Abstract. Although acute myocardial infarction is one of the most common fatal diseases worldwide, the understanding of its underlying pathogenesis continues to develop. Myocardial ischemia/reperfusion (I/R) can restore myocardial oxygen and nutrient supply. However, a large number of studies have demonstrated that recovery of blood perfusion after acute ischemia causes reperfusion injury to the heart. With progress made in the understanding of the underlying mechanisms of myocardial I/R and oxidative stress, a novel area of research that merits greater study has been identified, that of I/R-induced endoplasmic reticulum (ER) stress (ERS). Cardiac I/R can alter the function of the ER, leading to the accumulation of unfolded/misfolded proteins. The resulting ERS then induces the activation of signal transduction pathways, which in turn contribute to the development of I/R injury. The mechanism of I/R injury, and the causal relationship between I/R and ERS are reviewed in the present article.

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1. Introduction
Myocardial infarction (MI) is one of the leading causes of mortality worldwide and occurs due to the acute occlusion of the coronary arteries (1). Although revascularization treatment has conferred proven efficacy for patients with MI, it also causes undesired ischemia/reperfusion (I/R) injury following the restoration of epicardial blood flow (2,3). I/R injury is defined as tissue injury that occurs when the blood supply to organs is interrupted and then returns (4). To the frustration of interventional cardiologists and other health professionals, the desire of whom is the fast restoration of blood flow to the heart muscle, successful therapeutic strategies that can prevent I/R injury in the clinic have yet to be established (5).

The endoplasmic reticulum (ER) is an important organelle for eukaryotic cell survival and development (6,7). It is responsible for the biosynthesis, folding, assembly and modification of most secreted and transmembrane proteins. Furthermore, it serves a role in cellular lipid and steroid synthesis (8). Approximately 33% of cellular protein production and folding occurs in the ER (9). Excessive protein synthesis, beyond the capacity of the folding mechanism in cells, or excess accumulation of unfolded/misfolded proteins in the ER lumen will disrupt ER homeostasis and trigger the unfolded protein response (UPR), eventually leading to ER stress (ERS) (10). Events in the process of I/R can alter ER function and consequently influence the accumulation of unfolded/misfolded proteins. The resulting ERS then induces the activation of three signal transduction pathways, including the protein kinase R-like endoplasmic reticulum kinase (PERK)-eukaryotic translation initiation factor 2A (eIF2a)-activating transcription factor (ATF) 4-C/EBP homologous protein (CHOP) pathway, pro-ATF6-ATF6-CHOP pathway and inositol requiring enzyme 1 (IRE1)-X-box binding protein 1 (XBPI) pathway, which in turn promote the development of I/R injury (11).

The aim of the present review was to summarize current understanding of the multifactorial mechanisms that contribute to the genesis of I/R injury, and the relationship between I/R and ERS. In addition, possible future targets of therapeutic interventions to enhance recovery after I/R were discussed.
2. Mechanisms of I/R injury

Calcium (Ca\(^{2+}\)) overload. Ca\(^{2+}\) overload is a complex process that serves a fundamental role in I/R damage. During ischemia, anaerobic metabolism dominates, which causes a reduction in intracellular pH. To buffer the resulting accumulation of hydrogen ions, the sodium ion exchanger discharges excessive hydrogen ions, resulting in a sodium ion influx (12). Simultaneously, ischemia also depletes ATP, which inactivates ATPases such as the Na\(^+/\)K\(^+\) ATPase and reduces the efflux of Ca\(^{2+}\) whilst restricting the re-uptake of Ca\(^{2+}\) into the ER, causing Ca\(^{2+}\) overload (13). Opening of the mitochondrial permeability transition pore (MPTP) also occurs with the aforementioned physiological changes in the cell, leading to the dissipation of mitochondrial membrane potential and further impairments to ATP production (14). Ca\(^{2+}\) reuptake into the ER/sarcoplasmic reticulum (SR) via the SR/ER Ca\(^{2+}\) ATPase (SERCA) is damaged by I/R, whereas Ca\(^{2+}\) release through the ryanodine receptor is enhanced, both of which potentiate an increase in Ca\(^{2+}\) levels in the cytosol (15). The ryanodine receptor is a Ca\(^{2+}\) channel that is located on the ER/SR network. It rapidly releases Ca\(^{2+}\) from the ER/SR network and exerts a wide range of physiological functions, such as functioning in myocardial cell excitation and Ca\(^{2+}\)-dependent acceleration of ATP production, which serve an important role in maintaining the intracellular Ca\(^{2+}\) balance (15,16).

Ca\(^{2+}\) overload can damage cardiac function. Rapid accumulation of Ca\(^{2+}\) in cardiomyocytes after reperfusion can induce dynamic uncoupling, increase electrical conduction dispersion, and facilitate re-entry formation and arrhythmias. In addition, it can induce early or late depolarization contact, ventricular tachycardia or even ventricular fibrillation with short syndromic intervals (17,18). Ca\(^{2+}\) overload also promotes the damage or death of cardiomyocytes during reperfusion in multiple ways. The opening of the MPTP results in a large number of hydrogen ions entering the mitochondrial matrix from the mitochondrial intermembrane space, leading to the dissipation of the transmembrane potential gradient and obstruction of the electron transport chain. Water can also simultaneously enter the matrix down an osmotic gradient, causing mitochondrial edema, rupture or disintegration, which may lead to cell necrosis (19). Upon myocardial I/R, SERCA accelerates Ca\(^{2+}\) uptake and renders the cytoplasmic SR cycle in a state of high load, which leads to Ca\(^{2+}\) oscillation and affects the expression of Ca\(^{2+}\) in cells (20). Intracellular Ca\(^{2+}\) overload can result in excessive myocardial fiber contraction, which not only damages the cells themselves, but can also cause metabolic disorders or damage the structure of adjacent cells by mechanical forces such as traction (21). Increases in intracellular Ca\(^{2+}\) during myocardial ischemia can promote calpain translocation, but low intracellular pH in ischemia prevents it from being activated. During blood flow reperfusion, with the recovery of intracellular pH, calpain can be activated (22). The calpain family of cysteine proteases is activated by the elevation of Ca\(^{2+}\). Excessive calpain degrades a multitude of intracellular proteins in the cytoskeleton, ER and mitochondria, in turn causing damage to cells or organelles (23).

Accumulation of reactive oxygen species (ROS). ROS are a group of unstable, active molecules, including superoxide (O\(_2^−\)), hydrogen peroxide (H\(_2\)O\(_2\)) and hydroxyl radicals, which were first described as free radicals in skeletal muscle (24). ROS are generally considered to be toxic byproducts of aerobic respiration and are the major cause of macromolecular damage (25). ROS are produced by organelles and enzymes, including: i) Mitochondria, where oxygen functions as the terminal electron acceptor of the electron transport chain; ii) the ER, where H\(_2\)O\(_2\) is produced as a by-product of protein folding; iii) peroxisomes, where enzymes that produce H\(_2\)O\(_2\), such as polyamine oxidase, are localized; and iv) NADPH oxidase (NOX), a membrane bound enzyme complex that has a role in killing intracellular pathogens (26). Function of these organelles and enzymes will be affected following exposure to environmental cues, including chemotherapeutic drugs, ionizing radiation and environmental damage (27). O\(_2^•−\) is a single electron reduction product of oxygen that exists in large quantities in the human body that can mediate cellular damage. O\(_2^−\) is produced by complexes I and III of the mitochondrial electron transfer chain, where oxygen is reduced by electron leakage. Additionally, the plasma membrane NOX (NADPH oxidases), a family of flavoenzymes, which catalyzes the oxidation of NADPH, can generate O\(_2^−\) (28,29). O\(_2^−\) is eliminated by superoxide dismutases (SODs) 1 and 2, and is then rapidly converted into H\(_2\)O\(_2\) with low toxicity (30). A disruption of the homeostasis between ROS and endogenous antioxidant production results in oxidative stress (31), which leads to cellular dysfunction, DNA damage, lipid peroxidation and apoptosis induction (32). In addition, oxidative stress affects the normal function of a wide range intracellular signaling pathways and promotes the pathological development of cardiovascular diseases (33).

During cardiac ischemia, myocardial cells are in a state of hypoxia, where mitochondrial electron transfer chain complexes are significantly reduced and SOD anions are produced (34). During reperfusion, ROS levels are increased significantly due to the reduction in electron leakage and mitochondrial detoxification (34), causing oxidative stress. Free radical explosion and oxidative stress are important mechanisms of myocardial I/R injury. Mitochondrial electron transfer chain complex I is inactivated during myocardial ischemia because of the highly reductive environment with low PO\(_2\) and low ADP (35). After reperfusion, the impaired activity of complex I can also lead to ROS-induced damage to the mitochondrial phospholipids and respiratory chain super complex, potentiating the electron leakage of complex I further. This process promotes a vicious cycle of oxidative stress that ultimately leads to mitochondrial dysfunction (36). Under these conditions, excessive mitochondrial ROS cause oxidative damage to proteins, lipids and DNA, as well as excitation-contraction uncoupling, arrhythmia, cardiac hypertrophy, apoptosis, necrosis and fibrosis (37). However, low levels of ROS attenuate myocardial I/R injury through ischemic preconditioning. Recent evidence has suggested that short-term intermittent hypoxia (IH), similar to ischemic preconditioning, can serve a cardioprotective role (38). A previous study demonstrated that IH increased mitochondrial tolerance to Ca\(^{2+}\) overload and delayed MPTP opening induced by oxidative stress (39). In addition, a previous study has shown that IH may increase the expression of SOD and glutathione peroxidase (40).

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Inflammatory cytokines and apoptotic factors. Long-term ischemia can lead to irreversible cellular necrosis, which triggers the release of a variety of pro-inflammatory mediators, including cytokines and growth factors, leading to inflammatory cell infiltration (41). During late stage I/R, genes associated with inflammation are activated to produce mediators, including IL-1, IL-6, TNF-α, IFN-regulating factor and NF-κB, all of which promote neutrophil adhesion and transmembrane migration, leukocyte infiltration, and cytokine and chemokine release, eventually leading to cell death. I/R can activate the inflammation cascade to cause further tissue damage (42). TNF-α participates in the development of myocardial injury during I/R injury, during which its expression level is increased, promoting adhesion and interaction between leukocytes and endothelial cells (43). This increases the infiltration of granulocytes into the I/R region to mediate myocardial cell damage (43). IL-1 is secreted by activated monocytes and macrophages, and its expression is also significantly increased during I/R. Intercellular adhesion molecule 1 (ICAM-1) participates in the adhesion of leukocytes to vascular endothelial cells and induces cytotoxicity by adhering to cardiomycytes (44). Enhanced ICAM-1 binding can feed back to endothelial cells and macrophages to promote the expression of inflammatory mediators or cytokines (44). During I/R, the release of inflammatory cytokines and chemokines leads to the activation of neutrophils and macrophages, which promotes tissue damage (45). Neutrophil infiltration serves an important role in myocardial I/R injury. This step is initiated by the binding of vascular endothelial adhesion molecules with corresponding ligands on neutrophils to mediate the adhesion of neutrophils to endothelial cells. Mast cells serve an important role in stimulating the inflammatory response by releasing regulators that can trigger the cascade of cytokine release (46). Cyclic inflammatory markers, including C-reactive protein, IL-6 and IL-1, are associated with increased infarct size and poor prognosis. In recent years, pro-inflammatory cells such as monocytes and macrophages have been documented to be a potential cause of MI using a number of cell tracking and molecular imaging techniques (47).

During I/R, different gene families can also serve distinct roles in apoptosis. Apoptosis is a tightly controlled process that is conserved among species and involves the Bcl-2 and caspase families of proteins in addition to oncogenes, such as c-Myc and p53 (48). The activation, upregulation, translocation and integration of precursor Bcl-2 proteins, including Bax, BH3 interacting-domain death agonist, p53 upregulated modulator of apoptosis (PUMA) and Bcl-2 interacting protein 3 (BNIP3), into the mitochondrial membrane within ischemic injury tissues has been previously reported (49,50). In addition, pro-apoptotic and anti-apoptotic Bcl-2 proteins have been found to regulate Ca²⁺ homeostasis, which is an important mechanism of I/R injury (51). The caspase family also serves a key role in I/R-induced cell death. Pan-cysteine aspartate inhibitors, including zVAD-FMK and MX1013, can attenuate apoptosis and cell death induced by I/R (52,53). However, it has been previously reported that caspase inhibition may instead drive the cell towards necrotic death (54). A number of studies have demonstrated that the overexpression of BNIP3 in HL-1 myocardial cells can activate Bax to promote the opening of the MPTP and increase cell death in response to I/R injury (55,56).

Changes in microRNAs (miRNAs/miRs). miRNAs are short, single-stranded non-coding RNAs that are 21-23 nucleotides in length and regulate gene expression by inhibiting translation or promoting the degradation of RNA (57). Mature miRNAs are processed from primary miRNA, which is cleaved by a microprocessor complex that consists of the RNase-III endonuclease Drosha, RNA-binding protein DiGeorge syndrome critical region gene 8 and other cofactors, to produce 70-100 nucleotide hairpin precursor small RNAs. Following export to the cytoplasm by the nuclear export protein exportin-5, they are trimmed by the RNase III ribonuclease dicer to produce a mature miRNA duplex that is ~21 nucleotides in length (58).

Several studies have demonstrated that miRNA function is closely associated with cardiovascular disease, and a number of non-cardiac miRNAs are reported to be biomarkers of myocardial injury and predictors of clinical outcomes after acute MI. miR-633b and miR-1291 have been documented to indicate MI with high specificity and sensitivity (59), whereas miR-150 and miR-486 expression levels could be used to distinguish between patients with and without ST-elevation MI (60). A previous study revealed that heart biopsies from patients with heart failure demonstrated a significant increase in miR-377 expression compared with that in normal control hearts (61). In a mouse cardiac I/R model, human CD34⁺ cells in immune-deficient mice were silenced following the intra-myocardial transplantation of miR-377, which promoted neovascularization and reduced interstitial fibrosis 28 days after I/R induction to improve left ventricular function (61).

MiRNAs serve significant roles in cardiac I/R injury and function by a wide range of different mechanisms. A previous study demonstrated that miR-1 and miR-133 mediated opposite effects when regulating myocyte survival in I/R models, where miR-1 was pro-apoptotic and miR-133 was anti-apoptotic (62). This difference may be due to their respective downstream targets. Increased miR-1 expression resulted in the down-regulation of several anti-apoptotic genes, including heat shock protein (hsp)60, hsp70, insulin-like growth factor-1 and Bcl-2, whereas miR-133 negatively regulated the expression of pro-apoptotic genes, such as caspase-9 and caspase-3 (62-64). Another study revealed that miR-133 overexpression reduced cardiac fibrosis after transverse aortic banding compared with that in normal controls, implicating the cardioprotective effects of miR-133a on I/R-triggered cardiac remodeling (65). miR-21 has been demonstrated to protect cardiomycocytes from I/R injury by targeting several apoptotic genes, including phosphatase and tensin homolog, cell death 4 and Fas ligand (66-68). Furthermore, miR-21 has been reported to inhibit the proliferation, migration and tubulogenesis of endothelial cells, and promote the survival of cardiomycocytes and cardiac fibroblasts after myocardial I/R (69). miR-25 and miR-145 can reduce mitochondrial ROS stress and Ca²⁺ overload by inhibiting the expression of mitochondrial Ca²⁺ uniporter and Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) (70). miR-214 may protect cardiomycocytes from oxidative damage induced by ROS formation initiated by Ca²⁺ overload by inhibiting sodium/Ca²⁺ exchanger 1 (71-73).

From the aforementioned studies, it can be concluded that miRNAs regulate the expression of pro-apoptotic/anti-apoptotic genes to regulate cardiac fibrosis, inflammation, ROS generation and Ca²⁺ homeostasis. A number of studies have
demonstrated that various miRNAs, including miR-21 (67), miR-144/451 (74), miR-192 (75) and miR-199a (76), are associated with ischemic preconditioning. Additionally, some experimental studies have revealed that inhibition of miR-15 and miR-92a in pig models of acute myocardial I/R, especially at the beginning of reperfusion, can reduce the size of the MI (77,78). This suggests that miRNA treatment may be a feasible therapeutic approach (75).

3. Pathways of ERS

ERS is an evolutionarily conserved cell stress response that is associated with numerous diseases, including cardiovascular, Alzheimer's and Parkinson's diseases, and diabetes, renal failure, osteosarcoma and pancreatic ductal adenocarcinoma (79-85). Under physiological conditions, the ER is an important organelle that serves a key role in cellular processes, including protein folding, assembly, modification and secretion, lipid synthesis and Ca\(^{2+}\) storage. However, when the ER is exposed to stress stimuli, such as ROS exposure and Ca\(^{2+}\) overload, homeostasis is impaired, which results in the accumulation of unfolded/misfolded proteins (86). These changes may eventually lead to ER dysfunction, collectively known as ERS (86).

Several ER transmembrane sensors are expressed to detect the accumulation of unfolded proteins, including PERK, ATF6 and IRE1, which activate the signal pathways of eIF2\(\alpha\)-ATF4-DNA-damage-inducible transcript/CHOP, pro-ATF6-cleaved ATF6-CHOP, and IRE1-spliced (Xbp1), respectively (79). This upregulates the expression of ER chaperones and ER-related degradation components (6). The UPR can activate the ER chaperone glucose-regulated protein 78 (GRP78) following isolation by any of the three ER sensors (PERK, ATF6 and IRE1). In the absence of ERS, binding to GRP78 results in the inactivation of these sensors. GRP78 is released from the sensors, where they can interact with misfolded and unfolded proteins when ERS occurs. Ultimately, the UPR is triggered by the transcription of genes encoding proteins involved in this process, leading to a reduction in global protein synthesis (87). The ultimate purpose of the UPR is to restore normal ER function, the failure of which results in apoptosis (88,89). The three main ERS pathways are described in the following sections.

**PERK-eIF2\(\alpha\)-ATF4-CHOP pathway.** A previous study indicated that the PERK signaling pathway serves an essential role in preventing the abnormal accumulation of unfolded proteins in the ER to promote cell survival (90). PERK is a type 1 transmembrane ER protein that has a ligand-independent dimerization domain at the N-terminus, which is concealed by binding immunoglobulin protein (BIP)/GRP78 in the absence of ERS, and a serine/threonine protein kinase domain at the C-terminus without endonuclease activity (91). PERK can block the translation of most proteins, leaving only a specific few, such as ATF4 and CHOP, to be translated (92,93). Translation of ATF4 activates the expression of CHOP by directly interacting with its 5'-untranslated region (92).

Activation of PERK leads to eIF2\(\alpha\) phosphorylation. In addition, it promotes caspase-12 and CHOP overexpression, which can direct ERS towards cell apoptosis (94). CHOP can in turn activate downstream targets during ERS, resulting in apoptotic cell death (95).

**Pro-ATF6-ATF6-CHOP pathway.** One arm of the UPR is the activation of the ER membrane protein ATF6, a fragment of which is translocated into the nucleus to activate the transcription of genes that mediate protein folding (96). ATF6 has two subtypes: ATF6\(\alpha\) and ATF6\(\beta\) (96). The accumulation of misfolded proteins causes ATF6\(\alpha\) to be transported to the Golgi apparatus (97,98). There, it is sheared and the N-terminal fragment, p50-ATF6a, is transferred to the nucleus, where it regulates the transcription of genes associated with protein quality control, translocation, folding and degradation (99). ERS leads to the vesicular exit of ER ATF6, which is subsequently degraded by site-1 and site-2 proteases (SIP and S2P) in the Golgi complex. This cleavage cuts off the cytoplasmic domain of ATF6 from its transmembrane anchorage and intraluminal domain, following which the cytoplasmic ATF6 domain enters the nucleus to transcriptionally upregulate UPR target genes (100).

**IRE1-XBRLP1 pathway.** IRE1 is a type 1 transmembrane glycoprotein that can be divided into two categories: IRE1\(\alpha\) and IRE1\(\beta\). IRE1\(\alpha\) is widely expressed in different tissues, whereas IRE1\(\beta\) is only expressed in intestinal epithelial cells (101). IRE1\(\alpha\) senses the accumulation of unfolded proteins and is activated by dissociation with the ER chaperone GRP78/BIP (102-104). IRE1 then dimerizes and trans-autophosphorylates itself to activate its endonuclease domain under ERS. This endonuclease domain then acts on the Xbp1 gene and performs an unconventional splicing. After 26 nucleotides are removed, a spliced mRNA is produced, which increases the transcription of UPR target genes (105). Activation of the ER splicing factor IRE1\(\alpha\) and the splicing transcription factor Xbp1 can induce the transcription of chaperones, which are necessary for facilitating protein folding (105). A previous study reported that the activation of the PERK-eIF2\(\alpha\) and IRE1\(\alpha\)-Xbp1 signaling pathways inhibited apoptosis and promoted proliferation without affecting ERK and AKT signaling activation (93). The UPR has been associated with a number of diseases, including cardiovascular, Alzheimer's and Parkinson's diseases, and IRE1 has been the focus of several drug discovery projects such as ligands that interact with IRE1\(\alpha\)'s kinase and pre-emptive activation of IRE1\(\alpha\)’s homeostatic mode (79,80,106).

4. I/R as an activator of the UPR

The UPR is associated with numerous pathological processes, including cardiovascular disease, I/R injury, neurodegenerative diseases, diabetes mellitus, viral infection and cancer (107). Some of the earliest studies on the effects of I/R on the UPR were conducted in the brain (81,108). A previous study has demonstrated that several pathways of the UPR are activated in the ischemic rabbit brain such as that of PERK-Xbp1-eIF2\(\alpha\), leading to translation arrest (108). Several studies have demonstrated that Xbp1, genetic markers of GRP78 and the UPR are activated in hypoxic cultured ventricular myocytes or HL-1 atrial myocytes from neonatal rats or adult mice (109-111). Therefore, ischemia and I/R can activate numerous components
of the UPR in cardiomyocytes both in vivo and in vitro (112). In a neuronal study, ERS has been reported to be associated with neuronal cell death following ischemia (113). A study demonstrated that global cerebral I/R induced time-dependent differences in ER gene expression at both mRNA and protein levels, which was affected by pre-ischemic therapy (114).

Cardiomyocyte injury is induced by four pathophysiological events during I/R: Ca\(^{2+}\) overload, ROS accumulation, inflammatory cytokine release and apoptotic factor release. In addition, changes in the miRNA expression profile is another method by which I/R can regulate the UPR, as described in an earlier part of this review. As described in the present review, oxidative stress serves an important role in the I/R process, as ROS can activate apoptosis and ERS at various stages. The FOXO family of transcription factors is involved in a number of biological processes, including the oxidative stress response, cell proliferation, apoptosis and metabolism (115). The most well-studied members of the FOXO family include FOXO1, FOXO3, FOXO4 and FOXO6 (115). A previous study has demonstrated that FOXO4 serves an important role in ROS-induced apoptosis (116). Increased ROS production leads to acute renal ischemia by negatively interfering with the normal function of signaling pathways, inducing inflammatory infiltration and renal cell death (117). A previous study previously revealed that treatment with the bromodomain-containing protein 4 inhibitor, which exerts protective effects against renal I/R injury, suppressed I/R-induced apoptosis and ERS by activating PI3K/AKT signaling and blocking FOXO4-dependent ROS production (118). Blocking ROS using N-acetylcysteine has also been demonstrated to inhibit hypoxia/reoxygenation-induced apoptosis and ERS protein expression. The relationship between ROS and ERS-induced apoptosis has been confirmed, where ROS production can induce apoptotic cell death and ERS (118).

One previous study demonstrated that H\(_2\)S pretreatment and overexpression of miR-133a in the myocardium inhibited cardiomyocyte apoptosis and enhanced cell viability (119). In addition, co-treatment miR-133a overexpression has been revealed to significantly increase cardiomyocyte proliferation, migration and invasion, in turn reversing I/R-induced ERS and cardiomyocyte apoptosis in vitro and in vivo. This suggests that miR-133a protects cardiomyocytes against I/R-induced ERS and subsequent apoptosis (119). A long non-coding RNA named urothelial carcinoma-associated 1 (UCAI), is only expressed in the heart (120). It has previously been reported that cardiac I/R triggers the expression of UCA1, and the production of ROS in cells and mitochondria to mediate apoptosis by oxidative stress and ERS. Overexpression of UCA1 can also protect H9C2 cells from ERS and cell apoptosis induced by I/R (121). After co-treatment with TUDCA, a drug for clinical use that can protect cardiomyocytes from oxidative stress-induced injury (122), H9C2 cell injury induced by the effect of UCA1 siRNA was reversed (121). To summarize the activation function of I/R to UPR, as described hereafter, a general scheme is presented in Fig. 1A.

5. UPR in turn mediates I/R damage

The ER serves a pivotal role in cardiomyocytes, as the correct synthesis and folding of proteins in the ER is indispensable for the normal functioning of the heart (123). However, although ERS and the UPR have been extensively studied in non-muscle ER, there remains an insufficient number of studies on ERS and the UPR in the cardiovascular field (124).

If the UPR signal activation during the early stages of ERS is not sufficient in resolving stress, the persistent activation of proximal effectors (PRR, ATF6 and IRE1) will result in the appearance of a distinct UPR-induced protein setup, where other signaling pathways are activated, all of which combine to promote cell death (125,126). Notably, a previous study indicated that pre-activation of ATF6 in the hearts of transgenic mice conferred protective effects against I/R injury (127). In addition, a study indicated that the upregulation of GRP78 during ischemic preconditioning protected cultured cardiomyocytes from further ischemic damage (128). These studies suggested that when the UPR is activated in the heart during ischemia or I/R, it may exert protective effects against the stress response in myocardial cells. By contrast, several studies have demonstrated that UPR may lead to I/R injury of the heart. A previous study demonstrated that overexpression of the ERS response protein PUMA potentiated apoptosis in cultured cardiomyocytes via the UPR (129). Another study revealed that UPR activation promoted the activation of caspase-3, JNK and p53, which contributed to cardiomyocyte apoptosis (130). Additionally, in cultured cardiac myocytes, UPR mediated protective effects against ischemia activation in the early stages of ischemia, whereas the same response resulted in predominantly apoptotic characteristics in the latter stages (131). The distinct functions of the UPR may be dependent on the degree of ATF6, PERK and IRE-1 activation, and the nature of the ERS. ATF6 may mediate the activation of mostly protective proteins, whilst PERK may induce the activation of apoptotic genes (127). Therefore, brief ischemic stress may lead to changes in the proteome under the regulation of the UPR to promote protective effects, whereas prolonged ischemia may lead to changes in the proteome leading to cellular damage.

It has previously been reported that pathological ERS is relevant in a variety of physiological outcomes, including impaired Ca\(^{2+}\) homeostasis, increased apoptotic signaling, disrupted protein secretion and increased apoptotic signaling (132-134).

During ERS, CHOP has been demonstrated to induce the expression of ER oxidase 1, which activates inositol triphosphate receptor-mediated Ca\(^{2+}\) release into the cytosol and activates CaMKII to induce apoptosis (135-137). It has been revealed that Xbp1 and ATF6 may mediate the overexpression of GRP94, which could attenuate myocardial cell necrosis induced by Ca\(^{2+}\) overload or ischemia (138).

Ca\(^{2+}\) overload serves an important role in ERS-induced I/R injury. The Ca\(^{2+}\) dependence of cell death can be enhanced by a reduction in ATP. ATP concentration is decreased during ERS, which reduces the levels of intracellular Ca\(^{2+}\) stored in the ER (129). It has previously been reported that inhibiting calpain can improve ischemic myocardial injury and myocardial function in an experimental model of myocardial I/R (139-141).

The UPR can regulate a number of mitochondrial functions, including bioenergetics, membrane potential and the degree of cytochrome c release (142). The UPR can also
serve a role in immune function. A previous study revealed that cathepsin-induced ERS enhanced the recruitment of IFN regulatory factor-3 and cAMP response element binding protein (CREB/CBP)/p300 to the murine IFNB1 promoter during lipopolysaccharide stimulation. ERS-related inflammation occurred through Xbp1 binding to a potential enhancer element 6 kb distal to the IFNB1 gene, which may enhance the recruitment of CBP/p300 and IFN regulatory transcription factor to the IFNB1 enhanceosome (143). This observation indicated a novel role of UPR-dependent transcription in the regulation of inflammatory cytokines, which may be of significance to the pathogenesis of diseases involving ERS and type I IFN. One potential avenue of study may be the relationship among viral infection, I/R injury and inflammatory diseases (143). ERS can activate nucleotide binding oligomerization domain-like receptor protein 1 (NLRP1) inflammatory bodies by activating the NF-κB signaling pathway, which may then promote myocardial I/R injury (144). NLRPs are classified as typical inflammasomes that include NLRP1 and NLRP3 inflammatory bodies. They can activate caspase-1, resulting in the maturation and secretion of pro-inflammatory cytokines IL-1β and IL-18 (145). How the UPR in turn mediates I/R damage is summarized in Fig. 1B.

There are several important proteins that are activated by ERS, including ATF6, Xbp1, ATF4, CHOP and IRE1. ATF6 normally functions in the adaptive UPR to accelerate the remodeling of cellular physiology and recovery following acute physiological and pathological injury (146). ATF6 can dimerize with UPR-regulated basic leucine zipper transcription factors, such as Xbp1, by S1P/S2P-dependent proteolysis, or associate with other stress-responsive signaling pathways such as mTOR signaling (147,148). In addition, ATF6 has been reported to induce the expression of the Ca\textsuperscript{2+} pump SERCA2a and the expression of several antioxidant genes (149,150).

Xbp1 has been revealed to exert protective effects against I/R injury in the heart and the brain (133,151-153), as overexpression of Xbp1 can inhibit cell death induced by oxygen glucose deprivation/reoxygenation (OGD/R). These findings suggested that inhibiting Xbp1 activation may accelerate neuronal death after I/R, which can be exploited as a therapeutic strategy for brain I/R injury (154). Accumulating evidence has demonstrated that ERS serves a key role in I/R-induced cell dysfunction (155), where destruction of the ER pathway can result in neuronal cell death. ERS is associated with the pathology of brain I/R injury. OGD/R stress temporarily inactivates Xbp1 splicing, resulting in accelerated neuronal death due to ER dysfunction. Subsequent Xbp1 reactivation may be neuroprotective against OGD/R stress (154).

ATF4 induces the expression of CHOP under mild ERS. However, under chronic ERS, PERK then significantly increases
CHOP expression, in turn suppressing the expression of Bel-2 to increase cell death (156). In addition, PERK phosphorylates Kelch-like Ech-related protein 1, which releases Nrf2 from inhibition and translocates into the nucleus to activate the expression of antioxidant and detoxifying enzymes (157). CHOP has also been reported to upregulate the expression of PUMA and the pro-apoptotic protein Bim, thereby inducing mitochondrial-dependent apoptosis (158,159). IRE1 is associated with autophagy activation, which is an important pro-survival defense mechanism against cardiac pathology, including hypertrophy and I/R (160).

6. Conclusion and future perspectives

In the present article, numerous possible causes of myocardial I/R injury, including Ca\(^{2+}\) overload, ROS accumulation, increase in expression of inflammatory cytokines and apoptotic factors, miRNA change and ERS were described. These factors not only lead to secondary cardiac injury but can also hinder the reconstruction of blood vessels after clinical treatment (161). Cardiac I/R injury induces changes of ERS in a process that is mainly mediated by three pathways involved in the accumulation of unfolded proteins, which causes cell damage. At the beginning of the response, a cellular protective response ensues, which then becomes apoptotic in the latter stages. However, to understand the specific mechanism underlying these processes, further study is required. Appropriate intervention in the ERS process may serve as a potential therapeutic strategy for heart I/R injury, including intervention in the expression of ligands and their receptors in the ERS pathways. With further study of cardiac ERS and I/R injury, strengthening the understanding of the mechanism underlying I/R injury will facilitate the optimization of treatment regimens. If the occurrence and development of myocardial cell apoptosis can be prevented, it may become possible to alleviate I/R injury, which will facilitate the development of treatment strategies and drug discovery for myocardial I/R.

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Authors’ contributions

YR and LL conceived and designed the review. YR, JZ and QJ collected the related literature. MC, KJ and ZW analyzed the related papers. YR wrote the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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