INTRODUCTION

Myocardial infarction (MI) is generated by myocardial necrosis caused by myocardial hypoxia and myocardial cell energy failure, which are aggravated by long-term myocardial ischaemia due to coronary occlusion. Previous studies have shown that abnormal oxidative stress, dysfunction of the antioxidant system and cellular apoptosis play important roles in the occurrence of MI and post-infarction ischaemia-reperfusion (I/R). Mitochondria are the primary sites of energy and ROS production in eukaryotes. Moreover, mitochondria also participate in cell apoptosis and signal transduction. Therefore, normal mitochondrial function is crucial for regulating oxidative stress and apoptosis.
Therefore, stringent quality control of mitochondria is vital for improving and maintaining the normal function of myocardial cells following MI.  

2  |  CARDIAC MITOCHONDRIAL DYNAMICS: FISSION/FUSION

Mitochondrial dynamics involve fission and fusion. Mitochondrial fission is the process by which a mitochondrial network structure is broken, forming non-functional mitochondrial fragments or multiple independent mitochondria. In contrast, mitochondrial fusion is the process by which independent mitochondria or mitochondrial fragments fuse to generate a single mitochondrion.  

With changes to the cell environment, mitochondria continuously split and merge to promote the production of new mitochondria and to repair defective mitochondria. This dynamic process ensures the normal distribution of the mitochondrial metabolites within cells, which is crucial to maintaining the normal function and quality control of mitochondria.

The high expression of mitochondrial fission/fusion-related proteins in the myocardium suggests that they are essential for modulating cardiomyocyte functionality. Multiple studies have indicated that when the myocardium is injured by I/R, mitochondrial fission is increased, fusion is inhibited, the balance of fission/fusion is disordered and the structure and function of mitochondria are damaged, thereby impairing the function of myocardial cells. Consequently, a precise regulatory mechanism is indispensable for maintaining an equilibrium of fission/fusion, thus ensuring the minimum effective number of mitochondria that can efficiently engage in work.

2.1  |  Mitochondrial Fission of Cardiomyocytes

Mitochondrial fission can increase the number of mitochondria and/or cellular fragility. Fission in cardiomyocytes is primarily mediated by the guanosine triphosphate (GTP) enzyme and dynamin-related protein 1 (Drp1), which is located in the cytoplasm. It should be noted that the post-transcriptional modification of Drp1 is very important for mitochondrial fission. Phosphorylation is the main topic. The phosphorylation modification of different sites of Drp1 has reverse effects on mitochondrial fission. For example, cyclin-dependent kinase 1 (CDK1)/cyclin B (cyclin B) phosphorylates Drp1 S585 (serine 585) and S616 (serine 616), promoting mitochondrial division; On the contrary, cyclic AMP-dependent protein kinase A (PKA) can inhibit mitochondrial fission by phosphorylating Drp1 S656 whereas protein phosphatase dephosphorylates Drp1 S656 (serine 656) and S637 (serine 637) to promote mitochondrial fission. In addition, other post-translational modifications of Drp1, such as ubiquitination, s-nitrosylation and glycosylation, can also affect mitochondrial fission. Studies have proved that glycosylation of Drp1 facilitates the development of cardiomyopathy, still lacking research on ischaemic heart diseases.

A mechanistic study by Otera et al. found that during the course of division, the endoplasmic reticulum was coupled with and wrapped around the mitochondria, whereupon Drp1 in the cytoplasm was recruited and translocated to the mitochondria. Drp1 then assembled into a circular polymer by binding with mitochondrial dynamic protein 49/51 (Mid49/51) and Drp1 receptors including mitochondrial fission protein 1 (Fis1), mitochondrial fission factor (Mff) on the outer membrane of the mitochondria. This led to the subsequent hydrolysis of GTP and actuated the cleavage of the mitochondrial membrane (Figure 1). Therefore, Drp1-mediated

![FIGURE 1](image-url)
Among them, it was found that Fis1 is not required for mitochondrial fission, whereas Mff plays an important role in the recruitment of Drp1 and Mid49/51 facilitates a connection between Drp1 and Mff on the OMM surface. 

2.1.1 | Mitochondrial Fission after MI

Studies have revealed that hypoxia injury can enhance mitochondrial fission in cardiomyocytes (Figure 1). Drp1 is an important protein involved in mitochondrial fission. Studies have revealed that the expression and activity of Drp1 are significantly increased after MI, mitochondrial fission of cardiomyocytes is enhanced, the shape of the mitochondria becomes shorter and rounder, and the number of mitochondria rises. This eventually induces an increase in ROS production and cardiomyocyte apoptosis, implying that the abnormal variation of Drp1 after MI may result in an augmentation of mitochondrial fission. In contrast, Ding et al. found that mitochondrial fission was reduced, the oxidative stress of cardiomyocytes was decreased and the function of mitochondria was improved through drug-mediated inhibition of Drp1 activity. The above studies demonstrate that the increased Drp1-mediated mitochondrial fission following MI plays an important pathological role in I/R injury, and the suppression of Drp1 may lessen the degree of myocardial injury.

In a further study of the relevant mechanism by which Drp1 contributes to MI, Sharp et al. found that calcium overloading in the cytoplasm induced by I/R can activate calcineurin, which accordingly dephosphorylates and then activates Drp1 S637, which is then translocated from the cytoplasm to the outer membrane of mitochondria. This process thereby promotes mitochondrial swelling, cleavage and ROS generation, further aggravating the calcium overload and forms a vicious cycle. On the other hand, Liu et al. recently found that the expression of microRNA-138 (miR-138) in myocardial cells was down-regulated after MI, which gave rise to the up-regulation of hypoxia-inducible factor 1α (HIF-1α). The increase in HIF-1α promoted the expression of the mitochondrial division-related proteins, Drp1 and FIS1, so as to accelerate mitochondrial division. Taken together, the enhancement of Drp1 activity and expression can mediate increased fission, as well as alter the function and morphology of mitochondria.

In addition, regulation of other proteins involved in mitochondrial division may also play an important role. Zhou et al. indicated that the expression level of Mff increased in cardiomyocytes significantly after I/R. Genetic depletion of Mff could reduce the infarct area, ameliorating the vascular endothelial injury and the morphology and function of mitochondria. Samangouei et al. found that after knockout of Mid49/51, the mitochondrial debris of hypoxic cardiomyocytes was decreased, the morphological recovery of mitochondria after reperfusion was accelerated, mitochondrial calcium overload of hypoxic cardiomyocytes was reduced and thus the damage of hypoxic cardiomyocytes was alleviated.

Therefore, a vitally important direction for the treatment of MI may be to seek an appropriate method of inhibiting mitochondrial fission.

2.1.2 | Application of MI Therapies

Drp1 represents a pivotal protein in the promotion of mitochondrial fission. Moreover, suppression of the critical process of mitochondrial fission (e.g., the expression and activity of Drp1, translocation of Drp1 and the binding of Drp1 to regulatory proteins) has been shown to alleviate I/R injury after MI.

Studies have found that inhibiting the expression and activity of Drp1 can improve heart function. For instance, treatment with a PS3 inhibitor, PCSK9 inhibitor and melatonin can decrease the level of Drp1 S637 dephosphorylation and facilitate the phosphorylation and deactivation of Drp1, thus suppressing mitochondrial fission. Secondly, mitochondrial division inhibitor-1 (Mdivi-1), a kind of quinazoline derivatives, has been found to reduce the expression of Drp1 and inhibit mitochondrial fission. In addition, Li et al. found that baicalin can up-regulate the membrane-associated RING-CH 5 (MARCH5) in cardiomyocytes via the krüppel-like factor 4 (KLF4)-MARCH5-Drp1 pathway, so as to down-regulate the level of Drp1 expression in order to relieve I/R injury.

As mentioned above, as the down-regulation of miR-138 expression can promote cardiomyocyte apoptosis, Liu et al. found a down-regulation of Drp1 expression in mice and reduction in infarct size following injection with a miR-138 inhibitor. In conclusion, mitochondrial fission can be weakened by reducing the activity or expression of Drp1 using various inhibitors.

In addition, inhibition of Drp1 translocation to mitochondria and/or its binding to regulatory proteins can also promote heart function. Darwesh et al. found that inhibiting soluble epoxide hydrolase (sEH) can prevent Drp1 from translocating from the cytoplasm to the mitochondria, thus inhibiting mitochondrial fission. As mentioned above, Fis1 cooperates with Drp1 to mediate mitochondria. Disatnik et al. found that P110 can weaken the interaction between Drp1 and Fis1, consequently preventing left ventricular remodelling and reducing the infarct size in rats following MI. Some recent studies have found that the inhibition of Fis1 expression can also inhibit fission.

In conclusion, mitochondrial fission can be weakened by reducing the activity or expression of Drp1 using various inhibitors.
of mitochondrial permeability transition pore (MPTP) to expedite the release of various apoptosis factors, which induce apoptosis and lead to cardiomyocyte necrosis. In addition, research models of Drp1 are currently primarily limited to small rodents, with little research involving large mammals with inconsistent results. For example, Ong et al. found that there was no cardioprotective effect following Mdivi-1 therapy in small pigs because there are many affective factors (eg different dosage and administration routes), which require further detailed study.

2.2 Mitochondrial Fusion of Cardiomyocytes

Mitochondrial fusion can maintain the normal structure and function of mitochondria together with fission. Fusion relies on mitochondrial transmembrane GTP enzymes, including mitochondrial fusion protein 1 (Mfn1) and mitochondrial fusion protein 2 (Mfn2), which mediate outer mitochondrial membrane (OMM) fusion, as well as optic atrophy 1 (OPA1), which mediates inner mitochondrial membrane (IMM) fusion. 48

Mitochondrial fusion protein (Mfn, Mfn1 and Mfn2) is a highly conserved transmembrane GTP enzyme encoded by the Mfn gene that is expressed in large quantities in the myocardium. Moreover, Mfn is located in the outer mitochondrial membrane and participates in outer mitochondrial membrane fusion. Chen et al. found that mitochondrial fusion was inhibited after a knockout of the Mfn gene, which resulted in mitochondrial fragmentation and reduced volume, which indicated that Mfn is important in mitochondrial fusion.

OPA1 is a motilin-related GTP enzyme located in the inner membrane of the mitochondrial cristae and participates in the fusion of the mitochondrial inner membrane. Studies have indicated that inhibition of OPA1 expression can lead to significant changes in mitochondrial morphology (eg the rupture of mitochondrial cristae structure and the increase in mitochondrial fragmentation phenomenon). At the same time, there is a loss of the mitochondrial membrane potential and a distinct decline in mitochondrial function. 50 Therefore, OPA1 is also a critical protein involved in mitochondrial fusion and the function.

Mitochondrial fusion of cardiomyocytes can be divided into two steps (Figures 2 and 3): (1) OMM fusion: when two mitochondria are in close contact, the GTP domain of Mfn binds to GTP, resulting in the conformational change of Mfn, and subsequently, GTP hydrolysis promotes the formation of Mfn dimer, thus mediating the OMM fusion; (2) IMM fusion: after OMM fusion, OPA1 forms a polymer instantaneously to induce IMM curvature, which leads to lipid fusion of two IMM to form a fusion pore, thus mediating IMM fusion, and the specific mechanism is still unclear. 51

2.2.1 Mitochondrial Fusion after MI

Studies have revealed that hypoxia injury can decrease mitochondrial fusion in cardiomyocytes (Figures 2 and 3). Wang et al. found that the structure of the mitochondrial network of myocardial cells was obviously broken, the number of mitochondria increased and the volume decreased in a mouse model of cardiac I/R injury. Studies have found that after MI, the expression of Mfn1 was increased by drug intervention, which promoted mitochondrial fusion and significantly improved mitochondrial function. 53 Okatan et al. found that I/R caused a substantial decrease in Mfn2 expression, thereby decreasing mitochondrial fusion. These findings suggested that the abnormal expression of Mfn might be related to a decrease in mitochondrial fusion after MI. In contrast, Olmedo et al. found that MG132, a proteasome inhibitor which can inhibit the degradation of Mfn2, or the overexpression of Mfn2 could lessen the broken mitochondrial network of cardiomyocytes and promote mitochondrial fusion. 32,55 In summary, Mfn is a cardiac protective factor and accelerating the level of Mfn after MI is conducive to improving heart function. However, recent studies indicated that short-term knockout of Mfn1/2 can increase mitochondrial resistance to MPTP opening during MI, reduce calcium overload and oxidative stress and protect the heart from MI. These studies are contrary to the above
results, which may be related to the intervention time of Mfn1/2. Importantly, long-term depletion of Mfn1/2 is not beneficial to the heart which can lead to cardiac arrest.\textsuperscript{56,57}

OPA1, which mediates inner mitochondrial membrane fusion, is abundantly expressed in the heart. After I/R injury, the expression of OPA1 decreases and mitochondrial fusion is also significantly inhibited.\textsuperscript{15,43,58} Guan et al\textsuperscript{15} found that in myocardial I/R injury, the up-regulated expression of mitochondrial calcium uniporter (MCU) facilitates calcium influx, which causes mitochondrial calcium overload. This results in activation of a calcium-dependent protease to inhibit OPA1 expression and ultimately leads to decreased mitochondrial fusion. It is suggested that the modulation of mitochondrial fusion by the MCU-calpain-OPA1 signalling pathway may be one of the mechanisms of cardiac I/R injury.

In addition, some studies have reflected that the N-terminal imported peptide of OPA1 can be broken down into a long fragment (L-OPA1) and a short fragment (S-OPA1). L-OPA1 can interact with Mfn1/2 to jointly mediate mitochondrial fusion, whereas S-OPA1 can inhibit L-OPA1 function and mitochondrial fusion.\textsuperscript{59-61} After MI, the expression of mitochondrial membrane protein 1 (OMA1) increases, which can drive the transformation of L-OPA1 into S-OPA1, so as to inhibit the mitochondrial fusion and result in excessive division.\textsuperscript{43,62-65} It has been further demonstrated that there is increased transformation of L-OPA1 into S-OPA1 after MI, which can lead to decreased mitochondrial fusion, which is also an important pathological process of myocardial injury (Figure 3).

In general, the abnormal expression and function of Mfn1/2 and OPA1 play an important role in I/R injury. Therefore, promoting Mfn2 or OPA1 expression and the transformation of OPA1 may represent a potential therapeutic target for MI.

\textbf{2.2.2 | Application in MI Therapies}

As mentioned above, Mfn1/2 can be a potential target. Notch1 (a key molecule known to protect heart from IR), microRNA-140 inhibitor and long non-coding RNAs Malat1 can improve mitochondrial membrane potential and protect mitochondrial and heart function by up-regulating Mfn1 expression.\textsuperscript{53,66,67} Ferreira et al\textsuperscript{68} designed a peptide named SAMβA that selectively antagonizes the association between beta II protein kinase C (βIIPKC) and Mfn1 to deactivate Mfn1, thus attenuating heart failure after MI. Okatan et al\textsuperscript{54} initially found that azoramide can induce an elevation of Mfn2 in the myocardium to promote the fusion of mitochondria after I/R, which ultimately provided cardiac protection. Therefore, azoamine may represent a new regulatory drug for MI treatment. In addition, Manechote et al\textsuperscript{69} found that the administration of M1, the promoter of the mitochondrial fusion gene, before and after myocardial ischaemia, and after myocardial reperfusion, could up-regulate the expression of Mfn and reduce the infarct size.

OPA1 may also be a new therapeutic target. Zhang et al\textsuperscript{58} found that an injection of melatonin into the enterocoele before the induction of myocardial I/R in mice can up-regulate OPA1 expression and enhance mitochondrial fusion after reperfusion injury. Moreover,
this protective effect was obviously weakened in OPA1 knockout cells, which indicates that OPA1 is indispensable in the process of melatonin-regulated mitochondrial fusion. When studying its mechanism, the authors found that I/R can lead to the down-regulation of Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) and OPA1. Melatonin can reverse this effect, and the melatonin-regulated effect of OPA1 is significantly decreased after inhibiting AMPK. These findings further indicate that melatonin can modulate OPA1 by activating the AMPK signalling pathway. It has been well-established that melatonin has some important functions (eg scavenging free radicals and antioxidation) and few side effects, which provides insight into novel targets for the development of new drugs for MI.70,71 Similarly, irisin, a hormone secreted by muscle, and vitexin, a traditional Chinese medicine that has been used for the treatment of cardiovascular diseases, have all been shown to improve mitochondrial function by increasing the expression of OPA1.72,73 In addition, Wang et al74 found that 7,8-dihydroxyflavone (7,8-DHF), a natural flavonoid, can promote an increase in phosphorylated protein kinase B, which inhibits the OMA1 activity induced by ischaemia and hypoxia. Deactivated OMA1 thus up-regulates L-OPA1 and promotes mitochondrial fusion. Therefore, this may also provide a new idea for MI therapy.

The balance of mitochondrial dynamics requires the joint regulation of both fission and fusion. Nevertheless, the mechanism of balance regulation remains unclear yet. Some scholars indicate that fission and fusion are two independent processes, of which their rate is balanced. When one process is down-regulated, the frequency of another process will increase.74 Some studies have found that simultaneous interfering with fusion-related and fission-related proteins can maintain mitochondrial homeostasis. For instance, Gao et al75 found that C-Phycocyanin, a type of algae extract, can elevate the expression of OPA1 and Mfn2, and decrease the expression of Drp1 and Fis1 protein, so as to prevent excessive fission of mitochondria. Similarly, Zhao et al76 found that continuous short-term exercise after MI in old mice can inhibit Drp1 expression and increase OPA1 expression, thereby significantly ameliorating the morphology and function of mitochondria. In addition, Naruse et al77 found that increasing the expression of GLP-1 in the intestine after heart failure caused by hypertension can both boost the expression of OPA1 and Mfn1, as well as accelerate the phosphorylation and deactivation of Drp1, subsequently improving mitochondrial function. However, whether the increase in GLP-1 expression can function in MI by modulating mitochondrial fission and fusion simultaneously still remains to be studied.

In conclusion, the regulation of fusion-related proteins can ameliorate the apoptosis of myocardial cells after I/R. We speculate that the regulation of other fusion-related proteins can also be used as therapeutic targets, which requires further exploration.

3 | MITOPHagy OF CARDIOMYOCYTES

Mitophagy is the selective removal of damaged or ageing mitochondria through the lysosomal pathway, which is an important process required to maintain mitochondrial homeostasis. This includes cells receiving stimulating signals to form autophagy bodies that specifically recognize mitochondria to be removed. Subsequently, autophagy bodies wrap around abnormal mitochondria and turn to lysosomes to mitochondria. In particular, the specific recognition of mitochondria to be removed by autophagy bodies is a critical step in mitophagy.78,79

3.1 | Mitophagy of Cardiomyocytes

PTEN-induced putative kinase 1 (PINK1), a serine/threonine-protein kinase and Parkin, an E3 ubiquitin ligase, are primarily expressed in high energy-consuming organs, such as the heart and brain.80 After mitochondrial damage, the membrane potential decreased whereas the expression of PINK1 in OMM increased. PINK1 phosphorylates ubiquitin to activate Parkin, directly collecting autophagy receptor (eg NDP52) or labelling OMM protein by ubiquitination to collect the autophagosome receptor (eg 62/SQSTM1). This is then selectively transferred to damaged mitochondria and mediates the disruption of OMM induced by the proteasome and the degradation of most proteins in outer membrane space. Subsequently, IMM protein becomes the target of autophagy through binding with microtubule-associated protein light chain 3-II (LC3-II), thus inducing mitophagy. It is suggested that the PINK1/Parkin plays an important role in the removal of damaged mitochondria in normal cells (Figure 4).81-83

In addition, FUN14 domain-containing protein 1 (FUNDC1) and Bcl-2 [B-cell leukaemia/lymphoma 2]/adenovirus E1B 19KD-interacting protein 3 (BNIP3) are involved in Parkin-independent mitophagy. FUNDC1, a type of outer mitochondrial membrane protein, is involved in hypoxia-induced cardiomyocyte apoptosis and mitophagy.84 BNIP3 is a mitochondrial outer membrane protein involved in a variety of pathological processes, such as cardiomyocyte apoptosis and myocardial ischaemia.85 FUNDC1 and BNIP3 are mainly involved in mitophagy in pathological states mainly through interaction with LC3-II.83 Respectively, FUNDC1 is phosphorylated and inactivated in mitochondria of normal cells without affecting mitophagy. BNIP3 is also involved in mitochondrial clearance of mature red blood cells.83,86

3.2 | Mitophagy after MI

As mitochondria are the primary sites of ROS production, the opportune removal of abnormal mitochondria can decrease ROS production and provide an energy supplement when suffering from myocardial ischaemia and I/R, which plays an important role in maintaining normal cell growth.87 A variety of mitophagy-related molecules participate in the selective clearance of mitochondria. Thus, regulating these molecules for controlling mitophagy may become an important method for the treatment of MI. Recently, the three most studied pathways are FUNDC1, BNIP3 and PINK1/Parkin.
First, Zhang et al. further found that the autophagy of FUNDC1-knockout mice was significantly inhibited under hypoxia, suggesting that FUNDC1-dependent mitophagy plays an important role in hypoxia. Zhou et al. found that reperfusion could phosphorylate and inactivate FUNDC1, suggesting that an inhibition of FUNDC1-dependent mitophagy at this stage could lead to serious mitochondrial damage. Liu et al. further found that hypoxia could induce the dephosphorylation and activation of FUNDC1 in cardiomyocytes to enhance its interaction with LC3, which was induced by autophagy, thus increasing mitochondrial clearance. Moreover, Yu et al. found that the upregulated expression of mammalian STE20-like kinase 1 (Mst1), a protein kinase, after MI could inhibit the removal of damaged mitochondria by decreasing the activity of FUNDC1. After knocking out the MST1 gene, the infarct size was significantly reduced, which further illustrates that Mst1 is the upstream inhibitor of FUNDC1 and plays a crucial role in protecting the heart after MI by regulating Mst1 to properly inhibit mitophagy. The above studies show that appropriately enhancing mitophagy after MI and I/R can reduce apoptosis through FUNDC1, which may become potential therapeutic targets of MI.

Second, Lee et al. found that when the level of BNIP3 increased, there was an increase in mitochondrial membrane permeability and mitophagy, suggesting that BNIP3 is correlated with mitophagy. Zhang et al. and Song et al. respectively found that following myocardial I/R, increasing the expression of HIF-1α or inhibiting the expression of receptor-interacting protein kinase 3 (Ripk3), a cardiac apoptosis-related programmed necrosis protein, could elevate downstream BNIP3 expression, thereby increasing the clearance rate of damaged mitochondria in cardiomyocytes. These findings provide further indication that BNIP3 mediates mitophagy and modulating HIF-1α, or that Ripk3 can control the activity of BNIP3. Instead, more and more studies have proved that BNIP3 activation or upregulation can induce mitochondrial dysfunction. For example, Li et al. indicated that hypoxia-induced upregulation of BNIP3 expression in cardiomyocytes, and the depletion of BNIP3 improved hypoxia-induced cell damage. Cheng et al. found that BNIP3 knockout can reduce the expression of collagen, ANP, BNP and pro-apoptotic protein in myocardial tissue of MI.

Third, Zhu et al. found that the phosphorylation level of Parkin decreased after hypoxia injury, whereas overexpression of Parkin can attenuate the opening of MPTP induced by hypoxia, and inhibition of upstream Ripk3 can enhance the phosphorylation of Parkin and improve cardiac function by promoting AMPK phosphorylation. On the contrary, Yao et al. found that I/R can induce the expression of PINK1/Parkin and an increase in mitochondrial autophagy. Some studies have shown that down-regulating PINK1 and Parkin translocation to mitochondria could attenuate mitophagy and protect cardiac function after I/R.

The above studies present different controversial results. The role of mitophagy activation on hypoxic cardiomyocytes is not clear, which brings difficulties to the follow-up treatment research. It is known that autophagy is a double-edged sword. Appropriate enhancement of autophagy can protect cells, whereas excessive
enhancement or prolonged duration of autophagy can induce apoptosis, leading to tissue necrosis. Nevertheless, how to control the treatment time is a serious problem to be solved. In an article published on Cell in 2019, it is proposed that the beneficial effect of autophagy induction is based on MPTP closure and mitochondrial permeability reduction. Although there is a lack of research on the role of mitophagy in MI, we speculate that the effect of autophagy may be related to the cellular or mitochondrial environment. Moreover, BNIP3 has been proved to be related to MPTP opening in mitochondria, which can promote apoptosis, further proving our conjecture.98

3.3 | Application in MI Therapies

Li et al99 found that when suffering from myocardial hypoxia, pigment epithelium-derived factor (PEDF) can up-regulate FUNDC1 via activating protein kinase C, thereby decreasing the number of damaged mitochondria and increasing the tolerance of myocardial hypoxia. During the reperfusion stage, Zhou et al88 found that the inhibition of tyrosine kinase 2α can promote the dephosphorylation and activation of FUNDC1 to accelerate autophagy and ameliorate cardiomyocyte function. In contrast, Zhou et al100 found that melatonin can dephosphorylate and inactivate FUNDC1 to weaken mitophagy through up-regulating platelet peroxisome proliferator-activated receptor-γ (PPAR γ), ultimately reducing the platelet activity and the formation of thrombus after ischaemia and reperfusion. The above studies show that the function of FUNDC1 in MI has a duality in that the activation of FUNDC1 can benefit cardiomyocytes, but harm platelets. This suggests that we should pursue specific regulators for different cell types. For example, we can identify the regulators which target characteristically upstream regulatory signals of FUNDC1 in different cells, so as to improve cell function.

As mentioned above, BNIP3, which was found to be regulated by HIF-1α and Ripk3, plays an important part in mitophagy. Moreover, Yang et al101 found that sevoflurane, an inhaled anaesthetic, can restore BNIP3 expression by up-regulating HIF-1α and promote mitophagy before reperfusion treatment in mice with MI. In addition, HIF-1α selective inhibitors can block this protective effect, which provides a new option for preoperative anaesthetic with MI. Similarly, Liu et al102 found that panax notoginseng saponins, a type of Chinese medicine that has been used for the clinical treatment of MI, can also protect the heart by up-regulating HIF-1α/BNIP3. On the other hand, Shin et al102 found that after transfecting microRNA-105 into myocardial I/R cells, microRNA-105 could be coupled with Rip3 and BNIP3 mRNA, finally increasing BNIP3 expression and decreasing apoptosis. On the contrary, Jin et al44 found that DUSP1 could inhibit BNIP3 phosphorylation by inhibiting JNK pathway, thus improving mitochondrial function. Yeang et al104 found that E60, an antioxidant phospholipid antibody, can inhibit the expression of BNIP3 and reduce the infarct size after I/R by inhibiting oxidized phospholipids. Other drugs such as curcumin and dihydromyricetin also play the same role.105,106 In conclusion, BNIP3-mediated mitophagy has completely different effects. PINK/Parkin can mediate mitophagy during MI. It has been found that cardiac resynchronization therapy following heart failure caused by MI and berberine, which belongs to the traditional Chinese medicine, can all induce an increase in PINK/Parkin expression and mitophagy.107,108 Yao et al80 found that an injection of hydrogen-rich saline can attenuate inflammation and apoptosis of the damaged myocardium by enhancing mitophagy. The authors further found that after knocking out the PINK gene, the protective effect of hydrogen was partially reversed, suggesting that hydrogen can enhance PINK/Parkin-mediated mitophagy to attenuate MI. Particularly, Zhao et al106 further found that proper exercise can ascend the expression of PINK1/Parkin and accelerate the removal of damaged mitochondria after MI; however, this effect is significantly related to the time and frequency of exercise. Differing amounts of exercise may have various effects on mitophagy and the outcome of diseases. An excessive amount of exercise may lead to mitochondrial dysfunction and the attenuation of mitochondrial function by short-term exercise is not permanent, which suggests that exercise programmes should be reasonably formulated in clinical treatment.76,109-113 Besides, Ferulic acid or G protein-coupled oestrogen receptor 1 (GPER) can protect cardiac function after I/R by down-regulating PINK1 and Parkin translocation to mitochondria and reducing mitophagy,96,97 which gives us a problem again that how to control mitophagy via Parkin.

Modulating mitophagy and selectively targeting the heart may represent a new direction for the treatment of MI. In addition, some traditional Chinese medicine that has been proven to regulate mitophagy (eg berberine and panax notoginseng saponins) has been used clinically,108,114 and other clinically relevant drugs are still under study. East et al115 summarized that some compounds, including carbonyl cyanide m-chlorophenylhydrazone and antimycin/oligomycin, can non-specifically induce mitophagy; however, they have a high degree of toxicity and thus cannot be applied in the clinical treatment of MI. In addition, the authors discovered a mitophagy inducer (PMI), which could promote the mitophagy of both nerve and liver cells; however, there has not been any therapeutic research in an MI model.116 Notably, there are still controversies about the regulation of mitophagy in the heart. The role of BNIP3 in regulating mitophagy in MI remains exclusive. This kind of mitophagy may occur in a specific environment and at a specific time, and BNIP3 has a significant role in promoting apoptosis. More studies believe that inhibition of BNIP3 will bring beneficial effects. This makes it more difficult to treat MI with BNIP3 as the target. More experiments may be needed to prove which regulation is dominant after MI and cardiac I/R.117

4 | CONCLUSION

Increased attention has been paid to the role of mitochondrial quality control in MI, which provides a variety of therapeutic targets for the treatment of MI, whereas all aspects of mitochondrial quality control in MI, such as mitochondrial fission/fusion and mitophagy, are not isolated. For example, mitochondrial fission/fusion and mitophagy are interrelated. Mitochondrial fission is significantly increased after MI. Twig
et al.44 found that mitochondrial fission can produce non-functional depolarized mitochondria, of which the morphology was changed, membrane potential was lost, the OPA1 expression was decreased and the fusion ability was significantly weakened, finally becoming the target of mitophagy. In general, fission can promote mitophagy and remove depolarized mitochondria. In addition, the fusion ability of target mitochondria is significantly weakened before autophagy, which suggests that various processes of mitochondrial quality control should be considered, rather than treating them as an isolated unit, providing us with new ideas for the treatment of MI. However, there are currently no specific drugs that have been found for clinical treatment, and further experiments are needed to identify novel drugs.

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CONFLICT OF INTEREST
No conflict of interest was declared.

AUTHOR CONTRIBUTION
Chunfang Wang: Conceptualization (lead); Supervision (lead); Writing-original draft (lead); Writing-review & editing (lead). Leiling Liu: Writing-review & editing (supporting). Yishu Wang: Writing-review & editing (supporting). Danyan Xu: Supervision (lead); Validation (lead).

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ORCID
Danyan Xu https://orcid.org/0000-0003-2113-0800

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