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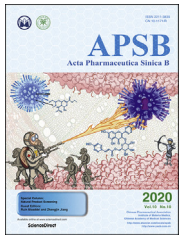

REVIEW

Mitochondrial quality control mechanisms as molecular targets in cardiac ischemia–reperfusion injury

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Necroptosis

Abstract Mitochondrial damage is a critical contributor to cardiac ischemia/reperfusion (I/R) injury. Mitochondrial quality control (MQC) mechanisms, a series of adaptive responses that preserve mitochondrial structure and function, ensure cardiomyocyte survival and cardiac function after I/R injury. MQC includes mitochondrial fission, mitochondrial fusion, mitophagy and mitochondria-dependent cell death. The interplay among these responses is linked to pathological changes such as redox imbalance, calcium overload, energy metabolism disorder, signal transduction arrest, the mitochondrial unfolded protein response and endoplasmic reticulum stress. Excessive mitochondrial fission is an early marker of mitochondrial damage and cardiomyocyte death. Reduced mitochondrial fusion has been observed in stressed cardiomyocytes and correlates with mitochondrial dysfunction and cardiac depression. Mitophagy allows autophagosomes to selectively degrade poorly structured mitochondria, thus maintaining mitochondrial network fitness. Nevertheless, abnormal mitophagy is maladaptive and has been linked to cell death. Although mitochondria serve as the fuel source of the heart by continuously producing adenosine triphosphate, they also stimulate cardiomyocyte death by inducing apoptosis or necroptosis in the reperfused myocardium. Therefore, defects in MQC may determine the fate of cardiomyocytes. In this review, we summarize the regulatory mechanisms and pathological effects of MQC in myocardial I/R injury, highlighting potential targets for the clinical management of reperfusion.

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1. Introduction

The heart is a strong muscular pump that enables tissue and organ perfusion. Therefore, a continuous supply of fresh blood is vital for cardiac function. In coronary artery disease, plaques or thrombi induce rapid occlusion, which restricts blood flow to the heart[1–3]. The primary effect of coronary artery disease is substantial cardiomyocyte death, which prevents the heart from effectively pumping blood to vital organs[4,5]. Emergency coronary recanalization through a coronary artery bypass graft or percutaneous transluminal coronary intervention can limit cardiomyocyte death[6]. However, laboratory experiments have revealed that a significant proportion of cardiomyocyte death occurs during the first few minutes of reperfusion, in what is known as myocardial ischemia/reperfusion (I/R) injury[7,8].

Several molecular mechanisms have been proposed to explain the pathological alterations in cardiac I/R injury, including rapid reactive oxygen species (ROS) release, calcium overloading, energy depletion, mitochondrial dysfunction and programmed cell death activation[9–12]. Mitochondria have been recognized as key triggers of cardiac I/R injury[13,14]. First, mitochondria are abundant in cardiomyocytes and determine more than 90% of their energy supply[15]. Second, mitochondria can promote cardiomyocyte death by inducing apoptosis or necroptosis in the reperfused myocardium[16]. Third, other pathological situations such as calcium overload, oxidative stress, endoplasmic reticulum stress and immune responses are triggered by, integrated with or augmented by mitochondrial dysfunction[17]. Therefore, it is highly important to understand the regulatory mechanisms and biochemical contributions of mitochondrial dysfunction in cardiac I/R injury.

In response to stressful conditions, the mitochondria can activate mitochondrial quality control (MQC) to preserve mitochondrial structure and function[18]. MQC is a group of adaptive responses that regulate mitochondrial protein turnover, mitochondrial fusion, mitochondrial fission and mitophagy[19] (Fig. 1). The main consequences of MQC are the rapid removal of defective mitochondrial debris and the timely replenishment of the mitochondrial network[20,21]. These biophysical processes protect the mitochondria from damage and therefore attenuate the vulnerability of cardiomyocytes to I/R injury.

This review summarizes how MQC protects the myocardium from I/R injury, focusing on mitochondrial fission, fusion, mitophagy and mitochondria-dependent programmed cell death (Fig. 1). Recent findings on the contribution of mitochondrial

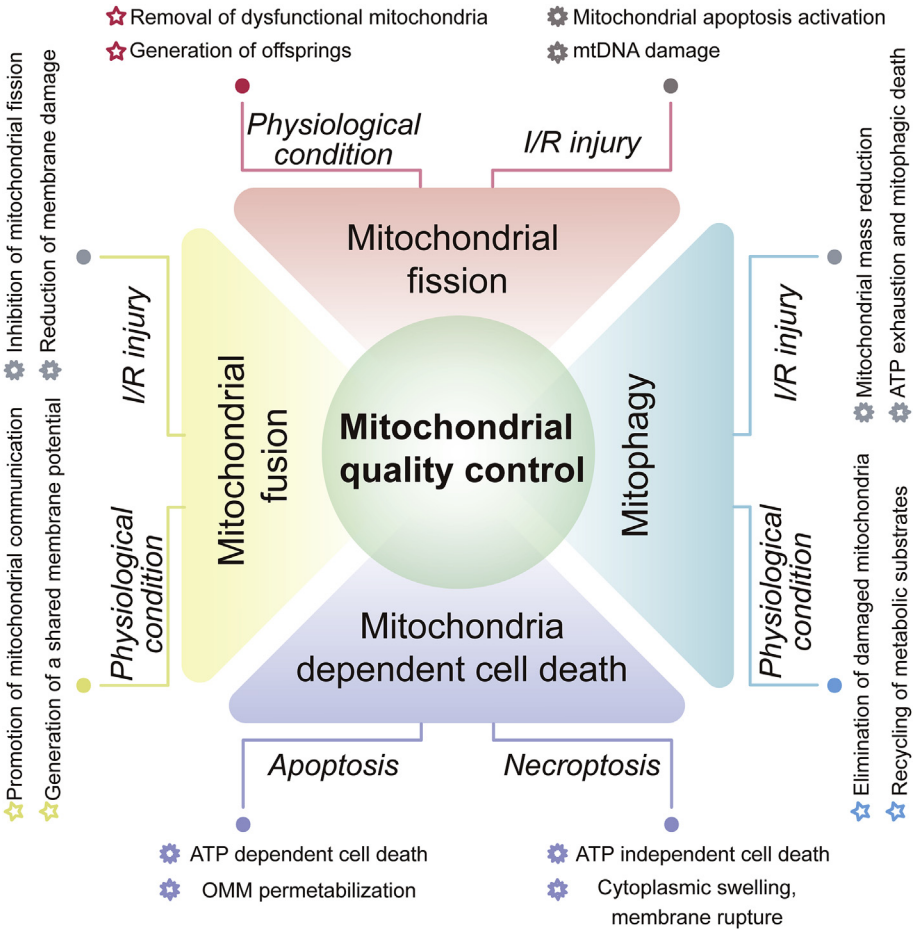

Figure 1 Overview of mitochondrial quality control (MQC) under physiological conditions and I/R injury. MQC coordinates various processes (fission, fusion, mitophagy and mitochondria-controlled cell death) to ensure cellular homeostasis. Mitochondrial dysfunction, amplified by failing quality-control processes, is believed to be a major mechanism of cardiac I/R injury. Several potential targets of MQC could be harnessed to treat cardiac I/R injury by inhibiting mitochondrial fission, promoting mitochondrial fusion, moderately activating mitophagy and inhibiting mitochondria-dependent cell death.

fission to mitochondrial damage and cardiomyocyte death (apoptosis and/or necroptosis) are discussed, along with receptor-dependent and -independent mitophagy-based mechanisms of cardiomyocyte mitochondrial protection. The debate over whether mitochondrial fusion induces or reduces I/R-related mitochondrial dysfunction is also analyzed[22,23]. A special emphasis is given to mitochondria-induced cell death, especially necroptosis, a novel mechanism that contributes to MQC and determines cardiomyocyte viability during cardiac I/R injury. We hope the information presented here will provide new insights into the molecular pathways underlying mitochondria-related myocardial damage in I/R, and will offer useful targets for cardioprotection.

2. Mitochondrial fission

Although mitochondria were originally believed to be static, it is now well accepted that mitochondria are dynamic organelles that are constantly reshaped by fusion and fission. Mitochondrial fission can remove dysfunctional mitochondria from cardiomyocytes, and the extent of mitochondrial fission is largely determined by the metabolic needs of the cells. Proper mitochondrial fission generates many offspring and thus provides the boost in cardiomyocyte oxidative phosphorylation necessary for myocardial development and performance[24,25]. Fission also enables mitochondria to separate damaged fractions from reticular mitochondria[26], and thus is indispensable for cardiomyocyte mitochondrial homeostasis.

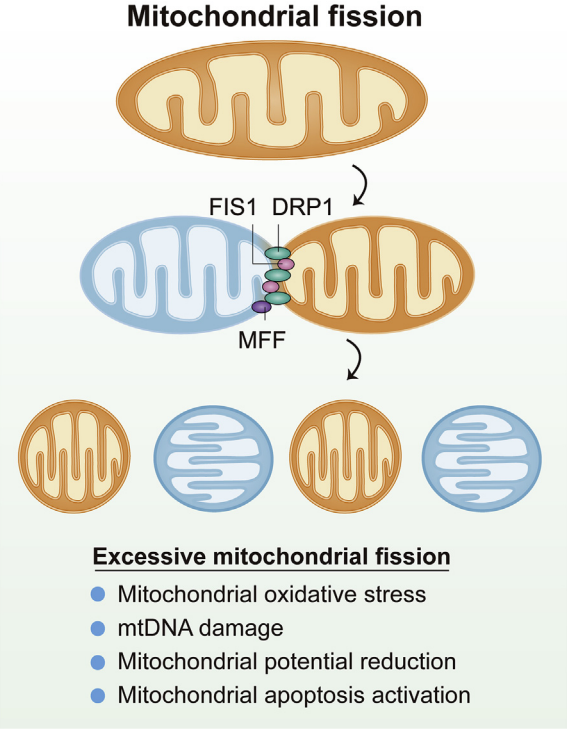

Figure 2 Mitochondrial fission is regulated by dynamin-related protein 1 (DRP1) and its receptors, including mitochondrial fission factor (MFF), mitochondrial fission one protein (FIS1). Increased mitochondrial fission is associated with oxidative stress, mitochondrial DNA (mtDNA) damage, mitochondrial membrane potential reduction and mitochondrial apoptosis activation.

Mitochondrial fission is regulated by dynamin-related protein 1 (DRP1) and its receptors (Fig. 2), including mitochondrial fission factor (MFF), mitochondrial fission one protein (FIS1), mitochondrial dynamics protein of 49 kDa (MID49) and mitochondrial dynamics protein of 51 kDa (MID51)[27]. Under physiological conditions, DRP1 is primarily free in the cytoplasm in an inactive form that cannot bind to its receptors, which are anchored to the outer mitochondrial membrane (OMM). Therefore, mitochondrial fission is relatively low under normal conditions. Interestingly, under stressful conditions, DRP1 undergoes conformational changes through post-transcriptional modifications including ubiquitination, acetylation and phosphorylation[28,29]. These structural alterations expose the binding site on DRP1 and increase its likelihood of binding to its receptors on the OMM, enabling cytoplasmic DRP1 to translocate to the surface of the mitochondria. On the other hand, the transcriptional upregulation of DRP1 is not a reliable measure of DRP1-induced mitochondrial fission[30].

Multiple post-transcriptional modifications of DRP1 have been discovered through mass spectrometry-based proteomics, as shown in the online open database PhosphoSitePlus[31] and a thorough recent review by Jhun et al.[32]. Two post-transcriptional modification sites on DRP1 have been well explored: the phosphorylation sites at Ser616 and Ser637. Ser616 phosphorylation promotes DRP1 oligomerization around the OMM, a prerequisite for the formation of a potential mitochondrial fission ring[33]. Phosphorylation at Ser637 has the opposite effect of impairing DRP1 oligomerization and therefore preventing mitochondrial fission[34,35].

Post-transcriptional modification also occurs on DRP1 receptors, including MFF[36], FIS1[37], MID49[38] and MID51[39]. Phosphorylation of MFF at Ser146 enhances its affinity for DRP1, and this alteration has been reported in cardiac microvascular I/R injury[36]. Interestingly, the N-terminal arm of FIS1 auto-inhibits its access to DRP1, whereas phosphorylation of this N-terminal arm enhances the binding of FIS1 to DRP1[37]. The effects of MID49/MID51 phosphorylation on DRP1-induced mitochondrial fission in cardiac I/R injury have not been described.

In the context of cardiac I/R injury, mitochondrial fission is associated with mitochondrial damage and cardiomyocyte death (Fig. 2). Following cardiac I/R injury, DRP1 phosphorylation at Ser637 decreases, so the mitochondrial localization of DRP1 increases[34]. Consequently, excessive mitochondrial fission occurs, which induces cytosolic calcium overload and thus promotes cardiomyocyte death and myocardial contractile dysfunction. In contrast, DRP1 phosphorylation at Ser616 increases after myocardial I/R injury[40], and ROS production and cardiomyocyte oxidative stress are elevated. The expression of MFF[41] and its post-transcriptional phosphorylation at Ser146[36] are found to be augmented in a mouse model of cardiac microvascular I/R injury, and genetic ablation of *Mff* is reported to attenuate mitochondrial DNA (mtDNA) breaks, restore mtDNA copying and transcription, improve mitochondrial respiration and enhance endothelial viability.

The increased fission under cardiac I/R injury is known to induce other pathological alterations, including the reduction of ATP levels, the translocation of cytochrome *c* (Cyt-*c*) from the mitochondria to the cytoplasm, the opening of the mitochondrial permeability transition pore (mPTP) and the dissipation of the mitochondrial membrane potential; these effects are coupled with

caspase-3 activation and cardiomyocyte apoptosis[42−45]. Of note, the cardiomyocyte antioxidant capacity, as reflected by the levels of superoxide dismutase two and heme oxygenase 1, is also found to be altered by mitochondrial fission, although the mechanism is unknown[46]. Moreover, autophagy, a procedure that degrades damaged intracellular components, is reported to be drastically repressed by mitochondrial fission, as demonstrated by the reduced LC3II/I ratio, beclin-1 expression and ATG5/7 expression[46]. *In vivo*, the extent of mitochondrial fission is found to correlate positively with the size of the myocardial infarction and negatively with cardiac function measures such as the left ventricular ejection fraction and left ventricular fractional shortening[46,47]. These results illustrate the sufficiency of mitochondrial fission to promote myocardial I/R injury.

On the other hand, genetic or pharmacologic blockades of mitochondrial fission can protect the reperfused heart[48,49]. Mdivi-1 pharmacologically inhibits mitochondrial fission by preventing DRP1 from binding to its receptors. Administration of Mdivi-1 to mice before myocardial I/R injury markedly inhibits DRP1 translocation to the mitochondria, and thus reduces serum cardiac troponin I levels and lactate dehydrogenase activity[48]. Mdivi-1 treatment primarily improves mitochondrial function by blocking mPTP opening and stabilizing the mitochondrial membrane potential[49,50]. Mdivi-1 treatment can also partly reverse mitochondria-induced apoptosis by suppressing Cyt-*c* release and caspase-9 activation[41]. Ding and coworkers[48] observed that Mdivi-1 treatment increases the activity of the antioxidant enzyme manganese superoxide dismutase and reduces the content of malondialdehyde, indicating that mitochondrial fission is also associated with the redox status.

Mitochondrial fission influences a variety of cardiac protective pathways, including the protein kinase B (PKB), extracellular-signal-regulated kinase (ERK), 5′-adenosine monophosphate-activated protein kinase (AMPK) and nitric oxide pathways[51−53]. Several of these proteins have been identified as upstream regulators of the post-transcriptional modifications of DRP1 and its receptors. For instance, ERK and AMPK can attenuate DRP1 phosphorylation at Ser616, whereas PKB can promote DRP1 phosphorylation at Ser637[40].

The above data indicate that mitochondrial fission is a complex and progressive process involving either positive or negative feedback signals between various signaling pathways. However, several critical events should be emphasized. First, Mdivi-1 can improve cardiac function when it is given during ischemia and at the onset of reperfusion, but to a lesser extent than when it is administered before ischemia[54]. One possibility is that inhibiting physiological mitochondrial fission impairs cardiac function, whereas pathological mitochondrial fission primarily takes place after ischemia or reperfusion. Second, the inhibition of fission attenuates apoptosis but exacerbates necroptosis in cardiomyocytes[55]. This unexpected phenomenon seems to be present in Mdivi-1-injected mice, but not in *Drp1*-deleted[56] or *Mff*-depleted mice[41]. Thus, it is possible that Mdivi-1 is not a specific blocker of mitochondrial fission. Actually, several findings have suggested that Mdivi-1 can repress mitophagy[51,57], a protective pathway that prevents cell death by impeding apoptosis or necroptosis. Lastly, Mdivi-1 treatment following ischemia primarily seems to reverse cardiac diastolic dysfunction, as evidenced by the improved left ventricular developed pressure and lower left ventricular end diastolic pressure after such treatment[34]. Thus, careful attention is needed when interpreting studies in which Mdivi-1 has been used to inhibit mitochondrial fission in myocardial I/R injury.

3. Mitochondrial fusion

In contrast to mitochondrial fission, fusion is a process that integrates several mitochondrial fractions into long filamentous mitochondria. Mitochondrial fusion can be divided into three distinct steps: tethering, outer membrane fusion and inner membrane fusion[58,59]. Like mitochondrial fission, mitochondrial fusion is regulated by large guanosine triphosphatases (GTPases). The transmembrane GTPases mitofusin one and 2 (MFN1/2) are OMM-localized proteins, whereas the dynamin-like GTPase optic atrophy 1 (OPA1) promotes IMM intermingling[60] (Fig. 3). Structurally, MFN1 and MFN2 on two physically contacting mitochondria promote homotypic or heterotypic coordination to stimulate OMM fusion[61]. The long isoform of OPA1 (L-OPA1) triggers IMM interactions between two mitochondria, resulting in the formation of the short isoform of Opa1 (S-OPA1) with the help of the proteases yeast mitochondrial escape one like one ATPase (YME1L1) and OMA1 zinc metallopeptidase (OMA1)[62].

Most experimental evidence indicates that mitochondrial fusion protects cells during stress by two independent mechanisms. First, fusion offsets the effects of excessive mitochondrial fission and thus limits fission-initiated mitochondrial apoptosis[63]. Second, fusion generates a long, shared electrochemical potential within the mitochondrial network, enhancing the timely detection of damaged parts in the mitochondrial mass[64]. Fusion also equilibrates mitochondrial proteins, lipids, metabolites and mtDNA, which is thought to alleviate the local stress response and restore mitochondrial homeostasis[65].

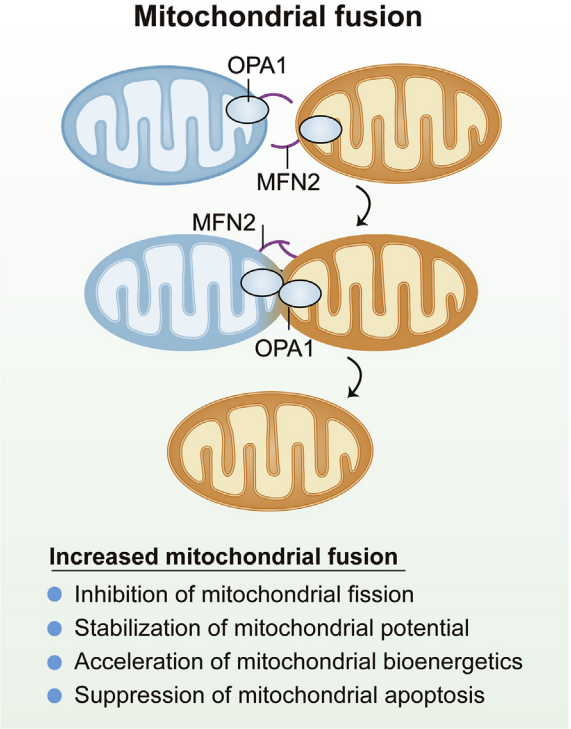

Figure 3 Mitochondrial fusion is controlled by outer mitochondrial membrane (OMM)-localized mitofusin 2 (MFN2) and inner mitochondrial membrane (IMM)-localized optic atrophy 1 (OPA1). Increased mitochondrial fusion inhibits mitochondrial fission, sustains mitochondrial potential, promotes mitochondrial bioenergetics and suppresses mitochondrial apoptosis.

While fused mitochondria may be protective under physiological conditions, the involvement of fusion-related factors in cardiac I/R injury is the subject of hot debate. First, *Mfn1*-null mice are healthy and fertile, whereas *Mfn2*-null mice die soon after birth[66]. *Mfn1* deletion seems to have little influence on cardiac function under either physiological or pathological conditions[67], whereas *Mfn2*-deficient hearts exhibit extensive mtDNA breaks and mitochondrial damage[68]. More surprisingly, cardiomyocyte-specific *Mfn1*-knockout mice display a normal respiratory repertoire and are protected from mitochondrial depolarization[69]. In addition, *Mfn1*-knockout cardiomyocytes exhibit improved viability in a hydrogen-peroxide-induced oxidative stress microenvironment due to their reduced mPTP opening rate[69], suggesting that *Mfn1* deletion may protect cardiomyocytes from oxidative-stress-induced injury. In contrast, *Mfn2* deficiency in cardiomyocytes promotes mPTP opening, augments ROS production and triggers cell death[70,71]. In a hypoxia/reoxygenation-mimicked I/R injury model *in vitro*, *Mfn2* silencing sensitizes H9C2 cells to apoptosis, and this process could be partly reversed through the inhibition of caspase-9 or the overexpression of BCL-x(L)[72]. In accordance with the effects of cardiomyocyte-specific *Mfn2* ablation, *Mfn1*/*Mfn2* double depletion causes defective mitochondria to accumulate and exhibit an unfolded protein response[73,74]. These data may reflect an additional function of MFN1 that has not yet been documented. However, relatively low levels of MFN1 have been detected in many tissues[75–77], especially the brain, which may explain why MFN1 loss is not so detrimental to cardiac function. This concept requires additional studies for verification. MFN2 and MFN1 may exert completely different effects on cardiomyocyte viability upon cardiac I/R injury, despite their similar functionality in promoting mitochondrial fusion.

Unlike the effects of MFN1 and MFN2, the effects of OPA1 on cardiomyocyte fate and mitochondrial function have been well established. The heart-specific knockdown of *Opa1* increases mitochondrial morphometric heterogeneity and ultimately induces ventricular dilation with irreversible contractile dysfunction[78]. In myocardial I/R injury, OPA1 expression is found to be reduced, while the genetic activation of OPA1 suppresses mitochondrial fission and cardiomyocyte death[63]. Knocking out *Opa1* expands the infarction size and induces cardiac dysfunction in reperfused hearts[79]. Reperfusion induces the self-cleavage and activation of OMA1, and cleaved OMA1 accelerates the conversion of L-OPA1 to S-OPA1, leading to mitochondrial fragmentation, Cyt-*c* release and apoptosis[80]. OPA1 dysregulation impairs mitochondrial bioenergetics and exacerbates oxidative stress[81]. Of note, other molecular mechanisms may account for OPA1-induced cardioprotection. For example, OPA1 is found to enhance myocardial fatty acid utilization and thus attenuate ROS generation and sustain the mitochondrial morphology in failing hearts[82,83]. However, this finding has not been validated in the process of cardiac I/R injury.

Like DRP1, MFN1/2 can be post-transcriptionally phosphorylated by a number of kinases. However, the phosphorylation of MFN1/2 partially reduces their GTPase activities and thus abolishes their ability to induce mitochondrial fusion. MFN1 phosphorylation at Ser86 by beta II protein kinase C (bIIPKC) leads to a buildup of mitochondrial fragments in heart failure[84]. In addition, mitogen-activated protein kinase/ERK phosphorylates MFN1 at T562[85], thereby reducing its efficiency in oligomerization and mitochondrial tethering but increasing the susceptibility to BAX-induced mitochondrial apoptosis. Similarly, MFN2 phosphorylation by PTEN-induced putative kinase protein 1 (PINK1) facilitates depolarization-induced PARKIN translocation onto mitochondria, thus promoting mitophagy and reducing the accumulation of morphologically and functionally abnormal mitochondria[86]. In contrast, after exposure to stress, MFN2 is primarily phosphorylated and then degraded by c-Jun N-terminal kinase, which impairs mitochondrial fusion and enhances cell death[87]. In the context of cardiac I/R injury, although post-transcriptional modifications of MFN1/2 have not been confirmed, MFN1/2 protein levels are significantly downregulated[88].

Of note, unlike MFN1/2, OPA1 is primarily regulated at the protein level by two mechanisms: redox status and mitochondrial proteolytic enzyme activity. OMA1 and YME1L1, which are mainly upregulated by stress or the mitochondrial unfolded protein response, have been acknowledged as upstream inducers of OPA1 degradation during cardiac I/R injury[82]. In addition, mitochondrial ROS levels are found to correlate with the extent of proteolytic processing of OPA1, while the scavenging of mitochondrial ROS is reported to prolong the protein stability of OPA1 in cardiomyocytes[89]. OPA1 transcription in cardiomyocytes is activated by STAT3 and RelA, which form a supercomplex that binds to the promoter region of OPA1[90]. Although STAT3 has not been observed to transcriptionally modify OPA1 in cardiac I/R injury, STAT3 activity is significantly downregulated in the reperfused heart[91–93]. This downregulation, together with OMA1/YME1L1-induced OPA1 degradation, may further reduce OPA1 expression during myocardial I/R injury. Additionally, in hearts under pressure overload or hyperglycemic conditions, OPA1 is found to be hyperacetylated[94] and *O*-GlcNAcylated[95], respectively. These structural modifications reduce the GTPase activity of OPA1, leading to mitochondrial morphological disorder and cardiomyocyte death. It would be interesting to explore the post-transcriptional hyperacetylation and *O*-GlcNAcylation of OPA1 in myocardial I/R injury.

Several drugs and gene-modifying technologies have been created to restore mitochondrial fusion[96–98]. Sevoflurane-induced anesthetic postconditioning has been demonstrated to reduce cardiac I/R injury in basic research and clinical surgery[99]. Interestingly, the benefits of sevoflurane are attributed to the upregulation of OPA1 and MFN2 in hypoxia/reoxygenation-treated neonatal rat cardiomyocytes[99,100]. OPA1 and MFN2 levels are also found to be induced by vagal nerve stimulation, which improves mitochondrial dynamics in the ischemic myocardium[52]. Epigallocatechin gallate effectively inhibits OPA1 degradation by OMA1, and therefore maintains mitochondrial morphological homeostasis in reperfused hearts[80,101]. Melatonin transcriptionally upregulates OPA1 expression through the AMPK pathway and thus increases the resistance of mitochondria and cardiomyocytes to I/R injury[79]. Based on this information, preserving mitochondrial fusion through MFN2 activation or OPA1 stabilization is critical when designing cardioprotective therapies for myocardial I/R injury.

4. Mitophagy

Mitochondrial components are eventually recycled through a specialized autophagic pathway known as mitophagy. Mitophagy is a kind of selective organelle autophagy that prevents the accumulation of abnormal mitochondria that might otherwise trigger cardiomyocyte dysfunction or death[102]. Proper mitophagy

also recycles metabolic substrates that are vital for cardiomyocyte metabolism under stressful conditions[103,104]. BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), FUN14 domain containing 1 (FUNDC1) and NIX are expressed on the OMM and therefore elicit receptor-dependent mitophagy (Fig. 4). However, PARKIN is mainly localized in the cytoplasm and translocates onto the mitochondria with lower membrane potential to initiate receptor-independent mitophagy after stimulation. Mechanismically, the targeted mitochondria are then engulfed by the pre-autophagosome, forming an autophagosome. Subsequently, microtubule-associated protein 1A/1B-light chain 3 (LC3) binds to phosphatidylethanolamine, generating the LC3-phosphatidylethanolamine conjugate (LC3II). Finally, the lysosome induces the proteolytic degradation of the autophagosomal proteins, nucleic acids, carbohydrates and lipids, which are recycled by the cell to restore homeostasis[105,106].

Since mitophagy is a "self-eating" process, excessive mitophagy is maladaptive and has been linked to cell death. Accordingly, genetically or pharmacologically blocking mitophagy can attenuate cell death[107,108]. Three molecular mechanisms have been proposed to explain mitophagic cell death. First, many stimuli can trigger both mitophagy and cell death, so the cell fate is mainly determined by the degree and duration of stress. Under mild stress, when parts of the mitochondria are damaged, the selective removal of mitochondria *via* mitophagy is protective for the cell. However, once stress becomes severe, the number of damaged mitochondria increases and may overwhelm the capacity of mitophagy, leading to cell death. Thus, mitophagy is pro-survival, and cell death occurs when mitophagy cannot preserve mitochondrial homeostasis[109,110]. Second, excessive mitophagy significantly reduces the mitochondrial mass and therefore causes ATP exhaustion. Cells with low ATP levels have a pronounced susceptibility to stress-induced death *via* necroptosis rather than apoptosis, because apoptosis is ATP-dependent programmed cell death. Therefore, mitophagy is fatal when it "eats" too many mitochondria[111]. Third, mitophagy is stimulated by many proteins that also induce apoptosis, such as the BCL2-family proteins NIX and BNIP3[112]. Although BNIP3 initiates mitophagy by promoting the binding between LC3 and mitochondria, BNIP3 overexpression sensitizes cells to the intrinsic apoptotic cell death pathway[113]. Thus, the death-suppressing or -promoting actions of mitophagy are determined by upstream adaptors. Lastly, we must emphasize that cell fate management *via* mitophagy may also depend on the tissue and cell type.

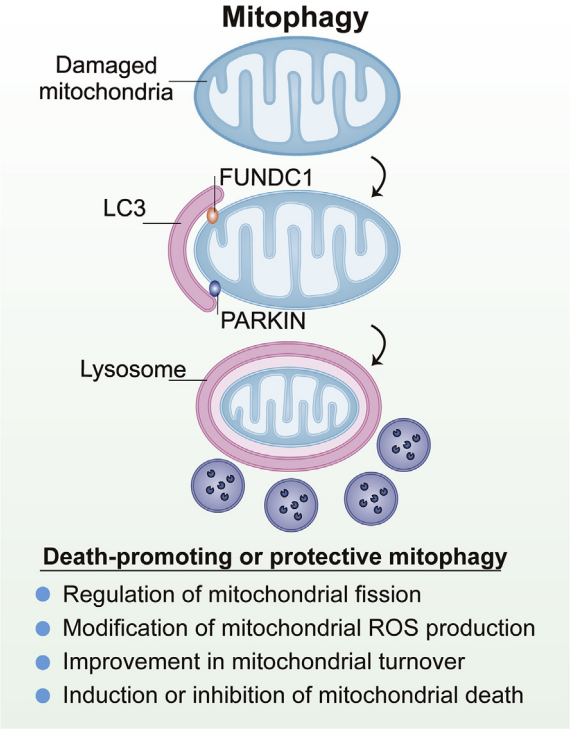

Figure 4 The most recognized mitophagy pathway in mammalian cells is mediated by PARKIN, a receptor-independent pathway. In addition to PARKIN-mediated mitophagy, receptor-dependent pathway for mitophagy induction includes Fun14 domain-containing protein 1 (FUNDC1). Mechanismically, the targeted mitochondria are engulfed by the pre-autophagosome, forming an autophagosome. Subsequently, microtubule-associated protein 1A/1B-light chain 3 (LC3) binds to phosphatidylethanolamine, generating the LC3-phosphatidylethanolamine conjugate (LC3II). Finally, the lysosome induces the proteolytic degradation of the autophagosomal proteins, nucleic acids, carbohydrates and lipids, which are recycled by the cell to restore homeostasis.

In the setting of cardiac I/R injury, numerous experiments have investigated how mitophagy influences myocardial function and cardiomyocyte viability. The effects of mitophagy (*i.e.*, suppressing or promoting cell death) mainly seem to depend on the adaptors involved. For example, reperfusion-induced cardiomyocyte death through calcium overload is followed by OPA1-induced mitophagy; however, the pharmacologic activation of OPA1-induced mitophagy is found to protect the heart against I/R injury[63]. Similarly, an early study indicated that the genetic ablation of *Opa1* impaires mitophagy and augments I/R-induced myocardial damage[79]. In addition, Saito et al.[114] demonstrated that protective mitophagy during myocardial ischemia is mediated by RAB9 for the first time. Phosphorylated RAB9 at Ser179 promotes the assembly of the ULK1−RAB9−RIP1−DRP1 complex, and then activates mitophagy to protect myocardium against ischemia. In contrast, PARKIN-induced mitophagy is found to be fatal for reperfused hearts because it enhances cyclophilin D (CypD)-induced mPTP opening, a feature of necroptosis[115]. In a cardiac microvascular I/R injury model, PARKIN-induced mitophagy causes excessive mitochondrial elimination and an ATP undersupply, thus conveying death-promoting signals to cardiac microvascular endothelial cells[116]. BNIP3-induced mitophagy is also demonstrated to be lethal in cardiac I/R injury[117]. Abrogating BNIP3 activity not only prevents mitophagy, but also suppresses necrotic cell death in cardiomyocytes[117].

Unlike PARKIN- and BNIP3-induced mitophagy, cardiolipin-induced mitophagy is a cardioprotective process that attenuates mitochondrial oxidative stress, reduces calcium overload and promotes cardiomyocyte survival during I/R injury[118,119]. Protective mitophagy can also be triggered by FUNDC1, an OMM protein that is regulated through post-transcriptional modification[120]. At the stage of ischemia, FUNDC1 is found to be activated (dephosphorylated) and to foster mitophagy, thus reducing reperfusion-induced myocardial damage[121]. FUNDC1-induced mitophagy has been reported to reverse the mitochondrial membrane potential, reduce mitochondrial ROS production and prevent mitochondria-induced apoptosis[36,122]. TNF-receptor-associated factor 2 (TRAF2), an E3 ubiquitin ligase, also has been found to trigger protective mitophagy and reduce mitochondrial fragmentation in reperfused hearts[123,124].

Although the induction of mitophagy by different adaptors can have distinct effects on cell fate, ranging from survival to death, little is known about the molecular crosstalk among these adaptors. Thus, the net effect of mitophagy on cardiac I/R injury remains unclear. Of note, some studies have found that mitophagy is activated during I/R injury[113,115], whereas others have found that it is inhibited[79,125]. This may be due to the different time points of reperfusion evaluated after ischemia. There is no doubt that ischemic/hypoxic stress induces autophagy (mitophagy)[126,127]. During reperfusion, autophagy flux is reduced in the early phase (0−24 h after I/R injury), but is augmented at the later recovery stage (1−3 days after I/R injury)[128,129]. In a careful recent study[130], autophagy reporter (CAG-RFP-EGFP-LC3) mice are generated and subjected to renal I/R injury. Autophagy is unaltered in the first 4 h after reperfusion, but autophagosome formation is overtly reduced from four to 24 h post-reperfusion. Thereafter, the autophagosome fuses with lysosomes to form the autolysosome from one to 3 day post-reperfusion[130]. This conclusion is also highlighted in a number of high-profile thematic reviews[131−133].

Actually, the early inactivation and late activation of mitophagy may be an adaptive and protective response. From a pathophysiological perspective, cardiomyocyte death mainly occurs within the early period of reperfusion due to ROS overproduction and calcium overload[134,135]. Under these conditions, cellular damage overwhelms the defense and/or repair systems of cardiomyocytes, including their anti-oxidative, anti-apoptotic and metabolism-remodeling capacities. Hence, either apoptosis or necroptosis is somewhat inevitable, so mitophagy is inhibited. Cardiomyocytes may thus avoid the possible activation of mitophagic cell death, which would otherwise accelerate or aggravate cardiomyocyte loss and myocardial dysfunction. However, in the late phase of reperfusion, the myocardium requires mitophagy to repair damaged mitochondria and restore cardiomyocyte viability, so the net result of mitophagy increases at this stage. Although mitophagy is inhibited or activated at different phases of reperfusion, we cannot conclude that various adaptors are inhibited or activated within a similar window. For example, in the early stage of reperfusion, PARKIN[116] seems to be upregulated, whereas FUNDC1[121] is rapidly inactivated. Thus, the ultimate effect of mitophagy results from the crosstalk among various mitophagy adaptors, although the time mapping of these adaptors has not yet been reported.

Although mitochondrial fission is reportedly to induce cardiomyocyte reperfusion damage through activating apoptosis, fission is supposed to occur prior to mitophagy at the stage of ischemia. A recent study[114] reported that Unc-51 like autophagy activating kinase-1 (ULK1) phosphorylates RAB9 at Ser179, which promotes association between RAB9 and RIP1, followed by phosphorylation of DRP1 at Ser616 and its activation. Then, DRP1-induced fission sequesters damaged mitochondria and facilitates mitophagy to attenuate myocardial ischemic injury. Besides, DRP1 SUMOylation also contributes to mitophagy activation in hypoxia-treated cardiomyocyte, which is followed by sustained mitochondrial potential and decreased cardiomyocyte apoptosis[136]. These observations demonstrate that mitophagy is induced by moderate fission under ischemia/hypoxia conditions. In fact, an early study has proposed that PARKIN-independent mitophagy requires DRP1 to maintain the integrity of mammalian heart[137]. When DRP1 is absent, PARKIN becomes necessary to sustain mitochondrial function and structural integrity[138]. This notion is also supported by several following studies that FUNDC1 requires DRP1-dependent fission to control mitophagy[139,140]. Interestingly, at the stage of reperfusion, fission is significantly upregulated whereas protective mitophagy is largely inhibited. Re-introduction of mitophagy has been found to stop fatal fission[79,141], resulting into mitochondrial potential stabilization and cardiomyocyte survival. These data suggest that mitophagy may in turn restrict abnormal mitochondrial fission. However, inhibition of DRP1-mediated mitochondrial fragmentation seems to impair autophagosome recognition and engulfing of damaged mitochondria[142], reconfirming that fission is the prerequisite for mitophagy induction. Overall, although abnormal mitochondrial fission is followed by cardiomyocyte death in cardiac I/R injury, mitophagy requires moderate fission to sequester damaged mitochondria at the ischemic stage whereas reperfusion-induced excessive fission could be in turn corrected by mitophagy.

Notably, because mitophagy is regulated by various adaptors, when one adaptor is inhibited, another may be induced in compensation. For example, germline *Parkin* ablation in mice has proven not to be an ideal experimental model for mitophagy depletion, in part due to the compensation from mitochondrial E3 ubiquitin protein ligase 1 (MUL1)-induced mitophagy in the physiological state[143]. Further, although ATG32 is the primary mitophagy receptor in yeast, its mammalian homologue BCL2 like 13 (BCL2L13) compensates somewhat for basal mitophagy activity in *Atg32*-null yeast[144]. Moreover, under normal conditions, nonselective autophagy compensates for the lack of mitophagy in *Mfn2*-knockout mice[145]. Since compensatory mechanisms ensure that mitophagy occurs under various conditions, the next key question is how the various mitophagy adaptors interact with and compensate for one another in cardiac I/R injury.

5. Mitochondria-dependent cell death

Cardiac I/R injury involves the rapid loss of functional cardiomyocytes through programmed cell death, the final step of MQC. Mitochondria induce or inhibit cardiomyocyte death by two routes (Fig. 5). The first approach is the hyper-permeabilization of

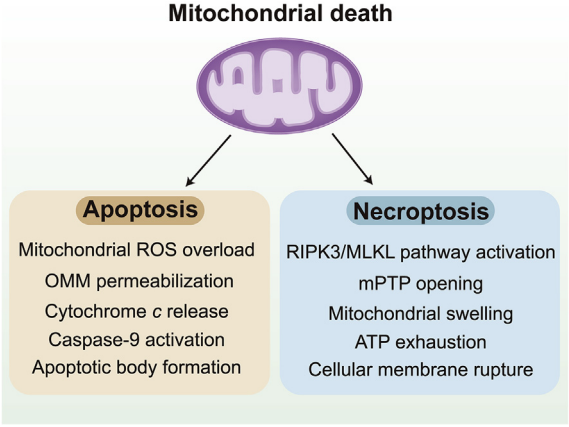

Figure 5 Mitochondrial death includes apoptosis and necroptosis. Apoptosis is regulated by outer mitochondrial membrane (OMM) permeabilization, mitochondrial membrane potential reduction, caspase-9 activation. Necroptosis is induced by the activation of RIPK3/MLKL pathway and the mPTP opening. Then, mitochondrial electron transport chain dysfunction and tricarboxylic acid cycle termination contribute to ATP exhaustion, cytoplasmic swelling, and membrane rupture.

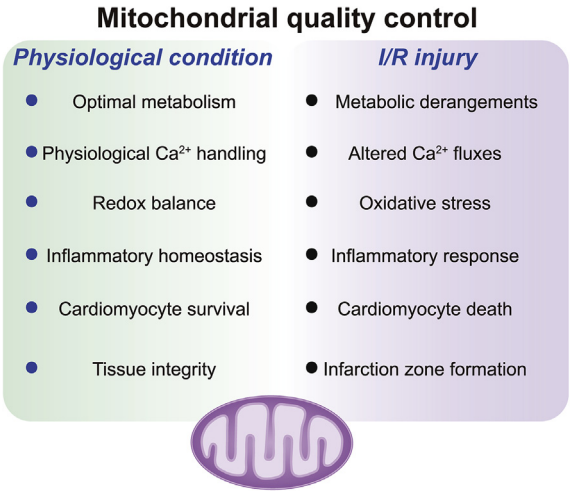

Figure 6 Involvement of mitochondrial quality control in cardiac I/R injury. Under physiological conditions, healthy mitochondria support the functions of cardiomyocytes by ensuring optimal catabolic and anabolic metabolism and regulating the intracellular trafficking of Ca^{2+}. Additionally, an intact mitochondrial network maintains inflammatory homeostasis and tissue integrity by preventing the activation of signal transduction cascades that lead to pro-inflammatory factor secretion and regulated cell death. Mitochondrial dysfunction is accompanied by metabolic derangements and alterations in the intracellular Ca^{2+} flux, and also promotes an inflammatory milieu and regulated cell death, which culminates in tissue loss.

the OMM, followed by the leakage of Cyt-*c* from the mitochondria into the cytoplasm. There, Cyt-*c* activates caspase-9, which subsequently cleaves caspase-3[146,147]. This classical mitochondria-induced apoptotic pathway is also characterized by mitochondrial membrane potential reduction, ROS overload, BAX upregulation and BCL2 downregulation[148,149]. The second death pathway is induced by the protracted opening of the mPTP due to voltage-dependent anion-selective channel multimerization, CypD phosphorylation and adenine nucleotide translocator upregulation, although the primary constituents of the mPTP complex are being intensely debated[150,151]. The mPTP induces the opening of the IMM by forming a non-specific pore, leading to mitochondrial swelling, mitochondrial electron transport chain dysfunction and tricarboxylic acid cycle termination[152,153]. Subsequently, due to ATP exhaustion, the cell undergoes cytoplasmic swelling, membrane rupture and organelle breakdown, which lead to cell death through necroptosis[154]. In contrast to apoptosis, necroptotic cell death does not require energy, and exhibits features such as cell/organelle swelling, extensive mitochondrial disruption, blebbing and irreversible plasma membrane disintegration[155,156].

Several regulators of mitochondrial apoptosis or necroptosis should be highlighted to illustrate the signal transduction pathways underlying mitochondria-induced cell death in cardiac I/R injury. First, with respect to apoptosis, BAX is an important inducer of OMM permeabilization, whereas BCL2 guards against BAX-induced OMM damage[157,158]. Under normal conditions, BCL2 heterodimerizes with BAX to inhibit its pro-apoptotic activity. However, certain stimuli upregulate the transcription of BAX, ultimately increasing the abundance of BAX proteins in the cytoplasm and enabling their homodimerization[159]. Subsequently, BAX homodimers migrate to and insert themselves into the OMM, thus permeabilizing it[160,161]. Accordingly, the levels of BCL2 and BAX, as well as the mitochondrial membrane potential, are usually used to monitor mitochondrial apoptosis[162,163].

Regarding necroptosis, the initial signals include receptor interacting serine/threonine kinase 3 (RIPK3), phosphoglycerate

Table 1 Compounds or drugs targeting mitochondrial quality control (MQC) in cardiac I/R injury.

Name	Target	Ref.
Mdivi-1	Mitochondrial fission (DRP1)	179,180
Propofol	Mitochondrial fission (DRP1)	181
Dapagliflozin	Mitochondrial fission (DRP1)	182
Dynasore	Mitochondrial fission (DRP1)	183
Isosteviol sodium	Mitochondrial fission (DRP1/FIS1)	184
Tetrahydrocurcumin	Mitochondrial fission and fusion (DRP1 and MFN2)	185
Pravastatin	Mitochondrial fission and fusion (DRP1 and MFN1)	186
Vildagliptin	Mitochondrial fusion (MFN2)	64
Mitochondrial fusion promoter M1	Mitochondrial fusion (MFN1/2 and OPA1)	187
Melatonin	Mitochondrial fusion and mitophagy (OPA1 and FUNDC1)	79 , 122
Tongxinluo	Mitophagy (PARKIN)	188
Bicarbonate	Mitophagy (PARKIN)	189
Simvastatin	Mitophagy (PARKIN)	190
Ellagic acid	Mitophagy (BNIP3)	117
Hydrogen-rich saline	Mitophagy (PARKIN)	191
Metformin	Necroptosis (RIPK1 and RIPK3)	192
Dexmedetomidine	Necroptosis (RIPK3)	193
Necrostatin-1	Necroptosis (RIPK1)	194
Baicalin	Necroptosis (RIPK3 and MLKL)	195
Ciclosporin A	Necroptosis (mPTP opening)	167
Tanshinone IIA	Apoptosis (BAX/BCL2)	196
Taxifolin	Apoptosis (BAX/BCL2)	197
Glutamine	Apoptosis (Cyt-*c*)	198
Febuxostat	Apoptosis (Cyt-*c*)	199
PD150606	Apoptosis (Cyt-*c*)	42
Ru360	Apoptosis (BAX)	200

mutase 5 (PGAM5) and mixed lineage kinase domain like protein (MLKL). At the stage of reperfusion, oxidative stress and calcium overload directly or indirectly activate RIPK3, which stimulates PGAM5 and MLKL phosphorylation and oligomerization on the membrane. MLKL then forms membrane pores to execute lytic cell death[16,164]. Of note, mPTP opening seems to result from RIPK3 activation in the setting of cardiac I/R injury, based on recent studies[165−167]. Ca^{2+}—calmodulin-dependent protein kinase (CaMKII) is a substrate of RIPK3, and activated CaMKII promotes mPTP opening[165,166]. Additionally, RIPK3 upregulation augments the expression of PGAM5, which enhances CypD phosphorylation[167,168], thus increasing the opening rate of the mPTP. Therefore, RIPK3 expression, MLKL phosphorylation and the mPTP opening rate are potential targets for the regulation of mitochondria-initiated necroptosis.

Apoptosis has traditionally been accepted as the main form of cardiomyocyte death responsible for myocyte loss during and after cardiac I/R injury. However, in recent studies[120,165], only 30% of the cell death during I/R injury could be reversed by the pan-caspase inhibitor zVAD. In contrast, the depletion of necroptotic genes such as *Ripk3* reduces cardiomyocyte death by 50% in I/R injury. These works demonstrate that the dominant form of programmed cell death in cardiac I/R injury is necroptosis, an unexpected result. Actually, the infarction site is known to have two different zones: the inner area of the infarcted myocardium (the umbra), and the surrounding ischemic penumbra. Necroptosis mainly presents in the core area of the infarcted zone, whereas apoptosis fills the ischemic region[16,169,170].

Although the regulatory mechanisms of apoptosis and necroptosis are relatively clear, their interactive effects remain to be elucidated. RIPK3 is also an upstream activator of caspase 8-induced apoptosis in myocardial infarction[171,172], but activated caspase-8 can degrade RIPK3 and thus inhibit necroptosis[173,174]. Mitochondrial apoptosis inhibitors such as c-IAP1 and c-IAP2 can induce RIPK3 ubiquitination and prevent necroptosis activation[175,176]. In a cellular reperfusion model[177], RIPK3 is linked to DRP1 activation and mitochondrial membrane potential reduction, suggesting that RIPK3 may promote mitochondrial fission and subsequent mitochondrial apoptosis. Interestingly, the deletion of *Ripk3* reverses FUNDC1-induced mitophagy and thus sends an anti-apoptotic signal to reperfused hearts[120]. On the other hand, the suppression of autophagy flux is found to trigger cardiomyocyte death *via* necroptosis[178]. These studies suggest that there is reciprocity between necroptosis and mitochondrial dynamics. Although necroptosis and apoptosis are regulated by completely different upstream signaling pathways, there is a striking pattern of overlap in their downstream events. Accordingly, when cardioprotective drugs are designed to reduce myocardial I/R injury, both anti-apoptotic and anti-necroptotic actions should be considered.

6. Conclusions

MQC is an adaptive response that adjusts the morphology and function of mitochondria during cardiac I/R injury (Fig. 6). After exposure to stress, cardiomyocytes employ anti-oxidative factors to neutralize mitochondrial ROS, reduce oxidative stress damage and ensure mitochondrial homeostasis. Concurrently, mitochondrial fission is activated so that damaged mitochondrial fractions can be removed from the mitochondrial network, with the cooperation of mitophagy. In contrast, healthy, long mitochondria can integrate with several small mitochondrial fragments to enhance the resistance of the entire mitochondrial population to stress. When these adaptive responses fail, programmed cell death by apoptosis or necroptosis is activated, and damaged mitochondria become the inducers of cell death, enabling the sequestration of incurable and dysfunctional cardiomyocytes. During this process, mitochondrial fission and mitophagy serve as a double-edged sword in the reperfused heart: on one hand, they exert pro-survival mechanisms by isolating damaged mitochondria, and on the other hand, if fission and mitophagy persist beyond a certain threshold, they may lead to cellular demise. Therefore, selective, effective, moderate and differential activation of mitophagy and mitigation of fission are essential for MQC, and could synergistically enhance cardiac function in I/R injury. Necroptosis and apoptosis, although activated by various stimulus, are functionally governed solely by mitochondria. As the final steps of MQC to maintain tissue homeostasis, necroptosis and apoptosis communicate with each other, and offer new targets for therapeutic approaches. The compounds or drugs targeting MQC are summarized in Table 1. More studies are required to further verify the therapeutic effects of these compounds/drugs in clinical practice.

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Author contributions

Jin Wang and Hao Zhou were responsible for original draft and visualization. Hao Zhou was responsible for review and editing, supervision, and funding acquisition.

Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analysis or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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