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Review

Role of mitochondrial-associated endoplasmic reticulum membrane in myocardial ischemia-reperfusion injury

Yiping Han[1,2], Lin Zhao[3], Pengshuo Lou[1,2], Chen Wang[1,2], Mingxin Yuan[1,2] and Yingli Yu[1,2,4,*]

[1] Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China
[2] Center of Drug Safety Evaluation, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China
[3] Hebei Provincial Hospital of Traditional Chinese Medicine, Shijiazhuang 050000, China
[4] State Key Laboratory of Component-based Chinese Medicine, Tianjin 301617, China

* **Correspondence:** Email: yuguyu88@sina.com; Tel: +862259596163; Fax: +862227386453.

Abstract: The endoplasmic reticulum (ER) and mitochondria (MT) are two essential organelles within cells. Endoplasmic reticulum stress (ERS) and mitochondrial damage are key drivers of cell death in myocardial ischemia-reperfusion injury (MIRI), and their interplay also exerts important regulatory effects on the progression of cardiomyocyte injury. As a structural hub for physical coupling between the ER and mitochondria, mitochondria-associated endoplasmic reticulum membranes (MAMs) play a pivotal role in the pathogenesis and progression of MIRI. Disruption of MAMs' architecture in cardiomyocytes can directly or indirectly trigger multiple pathological processes, including redox imbalance, ER stress, mitochondrial damage, energy depletion, and programmed cell death. This review first elaborates on the structural changes and functional consequences of the ER and mitochondria in MIRI, summarizes the structural features of MAMs and the regulatory functions and specific mechanisms of their enriched proteins in modulating calcium homeostasis, oxidative stress, and mitochondrial damage under MIRI pathology, and finally lists several bioactive components derived from traditional Chinese medicine that ameliorate MIRI by targeting MAMs-associated proteins.

Keywords: MAMs; calcium ion balance; mitochondrial damage; oxidative stress; myocardial ischemia-reperfusion

1. Introduction

In recent years, inter-organelle communication has emerged as a research hotspot in life sciences: organelles do not function in isolation but form a precisely regulated network through dynamic interactions to adapt to cellular demands. As the fundamental structural units of organisms, cells contain two core organelles, the endoplasmic reticulum (ER) and mitochondria (MT). The physical connection and functional coupling between these two organelles are extensively involved in multiple cellular pathways and play indispensable regulatory roles. Accumulating evidence has confirmed that homeostasis imbalance in ER–mitochondria interactions is commonly present in various pathological states, including cardiovascular diseases, diabetes mellitus, obesity, cancer, and neurodegenerative disorders. In this review, we focus on the pathological process of myocardial ischemia-reperfusion injury (MIRI), systematically delineate dynamic changes in ER–mitochondria interactions, and elucidate the core molecular mechanisms by which these interactions mediate the onset and progression of MIRI.

1.1. Overview of MIRI

MIRI is a characteristic pathological condition in which, following an episode of ischemic injury, the restoration of blood flow fails to reverse the ischemia-induced tissue damage and instead further exacerbates myocardial structural destruction and cardiac dysfunction. This injury is widely observed in various cardiovascular clinical interventions, including reperfusion therapy for acute myocardial infarction, coronary artery bypass grafting, and heart transplantation, and represents a common secondary complication in cardiac surgery and emergency management of myocardial infarction [1]. MIRI can induce cardiomyocyte apoptosis and necrosis, enlarge the myocardial infarct size, and subsequently lead to severe complications such as malignant arrhythmias and reduced myocardial contractility, thereby significantly increasing the risk of poor prognosis in cardiovascular diseases.

The core pathological mechanisms of MIRI primarily involve three major aspects. First, following ischemia-reperfusion injury, reactive oxygen species (ROS) are generated in large quantities and accumulate aberrantly, continuously damaging the integrity of the mitochondrial membrane, functional proteins, and nucleic acids in cardiomyocytes, thereby inducing irreversible cellular oxidative injury. Second, disruption of intracellular calcium homeostasis leads to calcium overload, which in turn triggers the aberrant opening of the mitochondrial permeability transition pore (mPTP) and activates the mitochondria-mediated endogenous apoptotic pathway. Third, excessive activation of the inflammatory response results in substantial infiltration of pro-inflammatory cytokines into myocardial tissue, producing a cascade effect that further exacerbates pathological damage. Currently, no effective intervention specifically targeting MIRI is available in clinical practice, making it difficult to block the pathological process at its root. Of note, these three core pathological hallmarks—oxidative stress, calcium overload, and excessive inflammatory activation—are all highly dependent on the functional coupling between the ER and mitochondria, suggesting that elucidating the molecular regulatory network underlying their dynamic interactions may open new avenues for MIRI prevention and treatment.

1.2. Mitochondria-associated endoplasmic reticulum membranes (MAMs) and their role in MIRI

The physical contact region between the ER and mitochondria is defined as the mitochondria-associated endoplasmic reticulum membranes (MAMs), or the ER–mitochondrial microdomains, which serve as a critical structure mediating information exchange between the two organelles [2]. MAMs precisely regulate, at both temporal and spatial levels, the structural remodeling and functional coordination of the ER and mitochondria, and are extensively involved in various biological processes, including lipid metabolism, oxidative stress, mitochondrial damage, calcium (Ca^{2+}) signaling, inflammatory responses, autophagy, and apoptosis [3].

Under MIRI pathological conditions, MAMs lie precisely at the converging core of the three major injury pathways: oxidative stress, calcium overload, and excessive inflammatory activation [4]. First, MAMs represent the central platform for calcium transfer from the ER to mitochondria, and their structural integrity is directly associated with the severity of calcium overload in cardiomyocytes during the reperfusion phase. Second, MAMs are enriched in multiple ROS-generating enzymes, which can locally amplify oxidative stress levels and reduce the mitochondrial membrane potential. Third, various proteins located at MAMs mediate the transmission of inflammatory signals and the initiation of apoptotic programs. Accordingly, it is conceivable that the structural integrity and functional homeostasis of MAMs may be critical determinants of cardiomyocyte fate following ischemia-reperfusion insult [5].

Based on the above background, this review systematically summarizes the molecular mechanisms and research advances regarding the involvement of MAMs in regulating MIRI, with a focus on three dimensions: ROS signaling regulation, calcium signaling transduction, and inflammatory cytokine signal transport. The aim is to provide novel molecular targets and theoretical support for the clinical prevention and treatment of myocardial ischemia-reperfusion injury and for improving long-term prognosis.

2. Dysfunction and synergistic mechanisms of the endoplasmic reticulum and mitochondria in MIRI

2.1. Endoplasmic reticulum

The endoplasmic reticulum (ER) is one of the core organelles in cardiomyocytes that regulates calcium signaling homeostasis, material synthesis, and stress responses [6]. Its dysfunction serves as a key initiating factor in the development and progression of MIRI. The ER is the primary site for the synthesis and processing of proteins, lipids, and steroids, and is responsible for the folding, modification, and transport of secretory and transmembrane proteins in cardiomyocytes, thereby maintaining normal cellular structure and physiological metabolic functions [7]. Additionally, as the main intracellular calcium reservoir, the ER membrane specifically expresses two types of critical calcium channels: the inositol 1,4,5-triphosphate receptor (IP3R) and the ryanodine receptor (RyR), which precisely regulate intracellular calcium signaling [8]. Under physiological conditions, the ER releases Ca^{2+} into the cytoplasm through these channels in a controlled manner according to cellular demands, and directs calcium transport to mitochondria via the mitochondria-associated endoplasmic reticulum membranes (MAMs), thereby moderately activating mitochondrial metabolic enzyme activity, maintaining myocardial energy metabolic balance, and ensuring normal cardiac systolic and

diastolic function [9].

During the pathological process of MIRI, injurious stimuli such as ischemia, hypoxia, redox imbalance, and energy depletion disrupt ER homeostasis, leading to the abnormal accumulation of large amounts of unfolded and misfolded proteins in the ER lumen, which in turn induces severe endoplasmic reticulum stress (ERS) [10]. Concurrently, this abnormal protein accumulation activates an adaptive response of the ER to alleviate ERS, a process termed the unfolded protein response (UPR) [11]. In this process, the accumulated misfolded proteins competitively bind to GRP78 and become activated [12]. This subsequently initiates the three classical UPR signaling pathways, namely the PERK, IRE1α, and ATF6 pathways, thereby transiently alleviating protein folding disorders, restoring ER function, and exerting cardioprotective effects.

However, under sustained severe damage stimulation in MIRI, the adaptive repair mechanisms of the UPR are insufficient to reverse ER dysfunction, and the protective stress response gradually transitions into a detrimental effect, mediating cardiomyocyte apoptosis and exacerbating myocardial injury [13,14]. On the one hand, persistently activated ERS triggers the endogenous apoptotic program in cardiomyocytes via the CHOP/TRAF2 signaling pathway. On the other hand, MIRI-induced ER dysfunction leads to dysregulation of IP3R and RyR channels, causing uncontrolled ER calcium release and exacerbating cardiomyocyte calcium overload. Excess calcium ions continuously enter the mitochondria via MAMs, further inducing abnormal opening of the mPTP, massive ROS burst, and energy metabolism collapse, thereby establishing a vicious cycle of ER dysfunction–calcium homeostasis imbalance–mitochondrial damage [15,16]. This ultimately aggravates cardiomyocyte necrosis and apoptosis, expands the area of myocardial injury, and promotes the pathological progression of MIRI. Current evidence has confirmed that excessive activation of ERS is one of the core pathological links in cardiovascular diseases, especially MIRI. Targeting ER homeostasis and inhibiting pathological ERS activation represent an important potential direction for ameliorating MIRI.

2.2. Mitochondria

As a high-energy-demanding organ, the heart relies heavily on mitochondrial metabolism for its physiological functions. In cardiomyocytes, mitochondria occupy approximately 30% of the total cell volume and continuously generate energy through oxidative phosphorylation, primarily using fatty acids as substrates, producing approximately 6–7 kg of ATP per day to support cardiac rhythmic contraction and relaxation.

Mitochondria are dynamic organelles that maintain their network homeostasis through continuous fusion and fission, which serves as an essential foundation for normal cardiomyocyte activities. Under physiological conditions, the dynamic balance between mitochondrial fusion and fission participates in regulating multiple key biological processes, including cell division, apoptosis, autophagy, and aging, while also ensuring core functions such as ATP synthesis, intracellular Ca^{2+} buffering, free radical scavenging, and stable transmission of mitochondrial genetic information, thereby preserving the metabolic and functional homeostasis of cardiomyocytes [17,18]. However, during the pathology of MIRI, the severe oxidative stress secondary to myocardial ischemia, hypoxia, and reperfusion primarily impairs mitochondrial function in two aspects: on the one hand, it induces uncoupling of oxidative phosphorylation, leading to a sharp decline in ATP synthesis and suppression of fatty acid oxidation efficiency, resulting in myocardial energy failure; on the other hand, it disrupts the dynamic

balance of mitochondrial fusion and fission, inducing excessive mitochondrial fragmentation and causing structural damage and functional inactivation. This imbalance in dynamic homeostasis can further trigger aberrant activation of autophagy and apoptotic programs in cardiomyocytes [19], while simultaneously inhibiting protective functions such as calcium buffering and free radical scavenging, thereby exacerbating oxidative stress injury and ultimately forming a vicious cycle of persistent myocardial damage.

Structurally, mitochondria consist of a double-membrane architecture comprising the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM). Their matrix is rich in various key metabolic enzymes and serves not only as the primary site for the tricarboxylic acid (TCA) cycle and fatty acid β-oxidation but also undertakes important functions in maintaining intracellular ROS homeostasis and storing calcium ions. The integrity of the membrane structure is a prerequisite for mitochondria to perform energy metabolism, redox regulation, and calcium signal transduction. Under the pathological condition of MIRI, calcium overload and ROS burst in cardiomyocytes synergistically damage the mitochondrial membrane structure, compromise the integrity of the double membrane, and inhibit the activity of key metabolic enzymes in the matrix, thereby impeding the TCA cycle and fatty acid β-oxidation, leading to the collapse of the myocardial energy metabolic pathway and making it difficult to meet the high energy demands of the heart.

From the perspective of functional regulation, apoptosis is mainly divided into the extrinsic death receptor pathway and the intrinsic mitochondrial pathway, with the mitochondria-mediated intrinsic apoptotic pathway representing the core route of cardiomyocyte death during MIRI. Upon MIRI insult, abnormal oxidative stress and calcium dyshomeostasis overactivate the mitochondrial apoptotic pathway, manifested as a severe reduction in mitochondrial membrane potential and massive release of cytochrome c (Cyt c) from mitochondria, ultimately triggering programmed cell death of cardiomyocytes. In addition to its involvement in apoptosis regulation, mitochondria are extensively involved in cardiomyocyte necrosis, maintenance of redox homeostasis, and energy metabolism. Mitochondrial dysfunction induced by MIRI not only triggers necroptosis of cardiomyocytes but also further exacerbates redox imbalance, thereby aggravating secondary injury to myocardial tissue.

Healthy mitochondria are characterized by efficient oxidative phosphorylation, low basal ROS production, and stable calcium regulatory capacity, which synergistically support normal cardiomyocyte function. On the one hand, under physiological conditions, mitochondria efficiently synthesize ATP while precisely scavenging ROS generated from metabolism, avoiding the accumulation of oxidative damage. In contrast, the ROS burst during the reperfusion phase attacks mitochondrial DNA, membrane lipids, and respiratory chain complexes, causing persistent structural and functional damage to mitochondria and further promoting massive ROS release, thereby forming a vicious cycle of oxidative damage–mitochondrial destruction–ROS accumulation that ultimately mediates cardiomyocyte death. On the other hand, mitochondria serve as important calcium buffers in cardiomyocytes, and maintenance of calcium homeostasis is a prerequisite for normal mitochondrial function. Intracellular calcium overload induced by MIRI leads to excessive mitochondrial calcium uptake, triggering persistent abnormal opening of the mPTP and accelerating cardiomyocyte injury and apoptosis.

Under physiological conditions, moderate accumulation of mitochondrial calcium ions activates key dehydrogenases in the TCA cycle, positively regulating oxidative phosphorylation efficiency. Among these, pyruvate dehydrogenase (PDH) is a key enzyme linking glycolysis and glucose oxidation, and its activity directly determines myocardial energy metabolic efficiency. Phosphorylation

of PDH inhibits its activity, whereas calcium ions promote PDH dephosphorylation by activating pyruvate dehydrogenase phosphatase, thereby enhancing glucose oxidation efficiency and increasing ATP production to maintain myocardial energy supply. However, under pathological calcium overload conditions mediated by MIRI, excessive mitochondrial calcium accumulation conversely suppresses PDH activity, blocks energy metabolism, reduces ATP synthesis, and ultimately induces energy failure and death of cardiomyocytes. Furthermore, severe mitochondrial dysfunction causes substantial leakage of Cyt c from mitochondria into the cytoplasm, sequentially activating caspase-9 and caspase-3 and initiating mitochondria-dependent apoptosis. This classical apoptotic pathway is significantly activated in MIRI-injured myocardial tissue and represents an important molecular mechanism responsible for extensive cardiomyocyte death, expansion of infarct size, and poor prognosis. Therefore, targeting the restoration of mitochondrial calcium homeostasis and energy metabolism may represent a promising strategy for ameliorating MIRI.

3. Structure of mitochondria-associated endoplasmic reticulum membranes

Mitochondria-associated endoplasmic reticulum membranes (MAMs) are critical functional microdomains connecting the ER and mitochondria [20]. They are dynamically assembled from ER-specific subdomains, the OMM, and various adaptor proteins, and serve as the core structural platform mediating physical coupling and signal crosstalk between the two organelles. MAMs precisely regulate membrane spacing, contact area, and the assembly status of anchoring proteins, thereby enabling real-time adaptation to physiological and pathological changes in cardiomyocytes. Their structural integrity significantly influences the pathological progression of MIRI [21].

Morphologically, in normal cardiomyocytes, the ER and mitochondria exhibit a highly organized spatial arrangement, with not only a subset of the OMM establishing functional contacts with the ER. The intermembrane distance between the two organelles is strictly maintained within the range of 10–60 nm, providing an optimal microenvironment for calcium ion transfer, lipid exchange, and signal transmission. Electron tomography has revealed that the connecting structures between the smooth ER and the OMM have an average length of 9−16 nm, whereas the approximately 20-nm gap between the OMM and the rough ER is precisely sufficient to accommodate ribosomes. Under MIRI pathological stress, ischemia, hypoxia, and oxidative stress disrupt the spatial conformation of MAMs, leading to aberrant widening of the ER–mitochondria membrane distance and a marked reduction in effective contact area, thereby severing the functional communication between the two organelles [22].

Stable anchoring between the ER and mitochondria depends on protein tethering complexes localized at MAMs, among which IP3R and mitofusin (Mfn) are the most core-anchoring proteins in cardiomyocytes [23]. Mfn maintains the structural stability of MAMs through mechanical coupling, whereas IP3R, functioning as an ER calcium release channel, exploits the spatial proximity conferred by MAMs to mediate the directed transport of calcium ions to mitochondria. During MIRI, oxidative stress and calcium overload induce Mfn degradation and IP3R dysfunction, thereby disrupting the MAMs anchoring architecture. This disruption, on the one hand, leads to ER–mitochondria uncoupling and abrogates protective signal transduction [24]; on the other hand, it triggers uncontrolled ER calcium release [25,26], allowing a large influx of calcium ions into mitochondria, which exacerbates calcium overload, promotes mPTP opening, and potentiates ROS burst, sequentially amplifying cardiomyocyte injury and driving the pathological deterioration of MIRI. Therefore, structural disorganization and functional instability of MAMs represent a critical nexus in the dysregulation of

ER–mitochondria crosstalk during the pathological process of MIRI, and in-depth elucidation of their regulatory mechanisms holds significant implications for understanding the pathogenesis of MIRI [27].

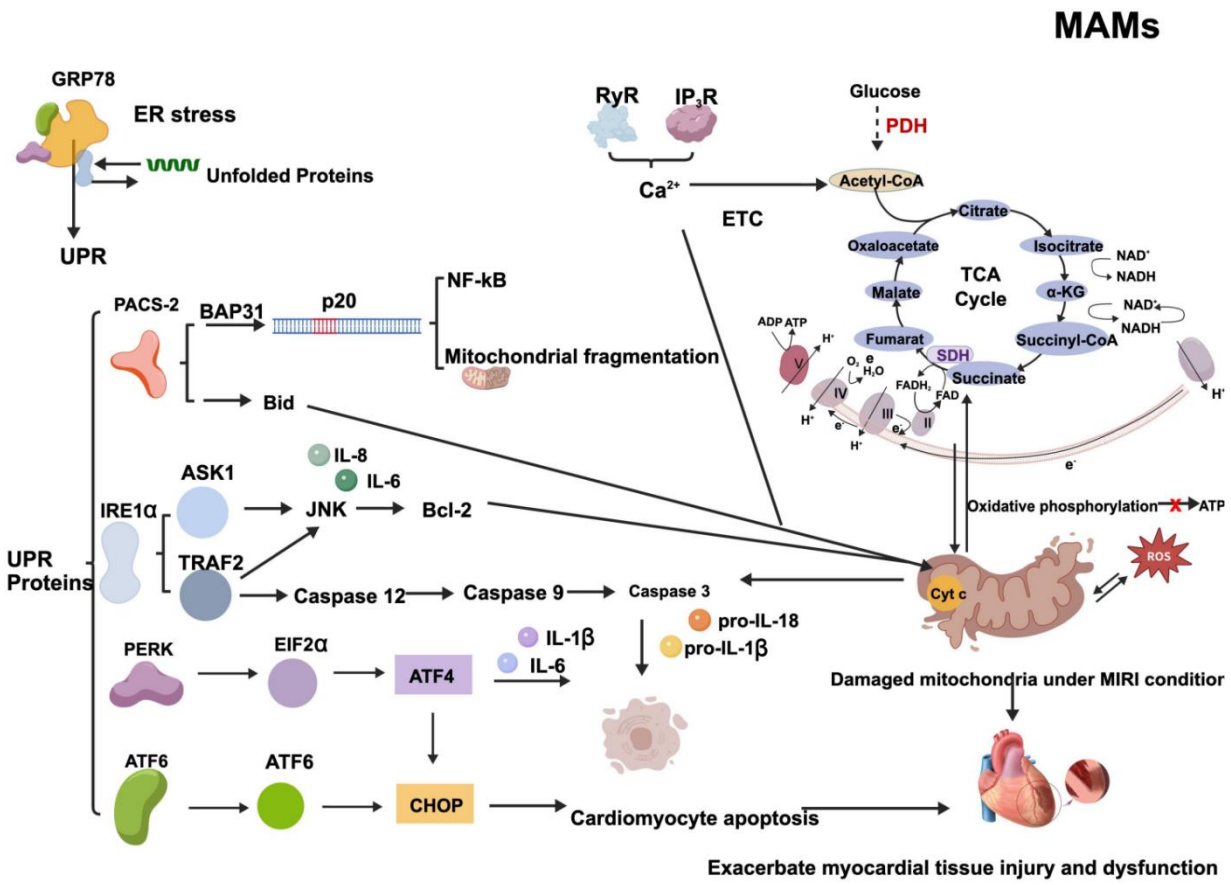

Figure 1. MAM-mediated injury pathways during MIRI: Under physiological conditions, MAMs mediate ER-to-mitochondria Ca^{2+} transfer, sustaining ER protein folding, the TCA cycle, and OXPHOS, with low ROS and suppressed apoptosis. During MIRI, ER misfolded proteins accumulate, activating PERK/IRE1α/ATF6-mediated UPR. IP_3R or RyR dysfunction triggers Ca^{2+} efflux, which causes mitochondrial Ca^{2+} overload via MAMs, inhibiting PDH and metabolism. Concurrently, mPTP opening, ROS burst, and Cyt c release activate the caspase cascade, including apoptosis, and establish an ERS–Ca^{2+} overload–mitochondrial damage vicious cycle. Moreover, MIRI is characterized by overactivation of the inflammatory response, during which MAMs-resident proteins mediate the inflammatory cascade via multiple pro-inflammatory pathways, driving the release of abundant cytokines, and the imbalance of their functional homeostasis further aggravates tissue damage and apoptosis.

4. Regulatory roles of MAM-enriched proteins in MIRI

MAMs serve as the core coupling platform between the endoplasmic reticulum and mitochondria for material exchange and signal crosstalk. Their protein components exhibit high dynamic diversity,

enabling the recruitment of various signaling molecules depending on the physiological or pathological state of the cell. In cardiomyocytes, the contact sites between the sarcoplasmic reticulum (SR) and mitochondria similarly harbor abundant conserved functional proteins. These proteins, on the one hand, maintain the structural stability of the physical tethering between the two organelles; on the other hand, they are extensively involved in multiple core biological processes, including intracellular calcium transport, maintenance of redox homeostasis, regulation of inflammatory responses, and remodeling of mitochondrial dynamics.

To date, four core anchor protein complexes have been unequivocally identified on MAMs, namely the mitofusins MFN1/2, the VAPB-PTPIP51 complex [28], the IP_3R-GRP75-VDAC1-Sig1R complex [29,30], and the Fis1-BAP31-PACS-2 complex. Based on their biological functions, MAM-resident proteins can be classified into six major categories: calcium signal–regulating proteins, chaperones, ER stress sensor proteins, mitochondrial dynamics–regulating proteins, apoptosis-related proteins, and multifunctional sorting proteins. These proteins collectively participate in the entire pathological process of MIRI and constitute the key molecular basis that mediates the disruption of ER–mitochondria crosstalk and amplifies myocardial damage.

The pathological mechanisms underlying MIRI are complex, and the core pathological alterations encompass massive accumulation of ROS, intracellular calcium overload, mitochondrial dysfunction, energy metabolism disturbance, excessive inflammatory response, and cardiomyocyte apoptosis and necrosis. During the ischemic and hypoxic phase, myocardial ischemia already induces substantial generation of oxygen-free radicals, which concomitantly disrupt endoplasmic reticulum calcium homeostasis and promote massive calcium release into the cytosol, thereby triggering calcium overload. Under the synergistic drive of the inflammatory cascade, calcium overload further induces irreversible structural and functional damage to mitochondria. Calcium homeostasis imbalance and mitochondrial injury are mutually causative, forming a vicious cycle that ultimately leads to extensive cardiomyocyte death. Current evidence confirms that endoplasmic reticulum stress and mitochondrial damage are the upstream key initiating events of MIRI; these two processes are structurally and functionally coupled via MAMs, jointly driving the persistent progression of injury.

Traditional Chinese medicine (TCM) and its bioactive components possess advantages such as multi-target actions and low toxicity, having been widely applied in the clinical prevention and treatment of cardiovascular diseases, including coronary heart disease and angina pectoris [31]. Extensive in vivo and in vitro studies have confirmed that various TCM saponins exert significant protective effects against MIRI, with mechanisms involving the regulation of energy metabolism, calcium homeostasis, oxidative stress, and inflammatory responses. For instance, ginsenosides ameliorate myocardial energy metabolism by modulating the TCA cycle, while concurrently suppressing inflammation and oxidative damage, thereby alleviating MIRI. Similarly, notoginsenosides regulate autophagy and apoptosis through the hypoxia-inducible factor-1α/BNIP3 (HIF-1α/BNIP3) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathways, exerting protective effects against MIRI.

This chapter will systematically elucidate the molecular regulatory network through which MAMs and their key resident proteins mediate MIRI, focusing on four core dimensions of injury: intracellular calcium homeostasis, oxidative stress, excessive activation of the inflammatory response, and mitochondrial dynamics. In addition, it will summarize the cardioprotective mechanisms of selected representative bioactive components derived from TCM that target MAMs.

4.1. Role of MAMs-mediated calcium signaling in MIRI

Calcium ions are one of the most common and highly regulated second messengers, playing a fundamental role in diverse life processes, including cell proliferation, differentiation, secretion, metabolism, cell death and survival, migration, and gene expression. The endoplasmic reticulum/sarcoplasmic reticulum (ER/SR) serves as the main intracellular Ca^{2+} store, from which Ca^{2+} is released into the cytosol via RyR and IP_3R, and is subsequently sequestered back into the ER/SR by sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA). Upon mitochondria uptake, Ca^{2+} activates dehydrogenases in the TCA cycle, thereby promoting oxidative phosphorylation and ATP synthesis; among these, PDH serves as a key enzyme linking glycolysis and glucose oxidation, and its activity is regulated by Ca^{2+}-mediated dephosphorylation [32]. The ATP generated by mitochondria in turn provides energy support for ER calcium transport, forming a tight energy-calcium homeostasis coupling between the two organelles. However, under MIRI conditions, dysregulated calcium transfer between the ER and mitochondria leads to cytosolic and mitochondrial Ca^{2+} overload, which triggers aberrant opening of the mPTP and initiates the mitochondria-dependent apoptotic pathway.

The IP_3R-GRP75-VDAC1-mitochondria calcium uniporter (MCU) axis is the core molecular complex at MAMs that mediates ER-to-mitochondria calcium transfer. In this complex, IP_3R is a calcium release channel localized on the ER membrane, VDAC1 is a channel protein in the OMM, and GRP75 serves as an adaptor molecule stabilizing the structural integrity of the IP_3R-GRP75-VDAC1 ternary complex [33]. This complex acts in concert with MCU on the IMM to mediate the directed transfer of Ca^{2+} from the ER into the mitochondrial matrix [34]. Dysfunction of this axis is a major contributor to mitochondrial calcium overload, which in turn triggers cardiomyocyte apoptosis. Studies have shown that H_2O_2-induced oxidative stress activates cAMP response element-binding protein (CREB), leading to upregulated transcription and expression of IP_3R and VDAC1, and consequently inducing cardiomyocyte calcium overload. Melatonin, however, inhibits CREB activity via the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway [35], thereby blocking the aberrant upregulation of the IP_3R/VDAC1 complex, alleviating calcium overload, and preserving mitochondrial structural integrity. Furthermore, the Qiliqiangxin capsule significantly downregulates the gene expression of the IP_3R-GRP75-VDAC1 complex at MAMs, suppresses abnormal calcium transfer following myocardial infarction [36], and reduces cardiomyocyte apoptosis. Sulforaphane restores the disrupted interaction between VDAC1 and IP_3R, attenuates mitochondrial calcium overload, and inhibits MCU activity [37]. Glycine reverses the abnormal distribution of IP_3R and VDAC1 induced by toxic stimuli, restores ER calcium stores, reduces cytosolic and mitochondrial calcium levels, and stabilizes mitochondrial membrane potential [38].

Bcl-2 family proteins are also important calcium-regulatory molecules enriched at MAMs [39,40]. Among them, the anti-apoptotic members Bcl-2 and Bcl-XL can directly bind to IP_3R via their BH_4 domains, thereby inhibiting IP_3R-mediated excessive Ca^{2+} release and preventing mitochondrial Ca^{2+} overload and mPTP opening. Mitochondrial respiratory chain damage resulting from myocardial ischemia leads to downregulation of Bcl-2 expression, rendering cardiomyocytes more vulnerable to oxidative stress injury during the reperfusion phase. Conversely, Bcl-2 overexpression improves myocardial energy metabolism [41], attenuates cytosolic acidification, and reduces infarct size following MIRI. In addition, sulforaphane upregulates Bcl-2 expression in cardiomyocytes, optimizes the Bcl-2/Bax ratio, and consequently inhibits endoplasmic reticulum stress-related apoptosis [42].

Cyclophilin D (Cyp D), a core component of the mPTP, specifically interacts with the IP3R-

GRP75-VDAC1 complex at MAMs, thereby enhancing Ca^{2+} transfer from the endoplasmic reticulum to mitochondria. In the hypoxia-reoxygenation injury model, the interaction intensity between Cyp D and IP3R is positively correlated with mitochondrial Ca^{2+} content. Treatment with the Cyp D-specific inhibitor NIM811 or the IP3R inhibitor 2-APB, as well as knockdown of GRP75 (another component of the complex), can disrupt the assembly of the IP_3R-GRP75-VDAC1 complex, attenuate mitochondrial Ca^{2+} overload, and consequently protect cardiomyocytes against hypoxia-reoxygenation injury. With regard to bioactive components of TCM, elatoside C and astragaloside IV have been shown to attenuate MIRI in rats by inhibiting aberrant mPTP opening and blocking calcium overload [43].

In addition, multiple MAM-resident proteins are also involved in the regulation of calcium homeostasis [44]. Glycogen synthase kinase 3β (GSK3β) is partially localized to MAMs, where it promotes IP_3R phosphorylation and enhances its activity; inhibition of GSK3β attenuates IP_3R-mediated Ca^{2+} release, thereby limiting cytosolic and mitochondrial Ca^{2+} overload and contributing to reduced cell death and infarct size following reperfusion [45]. Protein tyrosine phosphatase-interacting protein 51 (PTPIP51) is highly expressed at MAMs [46], and I/R upregulates its expression level, increasing sarcoplasmic reticulum–mitochondria contact and accelerating calcium transfer, which in turn induces mitochondrial Ca^{2+} overload and cardiomyocyte death; downregulation of PTPIP51 effectively improves post-reperfusion cardiac function and reduces cardiomyocyte death. SERCA2b is responsible for re-sequestering cytosolic Ca^{2+} into the sarcoplasmic reticulum, and its activity and expression levels are significantly decreased following MIRI. Reduced SERCA activity is associated with elevated cytosolic Ca^{2+}, excessive mitochondrial ROS production, and activation of the mitochondrial fission pathway, rendering cardiomyocytes more susceptible to mitochondria-dependent cell death. The MAM-resident protein TMX1 interacts with SERCA2b in a thiol-dependent manner under oxidizing conditions, suppressing SERCA function and exacerbating calcium homeostasis disruption; inhibition of TMX1 may reduce cardiac susceptibility to I/R injury [47].

4.2. MAM-mediated regulation of oxidative stress and ER stress

The generation of ROS in cardiomyocytes can occur in multiple cellular compartments, with the specific sources depending on cell type and pathophysiological status [48]. In eukaryotic cells, mitochondria and the ER are considered the primary sites of ROS production. Mitochondrial ROS are mainly derived from the electron transport chain, wherein complex I and complex III serve as major contributors to superoxide anion radical (O_2^-) generation. In addition, other mitochondrial enzymes, including glycerol-3-phosphate dehydrogenase, α-ketoglutarate dehydrogenase, pyruvate dehydrogenase, and flavoprotein-ubiquinone oxidoreductase, also participate in ROS production. The ER primarily generates ROS through oxidative protein folding, a process involving thiol-disulfide exchange reactions catalyzed by ER oxidoreductase 1α (ERO1α) and its isoform ERO1β, protein disulfide isomerase (PDI), and NADPH oxidase 4 (NOX4) [49]. During ischemia-reperfusion injury, the restoration of blood flow rapidly reintroduces oxygen-rich blood into the ischemic myocardium, and the abrupt elevation in oxygen partial pressure triggers a burst of ROS production through multiple pathways, thereby exacerbating oxidative stress injury, which impairs cellular and molecular structure and function and ultimately induces apoptosis and senescence. MAMs, as the structural interface for physical coupling and functional crosstalk between the two organelles, not only enrich various redox-regulatory proteins and constitute a local microenvironment for ROS production and exchange but also

serve as a critical integrative platform for the crosstalk between oxidative stress and ER stress signaling pathways, playing an important regulatory role in reperfusion injury.

ERO1α is a core enzyme that maintains ER redox homeostasis and is abundantly localized at MAMs [50]. Its catalytic mechanism is as follows: it accepts electrons from PDI and transfers them to molecular oxygen via the cofactor flavin adenine dinucleotide (FAD), generating hydrogen peroxide (H_2O_2)—the predominant ROS produced in the ER lumen. In parallel, ERO1α is also involved in the regulation of intracellular calcium homeostasis, and through modulating calcium fluxes, it synergistically exacerbates oxidative damage.

The adaptor protein p66Shc (the 66 kDa isoform of the Shc adaptor protein) is also localized to MAMs [51,52]. Under oxidative stress, p66Shc upregulates intracellular ROS levels and mediates p53-dependent Cyt c release, consequently triggering mitochondrial fragmentation and cardiomyocyte apoptosis. Of note, the abundance of p66Shc at MAMs increases with age, suggesting a potential role in aging-associated myocardial injury.

Protein kinase R-like endoplasmic reticulum kinase (PERK) is a core sensor of the UPR and is specifically enriched at MAMs [53]. In addition to its canonical function as an ER stress sensor, PERK also serves as a structural tether at MAMs, participating in ROS-induced cell death signaling and mediating inter-organellar functional crosstalk. Studies have demonstrated that excessive activation of PERK initiates the PERK-eIF2α-ATF4-CHOP apoptotic cascade, thereby exacerbating MIRI. Of note [54], PERK deficiency leads to fragmented ER morphology and disturbed Ca^{2+} signaling. However, it also protects cells against ROS-induced, ER stress-mediated apoptosis. Multiple bioactive components derived from traditional Chinese medicine have been shown to alleviate MIRI by modulating PERK and its associated pathways. Salidroside attenuates hypoxia/reoxygenation-induced ER stress and cardiomyocyte apoptosis by inhibiting the PERK and IRE1α signaling pathways [55]. Schisandrin B pretreatment downregulates PERK protein expression [56], enhances mitochondrial glutathione antioxidant capacity, reduces mitochondrial sensitivity to Ca^{2+}-induced mPTP opening, and upregulates heat shock protein 70 (Hsp70) expression to improve cellular stress tolerance, thereby exerting cardioprotective effects [57]. Furthermore, resveratrol alleviates ER stress through the PERK/eIF2α and ATF6/CHOP pathways, improving cardiac function and reducing cardiomyocyte apoptosis in animal models.

Glucose-regulated protein 78 (GRP78), also known as immunoglobulin heavy chain-binding protein, is a hallmark molecule of ER stress and is widely distributed at MAMs, where it participates in proper protein folding and maintenance of ER homeostasis. Studies have shown that elatoside C can block ER stress-mediated apoptosis by suppressing the expression of ER stress-related apoptotic markers, including GRP78, CHOP, and caspase-12, while simultaneously restoring mitochondrial membrane potential and reducing ROS accumulation, suggesting its potential therapeutic value in MIRI [58]. However, other studies have reported that morusin and *Saururus chinensis* extract upregulate GRP78 expression, activate ER stress pathways, and subsequently induce apoptosis, indicating that GRP78 may exert a dual regulatory role in stress responses [59].

Heat shock protein 70 (Hsp70) is also enriched at MAMs, where it enhances the antioxidant capacity and anti-apoptotic tolerance of cardiomyocytes under stress conditions. Unlike GRP78, Hsp70 is generally considered to exert protective functions under stress, and its upregulation contributes to cell survival [60,61].

4.3. MAM-mediated regulation of mitochondrial dynamics in MIRI

Mitochondrial dynamics, encompassing the continuous processes of fusion and fission [62], constitute the fundamental basis for maintaining mitochondrial morphology, structure, and functional homeostasis. In MIRI, mitochondrial damage resulting from restored blood flow triggers a pronounced enhancement of mitochondrial fission, leading to mitochondrial fragmentation and dysfunction, which ultimately suppresses cardiomyocyte viability, induces cell death, and impairs cardiac function [63,64]. Consequently, an imbalance of mitochondrial dynamics is recognized as a hallmark pathological feature of MIRI, and inhibition of mitochondrial fission has been demonstrated to effectively attenuate reperfusion injury. Multiple proteins localized at MAMs, including MFN1/2, OPA1, DRP1, Fis1, and PACS-2, serve as core regulators of the mitochondrial dynamics network and have emerged as important targets for MIRI intervention strategies.

Mitofusin1/2 (MFN1/2) are key tethering proteins at MAMs and are also involved in outer mitochondrial membrane fusion, playing a dual role in maintaining the structural stability of ER–mitochondria contacts and regulating intracellular calcium homeostasis [65,66]. MIRI leads to downregulation of MFN1/2 expression, resulting in MAMs structural dissociation and mitochondrial dynamics disruption. Gene knockout studies have demonstrated that MFN1/2 deficiency enhances cardiomyocyte tolerance to calcium overload and reduces infarct size following MIRI. Various pharmacological agents exert cardioprotective effects through targeted regulation of MFN1/2 expression. The Qiliqiangxin capsule inhibits the aberrant overexpression of MFN2 following myocardial infarction, thereby reducing excessive mitochondrial Ca^{2+} uptake. Sulforaphane downregulates MFN2 expression, increases the ER–mitochondria distance, alleviates mitochondrial Ca^{2+} overload [67], and reduces ROS generation. The protective effect of curcumin against thapsigargin-induced mitochondrial injury depends on normal MFN2 expression [68]; when MFN2 expression is knocked down, the protective effect of curcumin is completely abolished. Furthermore, calendula extract and GP-17 both reverse the downregulation of MFN1/2 expression, restore mitochondrial fusion–fission balance, and protect mitochondrial function, thereby attenuating MIRI [69]. OPA1 mediates inner mitochondrial membrane fusion [70−72]; salidroside and cinnamaldehyde upregulate OPA1 expression, stabilize mitochondrial morphology, and ameliorate ischemia-reperfusion-induced mitochondrial damage [73,74].

Dynamin-related protein 1 (DRP1) and mitochondrial fission protein 1 (Fis1) are key molecules mediating mitochondrial fission [75]. During MIRI, elevated phosphorylation of DRP1 at Ser616, in coordination with upregulated Fis1 expression, synergistically promotes excessive mitochondrial fission and exacerbates mitochondrial dysfunction [76−78]. Various pharmacological agents have been shown to attenuate MIRI by modulating the DRP1/Fis1 pathway. Salidroside reduces both total DRP1 protein and its phosphorylation levels [79], while also downregulating Fis expression, thereby inhibiting hypoxia-induced excessive mitochondrial fission. Cinnamaldehyde modulates DRP1 and Fis1 expression, enhances superoxide dismutase (SOD) activity and ATP content, and reduces ROS generation and apoptosis. The astragaloside IV derivative LS-102 specifically inhibits DRP1 phosphorylation at Ser616, blocks the mitochondrial fission pathway, and consequently exerts a protective effect against MIRI [80].

Phosphofurin acidic cluster sorting protein 2 (PACS-2) is a multifunctional sorting protein localized at MAMs, playing a critical role in maintaining tight ER–mitochondria coupling and regulating communication between the two organelles [81]. PACS-2 is not only involved in the

regulation of mitochondrial dynamics (fusion/fission) but is also deeply engaged in the maintenance of ER homeostasis and the modulation of the UPR. Loss-of-function studies have demonstrated that PACS-2 deficiency induces caspase-dependent cleavage of BAP31, generating the pro-apoptotic fragment p20, which in turn triggers mitochondrial fragmentation and ER–mitochondria uncoupling and activates ER stress, thereby disrupting MAMs' structural integrity. In terms of apoptotic signal transduction, PACS-2 facilitates the trafficking of full-length Bid to mitochondria, where Bid is subsequently cleaved to tBid, which then promotes Cyt c release and caspase-3 activation, and ultimately initiates the mitochondrial apoptotic pathway. Pharmacological intervention studies have shown that ferulic acid, through modulation of the PACS-2/IP3R/FUNDC1/VDAC1 signaling axis [82], maintains MAMs' structural integrity, balances mitochondrial fusion and fission processes, and ensures normal oxidative phosphorylation, thereby ameliorating stress-induced myocardial pathology .

4.4. Regulation of MAM-mediated inflammatory cascade in MIRI

In addition to oxidative stress, calcium overload, and mitochondrial dynamics disturbances, overactivation of the inflammatory response is also one of the core pathological features of myocardial ischemia-reperfusion injury (MIRI) [83]. During ischemia-reperfusion injury, damage-associated molecular patterns (DAMPs) are extensively released, accompanied by marked recruitment and infiltration of pro-inflammatory cytokines, such as tumor necrosis factor and interleukins, within the myocardial injury foci [84]. Acting synergistically, these factors trigger an inflammatory cascade that perpetuates myocardial structural disruption and cardiomyocyte apoptosis. As the critical interface for physical coupling between the two organelles and for trans-organellar functional signal integration, endoplasmic reticulum–mitochondria contact sites (MAMs) not only serve as the core microenvironment for the convergence and transduction of intracellular calcium and redox signals but are also enriched with numerous characteristic resident proteins that are directly involved in inflammatory signal transduction. By precisely modulating classical pro-inflammatory transcriptional signaling pathways, including NF-κB and JNK/AP-1, these MAM-localized proteins constitute a direct effector molecular network that mediates the inflammatory cascade effects [85]. An imbalance in the functional homeostasis of proteins within the MAM region represents a crucial molecular basis for the persistent dysregulation of the inflammatory response and the progressive aggravation of tissue damage during MIRI. Therefore, systematic elucidation of the molecular mechanisms by which these proteins mediate the inflammatory cascade will not only deepen our understanding of the pathological processes underlying MIRI but may also provide critical molecular targets and a theoretical foundation for the development of novel MAM-targeted anti-inflammatory strategies aimed at counteracting the inflammatory cascade in MIRI.

In the context of MIRI, PACS-2, a multifunctional sorting protein localized at MAMs, serves as a critical hub molecule that initiates the inflammatory signaling cascade. Loss of PACS-2 function induces caspase-dependent cleavage of BAP31, generating the pro-apoptotic p20 fragment. This fragment, on one hand, drives excessive mitochondrial fragmentation, and on the other hand, activates the NF-κB pro-inflammatory signaling pathway, markedly upregulating the transcriptional levels of pro-inflammatory cytokines such as TNF-α and IL-6. Concurrently, PACS-2 mediates the translocation of full-length Bid to mitochondria, where Bid is cleaved into its active form, tBid, which in turn promotes the release of Cyt c and subsequently activates downstream caspase-3. Moreover, caspase family proteins are also responsible for the cleavage and maturation of pro-IL-1β and pro-IL-18 [86].

Collectively, these lines of evidence indicate that, under MIRI conditions, the apoptotic and inflammatory signaling pathways mediated by PACS-2 are tightly interregulated at the MAM interface. Through signal crosstalk, these pathways form functional coupling that synergistically exacerbates ischemia-reperfusion-induced cardiomyocyte injury and amplifies the inflammatory cascade.

PERK, a core sensor of the UPR, is specifically enriched at MAMs. In addition to mediating the ERS response, the PERK-eIF2α-ATF4-CHOP signaling cascade initiated by hyperactivated PERK can, on one hand, induce cardiomyocyte apoptosis, and on the other hand, directly promote the gene transcription of multiple pro-inflammatory factors via ATF4, while synergistically amplifying the NF-κB-dependent inflammatory cascade. Notably, although loss of PERK function can attenuate ROS-induced ERS-related apoptosis, it also leads to endoplasmic reticulum fragmentation and disruption of intracellular calcium signaling, suggesting that PERK exhibits complex bidirectional regulatory characteristics within the inflammatory regulatory network of MIRI. Astragaloside IV [87], a major active component of *Astragalus membranaceus*, exerts pharmacological effects in alleviating myocardial inflammatory injury. During MIRI-induced excessive inflammatory activation, Astragaloside IV can downregulate the expression of p-PERK and inhibit ERS hyperactivation, thereby attenuating hypoxia/reoxygenation-induced inflammatory injury and apoptosis in cardiomyocytes. Volatile oil of *Acorus tatarinowii* (VOA) in combination with crebanine (Cre) can alleviate MIRI by suppressing endoplasmic reticulum stress via inhibition of the GRP78-PERK/ATF6-CHOP pathway, while also inhibiting the MAPK/NF-κB/TNF-α signaling pathway to downregulate the pro-inflammatory cytokines IL-6 and IL-1β [88]. Therefore, precise modulation of PERK activity may represent a potential therapeutic strategy for mitigating inflammatory injury in MIRI.

IRE1α is also enriched at MAMs. When hyperactivated under ischemia-reperfusion stress, it recruits TRAF2 via its cytoplasmic domain, which in turn activates the JNK/AP-1 pathway and the NF-κB signaling cascade, driving the transcriptional upregulation and massive release of pro-inflammatory cytokines such as IL-6 and IL-8, thereby promoting the amplification of the inflammatory cascade and myocardial tissue injury induced by MIRI.

As a hallmark molecule of ERS, GRP78 is widely distributed at MAMs and participates in maintaining protein folding homeostasis. GRP78 exhibits bidirectional regulatory characteristics in the modulation of inflammatory responses: moderate upregulation of GRP78 can suppress hyperactivation of the PERK and IRE1α pathways, attenuating the initiation intensity of pro-inflammatory signaling cascades and thereby exerting endogenous cardioprotective effects during the early phase of MIRI. However, when severe ERS is triggered by ischemia-reperfusion insult, the functional reserve of GRP78 becomes depleted, and its inhibitory effects on PERK and IRE1α are subsequently relieved, leading to persistent aberrant activation of multiple downstream pro-inflammatory signaling pathways, massive release of inflammatory cytokines, and ultimately exacerbation of MIRI-mediated myocardial inflammatory infiltration as well as cardiomyocyte apoptosis and necrosis. Studies have shown that oxysophocarpine (OSC) can ameliorate cardiac dysfunction induced by MIRI in rats by mediating GRP78 expression, downregulating the ERK/JNK pathway, alleviating oxidative stress, and suppressing inflammatory responses [89].

In addition to the pro-inflammatory signaling network constructed by MAM-enriched proteins, the assembly and activation of the NLRP3 inflammasome represent another core event in MAM-mediated inflammatory regulation. MAMs serve as a critical signaling hub for NLRP3 inflammasome assembly by facilitating physical coupling between the endoplasmic reticulum and

mitochondria, as well as local calcium flux. Through acetylated α-tubulin and dynein-dependent mitochondrial transport mechanisms, ASC on mitochondria associates with NLRP3 localized on the endoplasmic reticulum, thereby accomplishing the initial assembly of the inflammasome core components at the MAM interface. Moreover, the mediating roles of ORMDL3 and Fis1, together with calcium flux triggered by VDAC oligomerization, can further enhance NLRP3 assembly efficiency via endoplasmic reticulum–mitochondria contacts. Under MIRI conditions, mitochondrial calcium overload and excessive ROS production act synergistically to drive NLRP3 inflammasome activation, which in turn promotes the maturation and release of IL-1β and IL-18, eliciting a robust inflammatory response. 14-3-3ε enhances K63 deubiquitination of NLRP3 and promotes its translocation to MAMs, thereby achieving complete inflammasome activation. Collectively, these mechanisms indicate that MAMs, by mediating the assembly, activation, and full activation of the NLRP3 inflammasome, significantly exacerbate the inflammatory cascade during MIRI, promote the massive release of pro-inflammatory cytokines, and ultimately aggravate myocardial tissue injury and cell death. Artemisinin can reduce the mRNA transcription levels of TLR4 and NF-κB and downregulate the expression of downstream pro-inflammatory factors, thereby ameliorating MIRI-induced myocardial injury. Dan Shen Yin granules exert protective effects against MIRI by regulating oxidative stress and NLRP3 inflammasome activation pathways. Curcumin can attenuate hypoxia/reoxygenation-induced cardiomyocyte injury by downregulating mitochondrial ROS production and inhibiting NLRP3 inflammasome activation.

Table 1. Functional classification, regulatory mechanisms, and TCM intervention of MAM-resident proteins in MIRI.

Functional classification	Core proteins enriched at MAMs	Targeting mechanism	Functional effects in MIRI	Bioactive components of TCM amenable to intervention	Reference
Calcium signaling regulation	IP_3R-GRP75-VDAC1-MCU axis	ER–mitochondria calcium transfer channels	Mediates the directed transfer of Ca^{2+} from the ER into mitochondria. Dysfunction of this process leads to mitochondrial calcium overload and aberrant opening of the mPTP, thereby initiating cardiomyocyte apoptosis.	① Qiliqiangxin ② Capsulesulforaphane ③ Glycine ④ Melatonin	[35–38]
	Bcl-2 family	IP_3R calcium release channel and mitochondrial apoptotic pathway	Bcl-2 and Bcl-XL inhibit IP_3R-mediated excessive Ca^{2+} release to prevent mitochondrial Ca^{2+} overload, whereas downregulation of Bcl-2 expression during MIRI exacerbates oxidative stress and apoptosis.	① Sulforaphane	[42]

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Functional classification	Core proteins enriched at MAMs	Targeting mechanism	Functional effects in MIRI	Bioactive components of TCM amenable to intervention	Reference
	Cyp D	mPTP pore and IP_3R-GRP75-VDAC1 complex	Cyp D enhances Ca^{2+} transfer from the ER to mitochondria; its interaction with IP_3R is positively correlated with mitochondrial calcium content and serves as a key regulator of aberrant mPTP opening.	① Eleutheroside C ② Astragaloside IV	[43]
	GSK3β	Regulation of IP_3R phosphorylation	It promotes IP_3R phosphorylation and enhances its activity; its inhibition reduces Ca^{2+} release, restricts cytosolic and mitochondrial Ca^{2+} overload, and attenuates cardiomyocyte death and infarct size.	-	-

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Functional classification	Core proteins enriched at MAMs	Targeting mechanism	Functional effects in MIRI	Bioactive components of TCM amenable to intervention	Reference
	PTPIP51	SR–mitochondria contact sites and calcium transfer rate	Following I/R injury, upregulation of this protein enhances SR–mitochondria contacts and accelerates Ca^{2+} transfer, leading to mitochondrial Ca^{2+} overload and cardiomyocyte death; conversely, its downregulation improves cardiac function.	-	-
	SERCA2b	Cytosolic Ca^{2+} reuptake and SR Ca^{2+} stores	Following MIRI, the activity and expression of SERCA2b are markedly decreased, leading to elevated cytosolic Ca^{2+}, excessive mitochondrial ROS production, activation of the mitochondrial fission pathway, and exacerbated cell death.	-	-
	TMX1	Regulation of SERCA2b function	Under oxidizing conditions, it suppresses SERCA2b function, aggravating Ca^{2+} dyshomeostasis; its inhibition lowers cardiac I/R susceptibility.	-	-

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Functional classification	Core proteins enriched at MAMs	Targeting mechanism	Functional effects in MIRI	Bioactive components of TCM amenable to intervention	Reference
Regulation of oxidative stress and ROS production	ERO1α	ER protein folding, ROS generation, and Ca^{2+} flux regulation	It is a core oxidoreductase localized at MAMs. It catalyzes the generation of H_2O_2, the predominant ROS in the ER, while also modulating calcium flux, thereby synergistically exacerbating oxidative damage and calcium homeostasis disruption in MIRI.	-	-
	p66Shc	Intracellular ROS level, mitochondrial fragmentation, and Cyt c release	Under oxidative stress, it upregulates intracellular ROS level, mediates p53-dependent Cyt c release, and induces mitochondrial fragmentation and cardiomyocyte apoptosis.	-	-
	PERK	UPR, MAMs structural tethering, and ROS-induced cell death	It is a key UPR sensor. Its overactivation triggers apoptosis and worsens MIRI, whereas its loss disrupts MAM integrity, leading to ER fragmentation and Ca^{2+} dysregulation.	① Salidroside ② Schisandrin B ③ Resveratrol	[55−56]
	GRP78	ER protein folding and ER stress-mediated apoptotic pathway	GRP78, a marker of ER stress, participates in protein folding and homeostasis maintenance. It exhibits bidirectional regulation in MIRI: suppression of GRP78 prevents ER stress-induced apoptosis, while its upregulation triggers stress pathway activation.	① Eleutheroside C ② Mulberrin ③ *Acorus tatarinowii* extract	[58−59]

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Functional classification	Core proteins enriched at MAMs	Targeting mechanism	Functional effects in MIRI	Bioactive components of TCM amenable to intervention	Reference
	Hsp70	Antioxidant capacity and apoptotic resistance	During MIRI, it enhances cardiomyocyte antioxidant and anti-apoptotic defenses; its upregulation promotes cell survival and attenuates damage.	① Schisandrin B	-
	PDI/NOX4	ER protein disulfide exchange and ROS generation	It is involved in the oxidative protein folding process in the ER, catalyzing thiol-disulfide exchange reactions, and serves as a key participant in ER ROS generation. Its upregulation during MIRI further exacerbates oxidative stress.	-	-
Mitochondrial dynamics regulation	MFN1/2	Mitochondrial outer membrane fusion, MAM structural tethering, and calcium homeostasis regulation	They are key tethering proteins at MAMs, participating in OMM fusion and maintaining the stability of ER–mitochondria contacts. In MIRI, downregulation of their expression leads to MAM dissociation and dynamics disruption, whereas aberrant overexpression exacerbates mitochondrial calcium uptake.	① Qiliqiangxin capsule ② Sulforaphane ③ Curcumin ④ Marigold extract ⑤ GP-17	[67−69]

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Functional classification	Core proteins enriched at MAMs	Targeting mechanism	Functional effects in MIRI	Bioactive components of TCM amenable to intervention	Reference
	OPA1	Mitochondrial inner membrane fusion and mitochondrial morphology stabilization	It mediates inner mitochondrial membrane fusion. Its downregulation in MIRI impairs mitochondrial morphology, whereas upregulation stabilizes mitochondrial structure and ameliorates mitochondrial dysfunction caused by ischemia-reperfusion.	① Salidroside ② Cinnamaldehyde	[73,74]
	DRP1/Fis1	Mitochondrial fission and fragmentation	They are core mediators of mitochondrial fission. In MIRI, increased DRP1 phosphorylation and Fis1 upregulation act synergistically to drive excessive mitochondrial fission, aggravating dysfunction and apoptosis.	① Salidroside ② Cinnamaldehyde ③ Astragaloside IV derivative LS-102	[79,80]
	PACS-2	MAM structural integrity, mitochondrial fusion–fission balance, and ER homeostasis	PACS-2, a multifunctional sorting protein, sustains ER–mitochondria coupling, modulates mitochondrial dynamics and the UPR, and its loss disrupts MAM structure, induces mitochondrial fragmentation, and triggers ER stress.	① Ferulic acid	[82]
	BAP31	Regulation of mitochondrial fission and the apoptotic pathway	It is involved in regulating mitochondrial fission and, upon apoptotic signaling, undergoes cleavage to generate pro-apoptotic fragments that induce mitochondrial fragmentation, Cyt c release, and apoptosis.	-	-

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Functional classification	Core proteins enriched at MAMs	Targeting mechanism	Functional effects in MIRI	Bioactive components of TCM amenable to intervention	Reference
Regulation of inflammatory responses	PACS-2	BAP31, Bid, NF-κB signaling pathway, caspase family	As a hub at the MAMs, PACS-2 spatially couples the mitochondrial apoptotic execution pathway with NF-κB pro-inflammatory signaling. Its dysfunction concurrently amplifies both apoptotic and inflammatory outputs, creating a positive feedback loop that promotes tissue damage.	-	-
	PERK	eIF2α/ATF4/CHOP, NF-κB signaling pathway	Overactivation of PERK promotes apoptosis and inflammation, whereas its complete inactivation disrupts organelle homeostasis. Thus, the modulation of inflammation by PERK exhibits a double-edged effect: moderate activation is detrimental, while both overactivation and loss of function are unfavorable.	① Astragaloside IV ② VOA in combination with Cre	[87,88]
	IRE1α	TRAF2, JNK/AP-1, NF-κB signaling pathway	Under stress, IRE1α couples two classical pro-inflammatory cascades via TRAF2 recruitment, specifically triggering an inflammatory cytokine burst, thus acting as a positive modulator of pro-inflammatory signal amplification.	-	-

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Functional classification	Core proteins enriched at MAMs	Targeting mechanism	Functional effects in MIRI	Bioactive components of TCM amenable to intervention	Reference
	GRP78	PERK, IRE1α	At mild-to-moderate stress, it serves as a brake to limit upstream pro-inflammatory signals. Under severe stress, it switches to a pro-inflammatory permissive factor due to exhaustion, reflecting a dynamic bidirectional regulation.	① Oxysophocarpine	[89]
Regulation of other pathologic processes	Sig1R	IP_3R-GRP75-VDAC1 complex and Ca^{2+} signaling	It regulates ER–mitochondria calcium transfer and protects cells by modulating calcium signaling and mitochondrial function.	-	-
	VAPB-PTPIP51 complex	MAM structural tethering and calcium transfer regulation	As the major tethering protein complex at MAMs, they maintain organelle physical coupling and regulate calcium transfer and apoptosis; their aberrant expression in MIRI aggravates calcium dyshomeostasis.	-	-
	Caspase family	Apoptotic signaling cascade and ER stress pathway	They are core executors of apoptosis. During MIRI, they can be activated via the mitochondrial pathway as well as the ER stress pathway, thereby mediating cardiomyocyte apoptosis.	① Eleutheroside C	[90]

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Functional classification	Core proteins enriched at MAMs	Targeting mechanism	Functional effects in MIRI	Bioactive components of TCM amenable to intervention	Reference
	Bid/BNIP3	Mitochondrial apoptosis pathway and autophagy modulation	In MIRI, they are activated and translocated to mitochondria, promoting Cyt c release and apoptosis; concurrently, they are involved in the regulation of autophagy, which influences cardiomyocyte survival.	① Notoginsenosides	[91]

5. Conclusions

In summary, MAMs, as the central hub for physical coupling and functional interplay between the ER and mitochondria, pervade the entire pathological process of MIRI and constitute a critical structure modulating injury progression. This review systematically elucidates the molecular mechanisms by which MAMs mediate MIRI from three dimensions—calcium signaling, oxidative stress, and mitochondrial dynamics balance—and highlights the decisive role of MAM structural integrity and functional stability in determining cardiomyocyte survival. In parallel, we summarize the research progress on various bioactive components derived from TCM that target MAM-associated proteins to counteract myocardial injury, thereby providing new theoretical foundations and potential therapeutic targets for the prevention and treatment of MIRI with TCM.

However, current research in this field still faces several bottlenecks and challenges. First, as nanoscale dynamic membrane contact microdomains, MAMs undergo structural remodeling in real time in response to cellular stress states. Conventional detection techniques such as transmission electron microscopy and in situ proximity ligation assays are constrained by inherent limitations, including insufficient spatiotemporal resolution, structural damage incurred during sample preparation, and the lack of quantitative standards. These shortcomings make it difficult to fulfill the requirements for in situ real-time monitoring of MAMs' dynamic architecture under physiological or pathological conditions, thus constituting a critical technical bottleneck impeding further progress in this field. Second, the functional execution of MAMs is collectively mediated by the dynamic assembly and synergistic action of multi-protein complexes. Current studies predominantly focus on single molecules or single signaling pathways, and a systematic understanding of the MAM regulatory network as an integrated whole, along with corresponding intervention strategies, remains lacking. How to devise intervention regimens based on network modulation rather than single-target-oriented approaches represents a core scientific question for achieving precise MIRI intervention. Finally, although a large number of bioactive components from TCM have been confirmed to alleviate MIRI through MAM-related pathways, most studies have only verified their overall protective effects without thoroughly elucidating the direct interaction modes, binding sites, or structure–activity relationships between drug molecules and MAM protein complexes. Moreover, given the wide distribution of MAMs across multiple tissues throughout the body, nonspecific intervention is prone to induce off-target adverse effects. How to achieve tissue-selective regulation within the narrow therapeutic window of MIRI remains a significant obstacle to the clinical translation of these bioactive components.

In light of the current research limitations, future efforts should focus on three major directions. First, innovative techniques for in situ dynamic observation of MAMs with high spatiotemporal resolution should be developed to overcome the current technical shortcomings in quantitative characterization, thereby providing a reliable methodological platform for systematically elucidating the principles governing MAM structure–function coupling. Second, the binding modes, interaction sites, and structure–activity relationships between bioactive molecules from TCM and MAM multi-protein complexes should be rigorously dissected, propelling research on TCM-based cardioprotection from empirical screening toward target-based rational drug design. Third, MAM-targeted delivery systems with ischemic microenvironment-responsive properties should be engineered to achieve selective modulation within the pathological window of myocardial ischemia-reperfusion injury, offering the potential to develop safe and effective novel intervention strategies for the clinical

management of MIRI.

Use of generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Author Yiping Han: Investigation (literature search and screening), Writing – original draft, Visualization. Author Lin Zhao: Investigation (data extraction and synthesis), Writing – original draft. Author Pengshuo Lou: Investigation (validation of extracted data), Visualization (graphical abstract), Writing – review & editing. Author Chen Wang: Writing – review & editing. Author Mingxin Yuan: Writing – review & editing. Corresponding author Yingli Yu: Conceptualization, Supervision, Writing – review & editing, Funding acquisition, Project administration. All authors have read and approved the final version of the manuscript for publication.

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