygen, lipid peroxides, peroxynitrite, hypochlorite, ozone and hydroxyl, hydrogen peroxide and alkoxy radicals (17), are small reactive molecules involved in regulation of various cellular functions and biological processes. ROS at low-to-moderate levels serve as signaling molecules, while uncontrolled high levels of ROS lead to free radical damage associated with structural and functional changes in proteins, lipids and DNA (18,19). For example, ROS at moderate levels may activate cell signaling, augmenting production and release of proinflammatory cytokines, thereby perpetuating the well-controlled inflammatory responses, which are part of our body's innate immunity, protecting against invading pathogens (20). As ROS induces various types of cell death (such as apoptosis, necrosis and pyroptosis), ROS are considered to serve a key role in IRI in a number of organs (20). Furthermore, vascular endothelial dysfunction induced by ROS also contributes to the occurrence and development of IRI in different organs, such as the heart, cerebrum and liver (21,22). When overproduction of ROS exceeds the ability to clear them, oxidative stress occurs, leading to imbalance of oxidation and antioxidant systems and cell and tissue damage (23).

During IR, especially reperfusion, ROS levels increase due to multiple mechanisms such as increased xanthine oxidase formation, neutrophil respiratory burst and damage of the mitochondrial electron transport chain (24). The excessive ROS decrease membrane fluidity, increase calcium permeability, aggravate intracellular calcium overload and mitochondrial damage and contribute to release of pro-apoptotic factors, such as cytochrome C (CytC) (25). In addition, oxidative reactions between ROS and proteins cause loss of original protein structure and function and damage of nucleic acids and chromosomes (19). In addition, ROS may trigger the inflammatory cascade reaction and expression of adhesion molecules that result in leukocyte aggregation, endothelial cell swelling and the no-reflow phenomenon that refers to the incomplete and uneven reperfusion at the microvascular level even though the proximal artery has been re-opened after a period of ischemia (26). Oxidative stress induced by reperfusion after ischemia is considered to be the primary mechanism of IRI (20). Oxidative stress is involved in ventricular remodeling by causing endothelial dysfunction, myocardial cell injury, apoptosis and other pathological changes that promote formation and development of cardiomyopathy (27) and cause cardiac dysfunction. Among potential sources of ROS, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, mitochondria and uncoupled nitric oxide synthase (NOS) are key sources of reperfusion-induced oxidative stress (28). When ROS levels exceed the ability of the cellular endogenous radical scavenging system to remove them (29), uncontrolled ROS burst damages the membrane and proteins and indirectly causes damage by opening mitochondria permeability transition pore (mPTP) and promoting activation of the apoptosis pathway. Thus, ROS participate in myocardial injury and death through multiple mechanisms (30).

NO, synthesized by endothelial (e)NOS, is a key defense mechanism against MIRI (31-33). Studies by our group indicated that activation of PI3K/AKT and Janus kinase 2/STAT3 pathways attenuates MIRI (34-36) and the underlying mechanism is associated with activation of eNOS and increased levels of NO (32,37,38).

Intracellular calcium overload. Contraction and relaxation of myocytes are controlled by balance of calcium. In the steady-state, calcium influx and efflux are maintained in balance. Any increase in calcium influx (for example, during β-adrenergic stimulation) is met by a corresponding increase in calcium efflux (39,40). Under normal conditions, calcium influx and efflux balance ensures cells do not become overloaded with calcium. Sarcoplasmic reticulum calcium content is increased when calcium influx exceeds efflux until a new steady-state of influx and efflux is achieved (39).

After a certain period of hypoxia in cardiomyocytes, the intracellular anaerobic metabolism may result in accumulation of H^+, decreased intracellular pH and increased levels of intracellular Na^+ via Na^+/H^+ exchange (NHE) (41). The aggregation of Na^+ in cardiomyocytes increases the activity of Na^+/Ca^{2+} exchange (NCX) proteins, which decreases aggregation of intracellular Na^+ and transports extracellular Ca^{2+} into the cells, thus increasing the concentration of Ca^{2+} in the cytoplasm and causing calcium overload (42). Rapid reoxygenation increases the pH of extracellular fluid and H^+ gradient across the cell membrane, so that the activity of NHE and NCX increases, causing intracellular calcium overload (43). In addition to the aforementioned NHE and NCX mechanisms, the H^+/Ca^{2+} exchange mechanism is also a key cause of intracellular calcium overload (44).

Calcium processing and further inflow or outflow are regulated by protein channels (45). Strict regulation of intracellular calcium homeostasis is key for maintaining normal function and growth of myocardial cells and disruption of intracellular calcium homeostasis leads to ERS, aggravating ischemic injury of myocardial cells (19). Chen *et al* (46) indicated that diltiazem, a calcium antagonist, has protective effects on ischemic myocardium, which decreases oxidative stress, restores normal energy metabolism, improves endothelial function and decreases apoptosis. In addition, clinical trials have found that diltiazem exerts a cardioprotective effect in patients who exhibit post-transplant hypertension and vasospastic angina (47,48). As reported in the aforementioned studies, diltiazem improves left ventricular systolic function and coronary hemodynamics in patients with myocardial ischemia and prevents reperfusion arrhythmia in patients with ST segment elevation MI following treatment with PCI (46).

Energy metabolism disorder. Mitochondria, a key organelle responsible for production of adenosine triphosphate (ATP)

and energy metabolism in cells, also contribute to normal physiological function of the heart (49). Mitochondrial integrity and loss of function in cardiomyocytes are considered to be pathological factors underlying changes in cardiac structure and function (49). By forming a dynamic network, mitochondria continuously change shape by division and fusion to meet functional needs of cardiomyocytes (50). Since cardiomyocytes consume lots of energy, the density of mitochondria is relatively higher compared with other types of cell (51).

The function of mitochondria is regulated by numerous factors. Physiologically, mitochondrial Ca^{2+} is an active effector, which triggers activation of mitochondrial metabolic mechanisms that increase production of ATP. However, during IR, cytoplasmic calcium overload leads to mitochondrial calcium overload (52). Ca^{2+} enter mitochondria primarily via the mitochondrial calcium uniporter, a type of small conductance Ca^{2+} selective channel that regulates intracellular Ca^{2+}, production of ATP and cell death (52). The movement of Ca^{2+} across the mitochondrial membrane leads to amplification of mitochondrial Ca^{2+} overload, causing mitochondrial dysfunction (53). Overload of mitochondrial Ca^{2+} dissipates membrane potential, promotes opening of mPTP, a non-selective channel in the inner mitochondrial membrane that is considered to be one of the key participants in IRI, and leads to impaired ATP synthesis (54). The inner mitochondrial membrane is normally impermeable to ions and proteins and is responsible for maintaining formation of mitochondrial transmembrane potential pores, creating non-selective channels and causing potential to dissipate across the membrane. Our previous study found that the degree of mPTP opening degree corresponds to change of mitochondrial morphology, which indicates that mitochondrial function is associated with its morphology during MIRI (50).

Disturbance of mitochondrial homeostasis contributes to acute organ failure and cell damage following ischemia (22). The opening and closing of mPTP is the primary mechanism for maintaining mitochondrial membrane potential; ischemia induces mPTP closure whereas reperfusion promotes mPTP opening (54). During acute IR, mPTP remains closed during ischemia and opens due to mitochondrial calcium and phosphate overload, oxidative stress and rapid pH correction during reperfusion (55,56). ROS levels increase in a short period of time due to IRI, resulting in excessive cytoplasmic and mitochondrial Ca^{2+}, which induces opening of mPTP and depolarizes the mitochondrial membrane potential (54). The opening of mPTP may contribute to loss of ATP, mitochondrial swelling and CytC release, leading to apoptosis (57). Our previous study demonstrated that regulation of mitochondrial morphology, inhibition of mPTP opening and maintenance of mitochondrial membrane potential protect the myocardium against MIRI; the underlying mechanism involves regulation of mitofusin 2 (Mfn2), optic atrophy 1 (Opa1) and dynamin-related protein 1 (Drp1) proteins, which provides a theoretical basis for targeted therapy (50).

Apoptosis. Apoptosis is a form of regulated cell death that leads to cell contraction, condensation of cytoplasm and nucleus and formation of apoptotic bodies (58). Cytoskeletal and nuclear proteins are degraded and cleaved by caspases during the execution phase of apoptosis (59). Finally, apoptotic bodies are phagocytosed by macrophages that recognize externalized phosphatidylserine on the outer leaflet of the bilayer (60). Because apoptotic bodies are surrounded by cell membranes and are swallowed and digested by phagocytes such as neutrophils, macrophages, and dendritic cells (DCs), they eventually degrade without causing inflammation (61). However, part of the cell structures (e.g. cell membrane) can be preserved till the late stage of apoptosis (62).

There are three classic apoptosis signaling pathways: Extrinsic (death receptor), intrinsic (mitochondrial) and ERS pathway (63).

Extrinsic pathway-induced apoptosis is triggered by transmembrane death receptors, which are members of tumor necrosis factor receptor (TNFR) family containing the 'death domain'. Through the death domain, certain ligands and associated death receptors, including apoptosis-stimulating fragment ligand (FasL)/FasR, TNF-α/TNFR1, TNF-related apoptosis-inducing ligand (TRAIL)/death receptors and TRAIL/DR5, facilitate transmission of death signals from cell surface to intracellular pathways (63). For example, binding of FasL to FasR or TNF-α to TNFR1 causes recruitment of Fas-associated death domain (FADD) and binding to the ligand-receptor complex (64). FADD activates pro-caspase-8 consecutively and forms a death-inducing signaling complex (DISC) (65). DISC-activated caspase-8 leads to activation of caspase-3 and -7 to induce the apoptosis cascade response, which results in the execution phase of apoptosis (66,67). During of MIRI, ischemia and reperfusion increases levels of ROS, cellular injury and cardiovascular dysfunction, which leads to cardiomyocyte apoptosis. Upregulation of cardiac-specific caspase-3 increases post-ischemic infarct size and risk of mortality following MIRI (68). Furthermore, the Fas pathway serves as a critical mediator of the cardiomyocyte apoptosis caused by MIRI (69). In addition, TNF-α and TRAIL levels increase during onset of reperfusion in mouse models of MIRI (70).

The intrinsic pathway, which is activated by hypoxia, hyperthermia and low levels of growth factors (e.g. nerve growth factor), is triggered by mitochondria and contributes to apoptosis. The aforementioned stimuli promote opening of mPTP and block mitochondrial transmembrane potential, thereby increasing release of pro-apoptotic proteins (e.g. Bax) involved in CytC and apoptosis from the intermembrane to the cytoplasm (71). By binding and activating caspase-9, CytC promotes formation of caspase-3 and -7. These events induced by mitochondria are regulated by B-cell lymphoma 2 (Bcl-2) family proteins located in the mitochondrial outer membrane, which control the permeability of the mitochondrial membrane and regulate release of CytC. Bcl-2 family proteins are functionally divided into pro- and anti-apoptotic proteins (67). Bcl-2 family proteins lead to downregulation of apoptosis mediated by upregulation of tumor suppressor protein p53 in the nucleus or mitochondria. When expression of p53 is inhibited, Bax and Caspase-3 are downregulated in heart tissue in CHD (72-74). There is also an interaction between the extrinsic and intrinsic pathways (75). In the intrinsic apoptosis pathway, Bax is overexpressed in ischemic myocardial tissue and inhibition of Bax activation decreases apoptosis and improves MIRI (76). Furthermore, cardiac-specific overexpression of Bcl-2 markedly relieves cardiomyocyte apoptosis and infarct size following MIRI (77).

Previous studies have indicated that apoptotic cell death is one of the primary forms of cardiomyocyte death during MIRI (78-84).

ERS. ER is a key site for protein synthesis, modification and processing and its normal function serves an important role in maintaining cellular homeostasis (85). However, adverse stimuli such as ischemia and hypoxia lead to accumulation or misfolding of proteins in the ER. The accumulation of unfolded protein simultaneously activates three transmembrane stress sensors, inositol-requiring enzyme 1 (IRE1), activating transcription factor (ATF) 6 and PERK, known as the unfolded protein response (UPR) (86). ERS is a relatively novel pathway regulating apoptosis that is involved in multiple physiological functions and pathological injury, including protein folding, intracellular Ca^{2+} storage, oxidative stress, hypoxia, ischemia and lipid metabolism disorder (87). Although ERS is key for cell survival, chronic ERS leads to apoptosis.

IRI may be associated with ERS (87). Unfolded proteins in ERS induce myocardial injury, which further induces ERS, thereby affecting the metabolic state of cardiomyocytes and causing greater injury (86). During MIRI, ERS is increased and inhibition of ERS has been shown to attenuate MIRI (88-90). However, it has also been reported that not all ERS is harmful. For instance, ERS transcription factor ATF6 induces protective effects against IRI in cardiomyocytes (91,92). However, sustained ERS causes apoptosis (93).

ER and mitochondria are physically connected to form dedicated structural domains known as mitochondria-associated ER membranes (MAMs), which participate in key biological processes, including lipid and Ca^{2+} homeostasis, mitochondrial dynamics and associated cellular behavior, such as autophagy, ERS and apoptosis. Gao *et al* (94) demonstrated the role of MAMs in maintaining normal function of both ER and mitochondria, which are associated with occurrence of cardiovascular disease. Another study also suggested that GSK3β serves an important role in controlling Ca^{2+} flow from the sarcoplasmic reticulum to mitochondria via MAMs during MIRI (95).

Changes in ER oxidation lead to aberrant formation of disulfide bonds and accumulation of peptides, thus activating intracellular reactions called unfolded protein response (96), a form of acute response in cardiovascular disease (97). Stimulation of UPR leads to three primary response mechanisms, IRE1α, PERK and ATF6, which regulate the protein folding ability of ER (98). In the absence of PERK, endogenous apoptosis induced by ERS is weakened due to decreased MAM formation and inhibited ROS signal transmission to adjacent mitochondria (99). IRE1 in MAMs promotes effectiveness of inositol 1,4,5-trisphosphate receptor, which is responsible for transfer of Ca^{2+} to mitochondria (100). These mechanisms connect ERS and mitochondrial function, thus affecting the fate of cells.

Autophagy in MIRI. Autophagy is a phenomenon in which cells digest cytoplasm in lysosomes and is key to maintaining normal structure and function of the heart. Autophagy, the primary function of which is to remove and recover misfolded or damaged proteins and organelles, is not only associated with cell survival but also with cell death (101-103). Apoptosis and autophagy are both adaptive responses that are key for cell growth, survival and homeostasis (104). Specifically, apoptosis is type 1 programmed cell death, which involves early degradation of cytoskeleton but preservation of organelles until the late phase, whereas autophagy is type 2 cell death and involves early degradation of organelles but preservation of cytoskeleton until the late stage (105). However, it has been reported that activation of autophagy does not contribute to cell death in MIRI and may serve a protective role (106). A study has indicated that activation of autophagy via chloramphenicol therapy decreases infarct size in a pig model of MIRI (106).

During myocardial ischemia, autophagy degrades non-functional cytoplasmic proteins and provides key nutrients for cell growth and survival, thereby inhibiting apoptosis and necrosis. A recent study suggested that autophagy is necessary to decrease myocardial damage following acute myocardial ischemia and that autophagy limits activation of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome by removing damaged mitochondria (43). However, it is also reported that excessive autophagy during reperfusion may aggravate the injury of the heart (107,108).

Currently, three forms of autophagy are known: Macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) (109). In macroautophagy, the primary sources of membranes are ER and Golgi bodies. Autophagosomes are formed by completely including the object to be degraded and fusing it with the lysosomal membrane before degradation by lysosomal enzymes (110). In microautophagy, degradation products are directly encapsulated in lysosome membranes for degradation and digestion in lysosomes (111). In CMA, chaperone proteins are bind to the protein to be degraded to guide transport of the substance to lysosomes, which are digested and broken down by enzymes. CMA pathway is a lysosomal process with obvious selectivity, which is different from the aforementioned processes (112).

The molecular mechanism of autophagy is primarily composed of four pathways that involve mTOR complex 1, AMP-activated protein kinase (AMPK), ERS and p53. mTOR and Beclin1 are autophagy-associated molecules that serve key roles in different stages of MIRI. During the ischemic phase, mTOR acts via AMPK/mTOR and PI3K/AKT/mTOR pathways (78), while Beclin1 is upregulated during reperfusion (43,101,102). Beclin1 is a key autophagy protein that regulates formation and processing of autophagosomes. Upregulation of Beclin1 is responsible for autophagy activation during reperfusion (113). However, it is unclear how MIRI activates Beclin1. One potential mechanism is its association with Bcl-2. *In vitro* study have shown that Beclin1-mediated autophagy to nutritional deficiency (e.g. a lack of amino acids and serum) of cardiomyocytes is regulated by Bcl-2 protein (114). Moreover, ROS may also induce Beclin1-mediated autophagy during reperfusion. During reperfusion, high levels of ROS are not an energy crisis, but a key promoter of autophagy. Reperfusion results in increased oxidative stress with overexpression of Beclin1 (115,116). In addition to regulating expression of Beclin1, ROS may also oxidize and decrease activity of autophagy-associated proteins, leading to lipidation of light chain 3 (LC3) as well as initiation of autophagy. As Beclin1 is primary located in ER (117), it remains to be determined whether reperfusion-induced ERS also participates in upregulation of Beclin1.

Pyroptosis. Pyroptosis is a novel type of proinflammatory programmed cell death that is caused by activation of the NLRP3/apoptosis-associated speck-like protein (ASC)/caspase-1 pathway and high levels of interleukin-1β (IL-1β) (118). The primary biological features of pyroptosis are dependence on caspase-1 and the accompanying inflammatory cascade reaction. Under endogenous and exogenous stimuli, ASC acts on pro-caspase-1 to form inflammasome and activate pro-caspase-1 (119). The activated caspase-1 promotes activation and expression of downstream cytokines such as IL-1β and IL-18, resulting in cell and tissue damage (119). It is also a key host mechanism in response to pathogens and endogenous damage (119,120).

Compared with other modes of cell death, pyroptosis has unique features, including activation by intracellular inflammatory caspase, formation of membrane pores and DNA fragmentation/destruction (67). Pyroptosis leads to release of inflammatory cytokines and exhibits certain characteristics of apoptosis (121) (including DNA fragmentation and nuclear concentration) and necrosis (122) (such as loss of plasma membrane integrity and release of intracellular content such as lactate dehydrogenase).

Cell membrane rupture during pyroptosis is mediated by Gasdermin D protein (GSDMD) (67). In healthy cells, GSDMD stays functionally inactive via intramolecular interactions between its COOH-(inhibitory) and NH_2-terminal (pro-death) domains. Hydrolysis of inflammatory caspase-1 to GSDMD produces NH_2-terminal lysate (GSDMD-NT) (123). GSDMD-NT monomers oligomerize to form pores in the plasma membrane, leading to release of intracellular material and contributing to cell death; however, the underlying mechanism is unknown. GSDMD is also released in pyroptosis without damaging adjacent cells (124). As a novel form of cell death, pyroptosis is associated with development of the mouse model of MIRI (125,126).

ROS produced by mitochondria are hypothesized to serve as a signal for activation of NLRP3 inflammation downstream of MIRI-associated mitochondrial dysfunction (127). In addition, inflammasomes are activated by ROS production and potassium efflux with myocardial ischemia and hypoxia, resulting in activation of caspase-1 and cleavage of GSDMD, which aggravates MIRI (128). A study has indicated that silencing of calpain attenuates myocardial dysfunction caused by MIRI by suppressing activation of the NLRP3/ASC/caspase-1 axis (125). Furthermore, inhibition of microRNA-29a improves MIRI by targeting silent information regulator factor 2-related enzyme 1 via suppressing oxidative stress and NLRP3-mediated pyroptosis (129). Numerous studies have demonstrated that pyroptosis is a key mechanism in exacerbating MIRI (130,131).

Ferroptosis. Ferroptosis, a novel and unique iron-dependent non-apoptosis-regulated form of cell death; it is also called iron-dependent programmed cell death due to the destruction of glutathione-dependent antioxidant defense mechanism and accumulation of lipid peroxides, which are caused by the increased ROS level related to Fe^{2+} (132,133). Ferroptosis is characterized by the depletion of plasma membrane polyunsaturated fatty acids, condensed mitochondrial membrane densities, and vanishing of mitochondria crista (126). Studies have shown that ferroptosis is involved in regulation of tumor (133), liver cancer (134), Alzheimer's disease (135), cerebral ischemic (136) and acute kidney injury (137) and other types of disease.

Ferroptosis is dependent on intracellular iron and is morphologically, biochemically and genetically distinct from apoptosis, necrosis and autophagy (138). Iron participates in oxidative phosphorylation of mitochondria, thereby increasing ROS levels and ATP production (139). ROS levels that exceed cell antioxidant capacity lead to oxidative stress, which directly or indirectly damages large molecules such as proteins, nucleic acids and lipids, leading to cell damage and death (139-141). The ferric carrier protein transferrin and amino acid glutamine are hypothesized to be responsible for ferroptosis (142). The cell surface transferrin receptor and glutamine-mediated intracellular metabolic pathway glutamine breakdown serve critical roles in cell death (143). Almost all genes involved in ferroptosis are regulated by nuclear factor erythroid 2-related factor 2 transcription, including genes that regulate glutathione and NADPH regeneration, which are key for glutathione peroxidase 4 activity, lipid peroxidation and iron regulation (144).

It is hypothesized that during ischemia and early reperfusion, cellular acidosis, internal environmental instability and other factors promote release of ferrivalent or ferrous ions from enzymes containing iron and sulfur clusters and activate the iron-mediated Fenton reaction, resulting in increased generation of ROS, which leads to oxidative stress injury and ferroptosis of cardiomyocytes (145,146). In addition, deposition of iron in the periinfarct and non-infarct areas has been observed in a mouse model of MI (147). Moreover, Baba *et al* (148) observed positive iron staining in non-cardiac cells surrounding cardiac scar.

A recent study by our group indicated that myocardial ferroptosis (as well as apoptosis pyroptosis) is increased during MIRI in diabetes and is attenuated by effective treatment with antioxidant N-acetylcysteine (130). However, the interaction and underlying mechanism of apoptosis, pyroptosis and ferroptosis in MIRI have yet to be elucidated.

Necroptosis. In the death receptor pathway, necrosis is induced by activation of receptor-interacting protein kinase 3 (RIPK3), a serine/threonine kinase. RIPK3 is typically activated by phosphorylation of homologous RIPK1 (149). RIPK3 phosphorylates and activates pseudokinase mixed lineage kinase domain-like protein (MLKL), which oligomyelizes and permeates the plasma membrane, leading to necrosis (149). Necrosis is mediated by complex IIb including RIPK1, RIPK3, and MLKL. One of the key targets of RIPK3-induced necrosis is pseudokinase MLKL. RIPK3-mediated phosphorylation of MLKL exposes a four-helix bundle in MLKL that promotes cysteine-dependent tetramylation, progression to amyloid filaments and transfer and osmosis to the plasma membrane (150). MLKL phosphorylation is a key for programmed necrosis. Studies have shown that MLKL is the executor of the necrotic effect (150,151). MLKL contains an N-terminal four-helix bundle domain connected to a C-terminal pseudokinase; the helical bundle is the functional domain of MLKL. Under normal conditions, RIPK3 phosphorylates MLKL, resulting in conformational changes that counteract the autophagy effect of the

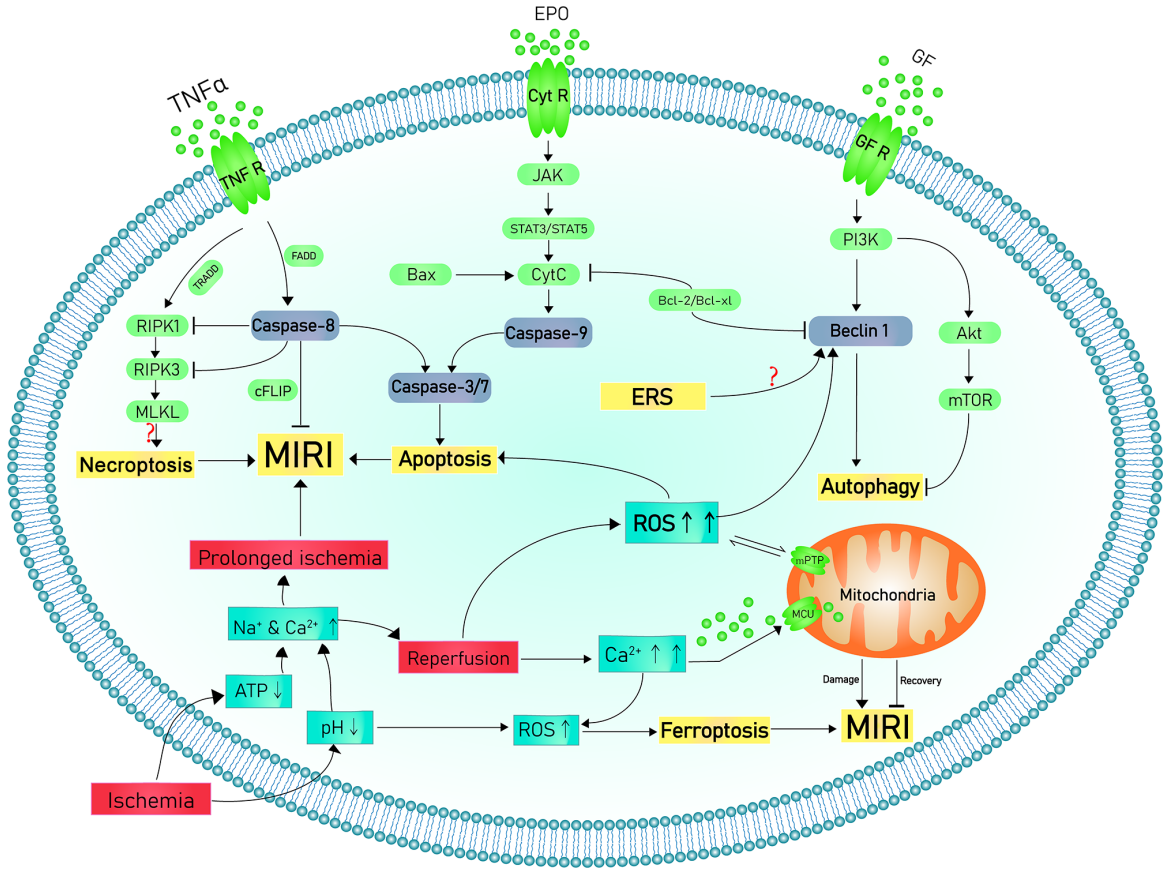

Figure 1. During ischemia, cardiomyocytes undergo anaerobic metabolism, which results in decreased ATP levels and pH, which increase levels of intracellular Na^+ and Ca^{2+}. Reperfusion leads to further increases in intracellular Ca^{2+} and ROS, which cause MIRI. The primary apoptosis signaling pathways are the intrinsic (mitochondrial) and extrinsic (death receptor) pathway. The intrinsic pathway is induced by release of CytC, which is regulated by Bcl-2 family proteins. The extrinsic pathway is triggered by death receptors (such as TNFR) that activate caspase-8. Programmed necroptosis is mediated by the complex RIP1-RIP3 and MLKL when caspase-8 is inhibited, but the downstream pathway of MLKL remains unclear. Necroptosis and apoptosis have certain commonalities. For instance, caspase-8 decreases MIRI via inhibiting necroptosis by binding to an anti-apoptotic protein (cFLIP). Three forms of autophagy are macroautophagy, microautophagy and chaperone-mediated autophagy. Macroautophagy is the primary pathway, which is promoted by PI3K, AMPK and Beclin1, while AKT/mTOR pathways inhibit this type of autophagy. Beclin1 is abundant in the ER. However, it remains uncertain whether ERS regulates expression of Beclin1 during ischemia or reperfusion. During ischemia and early reperfusion, cellular acidosis, internal environmental instability and other factors promote the release of ferrivalent or ferrous ions from enzymes, thereby activating the Fenton reaction, resulting in increased ROS, which leads to ferroptosis of cardiomyocytes. ROS, reactive oxygen species; MIRI, myocardial ischemia/reperfusion injury; CytC, cytochrome c; TNFR, tumor necrosis factor receptor; RIPK, receptor-interacting protein kinase; MLKL, mixed lineage kinase domain-like protein; cFLIP, CASP8 and FADD-like apoptosis regulator; AMPK, AMP-activated protein kinase; ERS, endoplasmic reticulum stress; JAK, Janus kinase; GFR, growth factor receptor; FADD, Fas-associated death domain; TRADD, tumor necrosis factor receptor type 1-associated death domain protein; MCU, mitochondrial calcium uniporter; mPTP, mitochondrial permeability transition pore; EPO, erythropoietin; ?, unknown mechanism.

kinase homologous C-terminal region in MLKL (152). MLKL is considered to be the primary target of necrosis but its downstream signaling pathway requires further investigation (153).

Expression levels of necroptosis-associated proteins, including RIPK1, RIPK3 and MLKL, have been shown to be increased in an *in vivo* MIRI model (154-160). However, reperfusion duration and species-specific susceptibility to cell death should be considered when evaluating necroptosis (161). A study has shown that RIPK3 is also involved in ERS and intracellular Ca^{2+} overload (162), which aggravates MIRI.

Our previous studies showed that RIP3-mediated necroptosis is a key mechanism of enhanced inflammation and lung tissue injury in high dose lipopolysaccharide-induced severe acute respiratory distress syndrome in mice (153) and in cardiomyocytes with H_2O_2-induced necroptotic and apoptotic cell death (163). To the best of our knowledge, studies regarding the role and mechanism of RIP3-mediated necroptosis and its interaction with apoptosis and other forms of cell death in MIRI are rare (157,164). Therefore, further studies in this area are required.

3. Conclusion

The present review summarizes research on the pathophysiology of MIRI, including the role of ROS in cell death during MIRI, ischemia- and hypoxia-induced metabolic and functional dysfunction of the electron transport chain in cardiomyocyte mitochondria, mitochondrial disorder caused by decreased ATP production and oxidative stress promoted by increased ROS production caused by mitochondrial damage and electrolyte imbalance during reperfusion. Increased ROS levels lead to cell damage and death via autophagy, apoptosis, programmed cell death inflammation, ferroptosis and necrosis. These interplay

with one another, which directly or indirectly leads to aggravation of the effect (Fig. 1).

To the best of our knowledge, the underlying mechanism of MIRI has not been fully clarified. Among the known mechanisms, explanations for Ca^{2+} overload, energy metabolism disorder, oxidative stress and autophagy are relatively complete, whereas the role of pyroptosis, necrosis and ferroptosis, as well as downstream molecules of known signaling pathways, need to be further investigated. Clinical trials have shown that infarct size can be limited by non-pharmacological strategies such as ischemic post-conditioning and remote ischemic conditioning, drugs, such as cyclosporine, insulin, glucagon-like peptide-1 agonists and β-blockers, or stimulation of cyclic guanosine monophosphate synthesis (165). Our clinical studies have shown that Captopril pretreatment (166) and intraoperative use of antioxidant therapy, such as propofol (167) and *Salvia miltiorrhiza* (168) alleviate MIRI and improve prognosis in humans. In addition, clinical treatments such as remote ischemic preconditioning (RIPC) attenuate MIRI and improve short-term prognosis. A key cardioprotective mechanism of RIPC is associated with decreased opening of mPTP in the heart (36,169).

MIRI is a complex process involving multilevel and multifactor interactions between genes, molecules, cells and tissue. A full understanding of the pathogenesis and mechanisms underlying development of pathophysiology may provide novel therapeutic targets for improving the prognosis of MIRI and decreasing mortality associated with cardiovascular disease.

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Authors' contributions

JH and DL drafted the manuscript. LXZ, JR and DZ collated and checked references. DL, JH and DZ prepared the figure. LQZ and ZX edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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