Mitochondria-associated endoplasmic reticulum membranes: Emerging regulators of cardiac microvascular ischemia/reperfusion injury (Review)

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Abstract. Ischemic heart disease remains the leading cause of global disease burden among cardiovascular disorders. In addition to cardiomyocyte injury, ischemia-reperfusion (I/R)-induced microvascular damage plays a crucial role in determining tissue dysfunction and overall prognosis. Mitochondria-associated endoplasmic reticulum membranes (MAMs), specialized contact sites between the ER and mitochondria, are now recognized as key regulators of cardiovascular pathophysiology. The present review summarized current knowledge of the structure of MAMs and their effects on endothelial cells under hypoxia/reoxygenation conditions. Particular attention was given to their role in regulating mitochondrial quality control processes, including fission, fusion, oxidative stress, mitophagy and Ca^{2+} homeostasis, within the context of cardiac microvascular I/R injury. Targeting MAMs may represent a promising strategy for microvascular protection in ischemic heart disease.

Contents

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1. Introduction

Cardiovascular diseases (CVDs) continue to be the primary cause of death worldwide, with myocardial infarction contributing markedly to global morbidity and mortality (1). The timely restoration of coronary blood flow through thrombolytic therapy or percutaneous coronary intervention (PCI) has been proven to effectively reduce infarct size (2). However, ischemia/reperfusion (I/R) injury induces secondary myocardial damage, mainly affecting cardiomyocytes and cardiac microvascular endothelial cells (CMECs). This secondary injury is characterized by myocardial stunning, microvascular dysfunction, reperfusion arrhythmias and lethal reperfusion injury (3). Microvascular I/R injury involves CMEC apoptosis, microvascular spasm and impaired perfusion, all of which exacerbate myocardial damage after reperfusion (4). Beyond conventional clinical risk scores and left ventricular ejection fraction, microvascular obstruction due to I/R injury has been identified as an independent predictor of infarct size and poor prognosis (5-7).

Mitochondria-associated endoplasmic reticulum membranes (MAMs) serve as key signaling hubs involved in fundamental cellular processes, including calcium (Ca^{2+}) and lipid homeostasis, mitochondrial dynamics and energy production (8). During cardiac microvascular I/R injury, abnormal mitochondrial dynamics and impaired mitophagy (2,9) further exacerbate microvascular dysfunction by compromising vascular patency, altering vascular tone

and amplifying inflammatory responses (10). Further, excessive mitochondrial Ca^{2+} uptake leads to overactivation of the electron transport chain (ETC) and excessive generation of reactive oxygen species (ROS) (11). This pathological cascade leads to the collapse of the mitochondrial membrane potential and promotes the opening of the mitochondrial permeability transition pore (mPTP) (12). Thus, mitochondrial dysfunction represents a central mechanism in microvascular I/R injury (13,14) (Fig. 1).

The endoplasmic reticulum (ER), the largest cellular organelle composed of a continuous network of tubules and sheets, plays a fundamental role in protein folding, lipid synthesis and Ca^{2+} storage (15,16). Maintenance of ER proteostasis is vital for secretory function, whereas prolonged ER stress drives cellular dysfunction and contributes to the pathogenesis of CVD (17). Research highlights dynamic crosstalk between the ER and mitochondria as a critical regulator of cellular homeostasis (18). First described by Wilhelm Bernhard in 1956 as the connection between the ER and mitochondria (19), MAMs were later isolated as unique subcellular structures using subcellular isolation techniques and density-gradient centrifugation (20). Disruption of MAM integrity impairs ER-mitochondria communication, leading to homeostatic imbalance and contributing to various diseases, including cancer, neurological disorders and CVDs (21). The present review summarized recent advances in MAM-mediated regulation of mitochondrial quality control and Ca^{2+} signaling, offering valuable insights for future investigations into the molecular mechanisms with particular emphasis on potential therapeutic strategies.

2. Mitochondria and MAMs in cardiac microvascular I/R injury

Mitochondria are central to cellular bioenergetics and are traditionally described as the powerhouse of the cell, producing ATP through oxidative phosphorylation driven by the ETC and oxygen reduction (22). As well as ATP generation, mitochondria regulate apoptosis, Ca^{2+} homeostasis, inflammation and immune responses (23). In microvascular endothelial cells, which primarily depend on glycolysis for energy, mitochondria exhibit a punctate distribution pattern (24). Mitochondria consist of a double membrane defining four compartments: the outer mitochondrial membrane (OMM), the intermembrane space (IMS), the inner mitochondrial membrane (IMM) and the matrix. The OMM contains porins that mediate exchange with other organelles (25), the IMS stores key apoptotic factors (26) and the IMM, with its highly invaginated cristae, harbors the ETC and ATP synthase, enabling efficient ATP synthesis (27). The IMM is characterized by its low permeability and high cardiolipin content (28).

MAMs are dynamic contact sites where the OMM and ER membranes are closely apposed but remain distinct (29). The distance between the two membranes ranges from ~10 nm up to 80-100 nm (29), as identified by electron microscopy, with smooth ER-mitochondria contacts typically closer (10-15 nm) than rough ER contacts (20-30 nm) (30), suggesting that gap width influences the degree of functional coupling (31). Based on the extent of ER-mitochondria membrane contact, MAMs are categorized into three forms: Type I (partial wrapping, ~10% OMM coverage), Type II (extensive contact, ≤50% of the mitochondrial surface) and Type III (complete encapsulation) (32). Type I predominates in most cells, encompassing 10-15% of the OMM (31).

Studies underscore the therapeutic potential of targeting MAMs to mitigate hypoxia-induced endothelial injury (33). Hypoxia directly damages endothelial mitochondria, characterized by elevated mitochondrial ROS (mROS), impaired mitophagy, reduced mitochondrial biogenesis and mitochondrial cristae disruption (34-36). Regulatory proteins and non-coding (nc)RNAs play key roles in this context. MARCH5, a key regulator of mitochondrial dynamics, apoptosis and mitophagy, protects endothelial cells against hypoxia-induced injury via Akt/eNOS signaling (37), whereas RIPK3 exacerbates damage by upregulating 1,4,5-trisphosphate receptors (IP_3R) expression, leading to Ca^{2+} overload and oxidative damage (38). The long (l)ncRNA Malat1 preserves microvascular function after myocardial infarction by regulating mitochondrial dynamics through the miR-26b-5p/mitofusin-1 (MFN1) axis (39). Similarly, the compound FL3 promotes MFN1-dependent mitochondrial fusion, stabilizes Ca^{2+} homeostasis and alleviates myocardial injury (40). These findings demonstrate that endothelial dysfunction and mitochondrial stress are closely associated with the pathogenesis of microvascular I/R injury. Targeted modulation of MAMs, therefore, represents a promising therapeutic strategy for protecting endothelial integrity and preserving cardiac function (41-43).

3. Mitochondrial dynamics and mitochondria-associated membranes

Mitochondrial dynamics and MAMs are key factors in the pathogenesis of CVDs. As a crucial component of the mitochondrial quality control (MQC) system, mitochondrial dynamics facilitates the selective removal of damaged organelles and renewal of functional ones (44). Mitochondria continuously undergo fission, fusion and degradation to preserve endothelial homeostasis in response to various cellular cues (45,46). The balance between these fusion and fission processes determines mitochondrial morphology and functionality (47-49). Enhanced fusion or reduced fission promotes the formation of an elongated mitochondrial network, whereas excessive fission or impaired fusion leads to mitochondrial fragmentation (50-52).

MAMs serve as a vital regulatory hub that coordinates mitochondrial by recruiting specific signaling molecules and effector proteins, ensuring precise spatiotemporal regulation of mitochondrial fission and fusion (53,54). Quantitative analyses indicates that >80% of fission and ~60% of fusion events occur at MAMs (55). These findings underscore their role as central hubs that coordinate mitochondrial dynamics and preserve endothelial homeostasis, particularly under stress conditions.

Mitochondrial fission in cardiac microvascular ischemia/reperfusion injury. Mitochondrial fission is markedly upregulated during myocardial I/R injury (56). This process is primarily initiated at MAMs, where the ER outlines the future division site even before dynamin-related protein 1 (Drp1) recruitment (57). Drp1 subsequently accumulates at

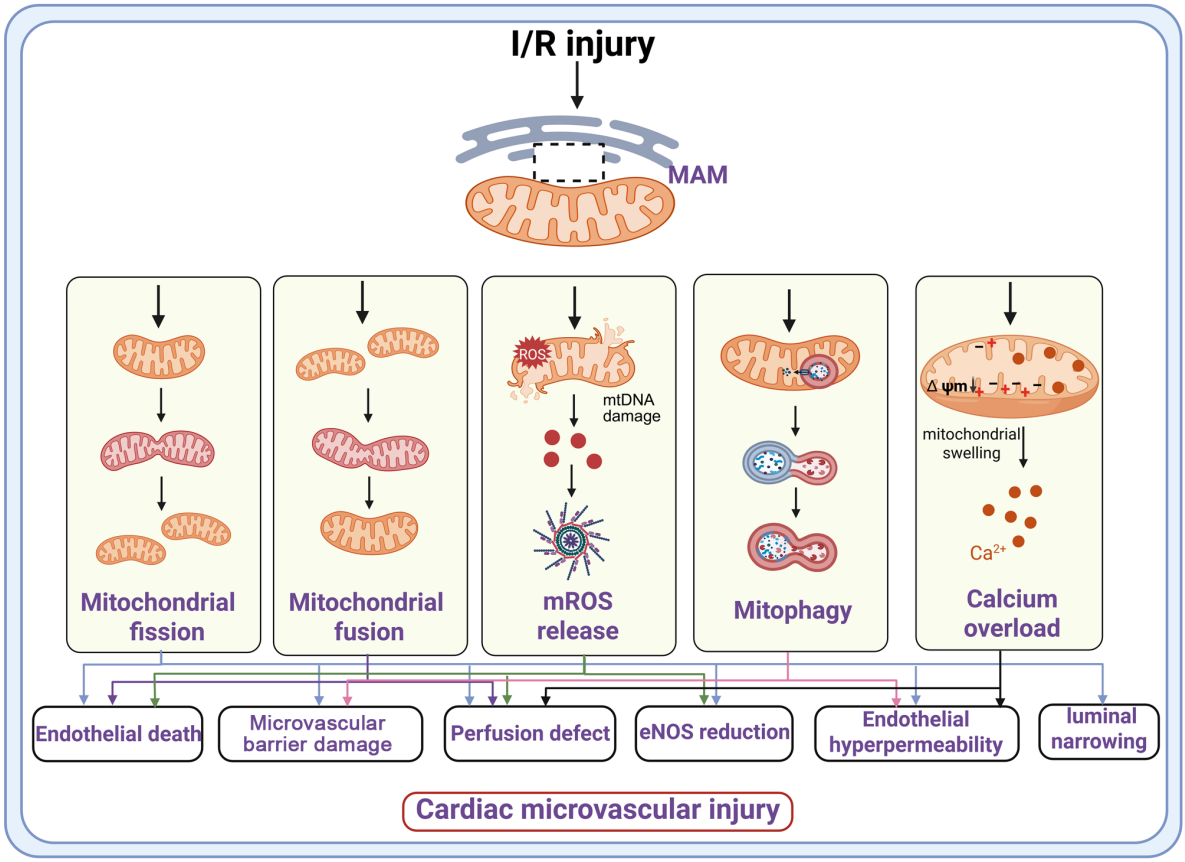

Figure 1. The pathological functions of mitochondrial dynamics, mitochondrial oxidative stress, mitophagy and calcium overload in cardiac microvascular I/R injury. I/R, ischemia-reperfusion; MAM, mitochondria-associated endoplasmic reticulum membrane; ROS, reactive oxygen species; mtDNA; mitochondrial DNA; mROS, mitochondrial ROS.

ER-mitochondria contact sites, where its fission activity is regulated by post-translational modifications (PTMs) such as phosphorylation, ubiquitination and acetylation. These PTMs are mediated by various enzymes, including cyclin-dependent kinases (CDKs) and protein kinase A (PKA) (58-60). For example, phosphorylation of Drp1 at Ser616 promotes its oligomerization and assembly into constrictive rings on the OMM (61), whereas phosphorylation at Ser637 prevents Drp1 translocation to mitochondria (62). Experimental studies have shown that inhibiting Drp1 improves microvascular endothelial function, reduces mROS and attenuates mitochondrial fission (61).

Special attention should be given to the role of mitochondrial fission proteins within the MAM-associated signaling network. During the fission process, Drp1 is actively recruited to the OMM (63). Drp1 then binds to receptors mitochondrial dynamics protein of 49 kDa (MiD49), mitochondrial dynamics protein of 51 kDa (MiD51), mitochondrial fission factor (MFF) and mitochondrial fission protein 1 (Fis1), constricting the mitochondrial membrane in a GTP-dependent manner, thereby dividing a single mitochondrion into two separate organelles (64,65). Immunofluorescence analysis of Drp1 has shown that Fis1 and MFF are key determinants of both the number and size of Drp1 puncta on mitochondria. Either MiD49 or MiD51 can independently mediate Drp1 recruitment and promote mitochondrial fission even in the absence of Fis1 and MFF (66). Modulation of mitochondrial fission protein expression markedly influences mitochondrial morphology: Suppression of MFF disrupts Drp1 foci from the OMM, leading to elongation of the mitochondrial network, whereas MFF overexpression facilitates Drp1 recruitment and promotes mitochondrial fission (67). MFF and Drp1 interact both *in vitro* and *in vivo* and MFF-dependent mitochondrial fission occurs independently of Fis1. In endothelial cells, MFF serves as the primary principal adaptor for Drp1 recruitment (67).

FUN14 domain-containing protein 1 (FUNDC1), a recently identified mitochondrial outer membrane protein, localizes to mitochondria-ER contact sites by interacting with the ER membrane protein calnexin under hypoxic conditions (68). During hypoxia, sustained mitophagy disrupts the FUNDC1-calnexin interaction, exposing the cytoplasmic loop of FUNDC1, which subsequently binds to Drp1 and initiates mitochondrial fission (68). Furthermore, at mitochondria-ER contact sites, inverted formin-2 (INF2) becomes activated and promotes actin polymerization (69). Actin filament formation between the ER and mitochondria likely generates mechanical force that facilitates mitochondrial constriction and enhance Drp1 assembly (70). Following fission, the severing and depolymerizing activity of INF2 enables the rapid clearance of actin filaments.

MFF expression is markedly increased following microvascular I/R injury (71) and transcriptional and post-translational mechanisms control both its abundance and activity. Under

I/R conditions, activation of the JNK pathway downregulates the dual-specificity phosphatase 1 (DUSP1) (72), thereby enhancing the fission-promoting capacity of MFF. Moreover, I/R upregulates the nuclear receptor 4A1 (NR4A1), which facilitates casein kinase 2α (CK2α)-mediated phosphorylation of MFF, further increasing its fission-inducing activity and exacerbating mitochondrial dysfunction and endothelial cell death (73). A summary of some proteins that mediate MAM structure and mitochondrial quality control is presented in Table I.

MFF-driven excessive fission promotes apoptosis through a number of mechanisms. Pathological fission contributes to mitochondrial outer membrane permeabilization (MOMP) and the subsequent release of cytochrome *c* into the cytosol (74,75), although whether fission precedes or follows MOMP remains unresolved. Studies suggest three major apoptotic pathways triggered by excessive mitochondrial fission. First, fission induces double-strand breaks in mitochondrial DNA (mtDNA), impairing transcription and replication. mtDNA damage disrupts ETC activity, increases proton leakage and elevates ROS generation (76,77). Second, mROS oxidize cardiolipin, decreasing its binding affinity for cytochrome *c* and facilitating its release into the cytosol, thereby activating apoptotic signaling (78). Third, mitochondrial fragmentation promotes the polymerization of voltage-dependent anion channel 1 (VDAC1) and displaces hexokinase 2 (HK2) from VDAC1 (79). These changes open the mPTP. The combined effects of oxidative stress, MOMP and mPTP activation exacerbate cardiac microvascular I/R injury, leading to impaired endothelial nitric oxide synthase (eNOS) synthesis, endothelial barrier breakdown, loss of vascular integrity, capillary obstruction and abnormal vascular permeability (80,81). Thus, MFF-mediated mitochondrial fission represents a key pathological mechanism in microvascular I/R injury and represents a potential therapeutic target (78).

In summary, excessive fission serves as a key pathological driver of I/R injury (82). Therapeutic intervention of MAM-associated molecular pathways, therefore, represents a promising strategy for attenuating cardiac microvascular I/R injury by suppressing pathological mitochondrial fission. Several agents have been shown to act through this axis. Shuangshen Ningxin formula, a traditional Chinese medicine compound, alleviates cardiac microvascular I/R injury by improving mitochondrial function through the regulation of the NR4A1/MFF/Drp1 pathway (83). Melatonin exerts protective effects against cardiac microvascular I/R injury by activating AMPKα and promoting inhibitory phosphorylation of Drp1 at Ser637, suppressing fission and enhancing ATP synthase activity. It also attenuates cardiac microvascular injury by targeting the mitochondrial fission-VDAC1-HK2-mPTP-mitophagy cascade (79). Similarly, Bax inhibitor-1 (BI1) preserves mitochondrial integrity under I/R conditions by reducing F-actin-mediated fission, suppressing xanthine oxidase (XO) activity and limiting ROS production, ultimately maintaining endothelial viability and barrier function (84). Furthermore, BI1 is also associated with microvascular protection in I/R injury via repressing Syk-Nox2-Drp1-mitochondrial fission pathways (85). The ROS-JNK-Drp1 pathway has been identified as a primary mechanism driving endothelial cell injury and mitochondrial fission during hypoxia-reoxygenation injury; its inhibition may provide a novel therapeutic strategy to prevent coronary no-reflow injury (86). Empagliflozin protects against microvascular I/R injury by suppressing mitochondrial fission via inactivation of the DNA-PKcs/Fis1 pathway (87). By contrast, pretreatment with 2'-hydroxycinnamaldehyde (HCA) reduces Drp1 expression and improves microvascular function during reperfusion (88).

MAMs exert multifaceted control over mitochondrial fission. Resident proteins and signaling cascades at MAMs facilitate mitochondrial constriction and Drp1 recruitment, promoting fragmentation. Protective mechanisms suppress pro-fission proteins or inhibit associated signaling pathways. These mechanisms collectively reduce mROS, prevent mPTP opening and preserve endothelial cell viability. The MAM-mitochondrial fission axis represents a promising therapeutic target for ameliorating cardiac microvascular I/R injury.

Mitochondrial fusion in cardiac microvascular ischemia/reperfusion injury. Compared with mitochondrial fission, mitochondrial fusion in endothelial cells during myocardial infarction has been less extensively studied. However, mitochondrial fusion is essential for mitochondrial repair and functional recovery, as it facilitates the exchange of matrix and membrane components, preserving mitochondrial integrity and maintaining bioenergetic homeostasis. Mitochondrial fusion involves the coordinated fusion of the OMM and IMM, which is regulated primarily by MFN1/2 and optic atrophy 1 (OPA1), respectively (56,89) (Table I). Mitofusin-2 (MFN2) is particularly important because it not only mediates OMM fusion but also regulates mitochondria-ER tethering at MAMs (90,91). MFN2 plays a crucial role in maintaining normal mitochondrial functions, including fusion, axonal transport, inter-organelle communication and mitosis (92). Unlike MFN1, which is confined to the mitochondrial membrane, MFN2 is distributed across the ER, OMM and MAMs. Homotypic interactions between MFN2 molecules on adjacent membranes, or heterotypic interactions between ER-localized MFN2 and mitochondrial MFN1, form dimeric or multimeric complexes that maintain an optimal distance of 10-30 nm between the two organelles (91,93). Loss or downregulation of MFN2 enhances both structural and functional coupling between the ER and mitochondria. Thus, MFN2 acts as a negative regulator of excessive ER-mitochondria tethering and its reduced expression disrupts this control, promoting aberrant and potentially harmful ER-mitochondria crosstalk (94). OPA1 then remodels the IMM, restoring membrane continuity and structural integrity. This step requires the cardiolipin-binding domain of OPA1.

Fusion of the inner and outer mitochondrial membranes is further regulated by proteolytic processing and ubiquitination (95). At the IMM, long OPA1 (L-OPA1) is cleaved at sites S1 and S2 to form short OPA1 (S-OPA1) (96,97). The AAA+ protease YME1L mediates S2 cleavage under basal conditions, whereas the stress-responsive metalloprotease OMA1 cleaves at S1, thereby disrupting the OPA1 isoform balance (98-100). Under physiological conditions, a near-equivalent ratio of L-OPA1 to S-OPA1 preserves membrane fusion activity (101,102). Pathological stimuli, particularly loss of membrane potential, activate OMA1 (103), shifting the ratio and impairing fusion, leading to fragmentation (104).

Table I. Proteins reported to directly mediate and/or regulate MAM structure and their functions.

Role	Protein	Functions and mechanisms	(Refs.)
Mitochondrial fission	Drp 1	Phosphorylates at Ser616 and dephosphorylated at Ser637 and forms a potential constriction ring.	(61,62)
		Interacts with receptors MFF, MiD49/51, and Fis 1 and mediates GTPase-dependent mitochondrial division.	(65,66)
	FUNDC1	Promotes mitochondrial fission through direct interaction with Drp1.	(69)
	INF2	INF2 becomes activated and promotes actin polymerization. Actin filament formation within the MAM likely generates mechanical force that facilitates initial mitochondrial constriction and enhances Drp1 assembly.	(70,71)
	MFF	Recruits Drp1 to mediate mitochondrial fission.	(68)
		Under I/R conditions, downregulation of DUSP1, improves the fission-promoting capacity of MFF.	(73)
		I/R upregulates the nuclear receptor NR4A1, which facilitates CK2α-mediated phosphorylation of MFF, further increasing its fission-inducing activity.	(74)
Mitochondrial fusion	MFN2	MFN2 not only mediates OMM fusion but also regulates mitochondria-ER tethering at MAMs.	(90,91)
		During I/R, knockout of MFN2 limits mPTP opening and increases cardiomyocytes' tolerance to the Ca^{2+}-induced injury.	(107)
		In other cell types or under pathological stress, silencing or deletion of MFN2 promotes Ca^{2+} transport into mitochondria, and increases susceptibility to Ca^{2+}-induced cell death.	(93)
	OPA1	OPA1 remodels the IMM, restoring membrane continuity and structural integrity.	(89)
Mitochondrial oxidative stress	NLRP3	MAMs serve as scaffolds that facilitate NLRP3 inflammasome assembly by enabling the interaction between NLRP3 and ASC.	(130)
	Ero1	Ero1 facilitates Ca^{2+} influx by activating the MCU.	(139)
		Ero1-PERK complex coordinates mitochondrial fusion, enhances ER-mitochondria interactions, restores mitochondrial bioenergetics, and modulates intracellular ROS levels.	(140)
	P66Shc	Under oxidative stress, activated PKCβ phosphorylates p66Shc at Ser36, triggering its translocation to mitochondria or the MAM, where it contributes to ROS generation.	(137,145)
Mitophagy	ATG5	Regulates the formation of autophagosomes and acts as an autophagy marker.	(163)
	ATG14	Interacts with STX17 and localizes to MAMs to facilitate autophagosome formation.	(165)
	mTORC2	Enriched at MAMs, plays a crucial role for autophagy regulation.	(164)
	PINK1	Recruits Parkin, and initiates ubiquitination of OMM proteins such as MFN2 and VDAC, thereby targeting mitochondria for degradation.	(167)
		Upon mitophagic activation, PINK1 translocates to the MAM and promotes the generation of PI3P. PI3P serves as a critical signal for autophagosome initiation.	(168)
	Gp78	A MAM-resident ubiquitin ligase, also contributes to Parkin-independent mitophagy.	(169)
	Beclin1	Increases autophagic flux and regulates ER-mitochondria interactions.	(171)

Table I. Continued.

Role	Protein	Functions and mechanisms	(Refs.)
		The serine residue at position 15 of Beclin1 can be phosphorylated by ULK1 and this modification is essential for Beclin1's association with MAMs during the mitophagic process.	(172)
	FUNDC1	Links Drp1-driven fission with mitophagy at the MAMs interface.	(69)
		Facilitates the removal of damaged mitochondria by interacting with LC3.	(176)
		FUNDC1 activates the UPR^{mt} to preserve mitochondrial quality control during reperfusion injury.	(180)

MAM, mitochondria-associated endoplasmic reticulum membrane; I/R, ischemia-reperfusion; Drp1, dynamin-related protein 1; MFF, mitochondrial fission factor; MiD49, mitochondrial dynamics protein of 49 kDa; MiD51, mitochondrial dynamics protein of 51 kDa; Fis 1, mitochondrial fission 1 protein; FUNDC1, FUN14 domain-containing protein 1; INF2, inverted formin-2; DUSP1, dual-specificity protein phosphatase 1; NR4A1, nuclear receptor 4A1; MFN2, mitofusin-2; OMM, outer mitochondrial membrane; OPA1, optic atrophy 1; NLRP3, pyrin domain-containing receptor 3; ASC, apoptosis-associated speck-like protein containing a CARD; Ero1, endoplasmic reticulum oxidoreductase 1; PERK, PKR-like endoplasmic reticulum kinase; ER, endoplasmic reticulum; ROS, reactive oxygen species; P66Shc, 66-kDa isoform of the growth factor adaptor Shc; PKCβ, protein kinase C beta; ATG5, autophagy-related protein 5; ATG14, autophagy-related protein 14; STX17, syntaxin 17; mTORC2, mechanistic target of rapamycin complex 2; PINK1, PTEN-induced putative kinase 1; PI3P, phosphatidylinositol 3-phosphate; Gp78, glycoprotein 78; ULK1, Unc-51-like autophagy-activating kinase 1; LC3, microtubule-associated proteins 1A/1B light chain 3B; UPRmt, mitochondrial unfolded protein response

MFN1 and MFN2 are not only central to mitochondrial structure but are also closely associated with angiogenic signaling pathways in vascular endothelial cells (105). Loss of MFN1/2 disrupts fusion and mitochondrial networks, leading to reduced membrane potential, impaired endothelial cell survival and reduced responsiveness to VEGF signaling, which then suppresses angiogenesis. Fusion is also essential for maintaining protein synthesis and energy metabolism, as well as preventing mitochondrial DNA loss (106). Despite these protective roles, MFN2 exerts context-dependent regulatory effects on cellular physiological and pathological processes. In cardiomyocytes, MFN2 depletion limits mPTP opening and increases tolerance to Ca^{2+}-induced injury, improving resistance to ischemia during I/R (107). In other cell types or under pathological stress, silencing or deletion of MFN2 enhances mitochondria-ER interactions, promotes Ca^{2+} transport into mitochondria and increases susceptibility to Ca^{2+}-induced cell death (93). These findings suggest that the function of MFN2 varies according to cell type and disease state. Moreover, MFN2 and OPA1 transcriptional levels are markedly reduced during I/R injury, consistent with functional inhibition of mitochondrial fusion. Regulation of mitochondrial function can mitigate hypoxic-stress-induced apoptosis (108). Overexpression of the sarcoplasmic reticulum Ca^{2+} pump sarco/endoplasmic reticulum Ca^{2+}ATPase (SERCA) in CMECs reverses MFN2/OPA1 downregulation, increases mitochondrial fusion, reduces fragmentation and improves microvascular integrity by restoring Ca^{2+} homeostasis (109).

ER stress and impaired intercellular connections are closely associated with mitochondrial fusion-related disorders. This pathogenic cascade is characterized by the loss of cardiac-specific Lon peptidase 1 (LonP1), disruption of the MAM structure, defective mitochondrial fusion and activation of the ER unfolded protein response (UPR^{ER}) (110). These interrelated changes contribute to metabolic reprogramming and cardiac structural remodeling. Fusion dysfunction also activates the nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing receptor 3 (NLRP3) inflammasome, triggering vascular inflammatory responses (111). During the early stages of I/R, impaired fusion leads to interstitial edema and endothelial cell swelling, further reducing microcirculatory perfusion (112). In female mouse models, I/R injury disrupts endothelial connections, decreases connexin 43 expression and alters the balance of MMP-3 and TIMP-1 (113,114). Restoration of MFN2 expression reverses these changes and increases endothelial progenitor cell marker expression, including platelet endothelial cell adhesion molecule 1 (CD31), vascular endothelial growth factor receptor 2 (VEGFR2), Fms-related tyrosine kinase 4 (FLT4) and Kinase Insert Domain Receptor (KDR) (114). Loss of cell junctions compromises endothelial barrier function, increasing susceptibility to platelet and coagulation system activation and exacerbating microvascular thrombosis (115). This mechanism impairs myocardial perfusion during reperfusion by promoting microvascular obstruction. Downregulation of MFN2 reduces mitochondrial Ca^{2+} overload by decreasing CypD-VDAC1-IP_3R1 interactions. However, MFN2 broadly supports endothelial integrity, microvascular structure and maintenance of fusion (116). These results suggest that MFN2 exerts a dual role in cardiac microvascular I/R injury by regulating endothelial cell metabolism, apoptosis and inflammatory responses while preserving MAM homeostasis.

Most of these findings are derived from loss-of-function studies using RNA interference to inhibit MFN1/2 or OPA1 expression in endothelial cells *in vitro* (51,117). However, the protective effects of MFN1/2- or OPA1-mediated fusion have not been conclusively validated in rescue experiments using transgenic mouse models or virus-mediated overexpression.

Moreover, interactions between mitochondrial fission and fusion in cardiac microvascular I/R injury remain poorly defined. For example, whether active induction of fusion can directly inhibit fission is unclear. Research suggests that the MFN2/Drp1 expression ratio may reflect the dynamic balance between fusion and fission (118), providing a potential avenue for further investigation; however, its clinical applicability has yet to be established.

4. Mitochondrial oxidative stress and mitochondria-associated membranes

Oxygen is transported from the bloodstream through endothelial cells to the surrounding perivascular tissues. Research indicates that endothelial dysfunction can impair this process by reducing the rate of oxygen diffusion across the arteriolar wall (119). Under hypoxic conditions, impaired respiration promotes excessive production of mROS (120). The mROS are primarily generated within the ETC of the IMM during oxidative phosphorylation (121,122). While moderate ROS levels act as second messengers in physiological signaling, excessive ROS induces oxidative stress, causing endothelial senescence and cell death. Ischemia- or inflammation-induced oxidative stress activates mitochondria-dependent apoptotic pathways, leading to further cell death (123,124). I/R injury is particularly associated with ROS accumulation. Activation of XO during reperfusion markedly increases ROS, reduces nitric oxide (NO) bioavailability and triggers microvascular spasm and impaired perfusion (125). Furthermore, mitochondrial superoxide oxidizes tetrahydrobiopterin (BH4) to dihydrobiopterin (BH2), preventing BH4 binding to eNOS. This uncoupling of eNOS decreases NO production and exacerbates vascular dysfunction (126).

Protective mechanisms also regulate oxidative stress. MAMs are implicated in multiple cardiovascular disorders, mainly by promoting oxidative stress and inflammation in cardiac tissue (127). They represent the only known binding platform for the NLRP3 inflammasome complex, contributing markedly to ROS-mediated oxidative injury (128). The NLRP3 inflammasome is composed of NLRP3, apoptosis-associated speck-like protein (ASC) and caspase-1 (129). NLRP3 is localized to the ER, whereas ASC is anchored on the OMM. MAMs serve as scaffolds that facilitate NLRP3 inflammasome assembly by enabling the interaction between NLRP3 and ASC (130). mROS are essential regulators of NLRP3 activation. They promote dissociation of thioredoxin-interacting protein (TXNIP) from thioredoxin (TRX), after which TXNIP binds to NLRP3, initiating caspase-1 activation and cleavage of pro-IL-1β and pro-IL-18 (131). This cascade drives robust inflammatory responses. In CMECs, TXNIP-dependent NLRP3 activation has been identified as a novel mechanism of injury during myocardial I/R (129). The extent of myocardial infarction and subsequent functional recovery is strongly affected by the intensity of this inflammatory response (132). Thus, NLRP3 activation serves as a critical mechanistic link between mitochondrial dysfunction and inflammation, playing a key role in microvascular dysfunction following I/R injury (128). Experimental studies demonstrate that early inhibition of NLRP3 inflammasome activity during reperfusion improves cardiac function and reduces infarct size, highlighting it as a promising therapeutic target (133).

Elevated ROS levels at MAMs can trigger the release of mtDNA and the opening of the mPTP. Within MAMs, mtDNA functions as a damage-associated molecular pattern, initiating NLRP3 inflammasome activation and downstream inflammatory signaling (134). During cardiac ischemia-reperfusion, necrotic cardiomyocytes release ATP, which binds to P2X7 receptors on neighboring non-ischemic cardiomyocytes. This interaction induces potassium ion (K^+) efflux, lowering cytoplasmic K^+ concentration. The resulting hypokalemic state activates NIMA-related kinase 7 (NEK7), promoting inflammasome assembly and NLRP3 activation (135). Moreover, decreased extracellular H^+ concentration increases Na^+/H^+ and Na^+/Ca^{2+} exchange, aggravating intracellular Ca^{2+} overload (135). This increases mitochondrial Ca^{2+} accumulation within MAMs and further stimulates ROS production. Excess ROS induces cardiolipin release from the IMM, enabling cardiolipin to bind NLRP3 and promote inflammasome formation. Inhibition of two voltage-dependent anion channel (VDAC1 and VDAC2) isoforms in the OMM markedly reduces NLRP3 inflammasome activation, caspase-1 cleavage and IL-1β production (127). These findings suggest potential therapeutic targets for reducing inflammation and improving heart function following myocardial infarction.

The MAM serves as an important site for ROS generation. Structural proteins located at the MAM, such as endoplasmic reticulum oxidoreductase 1 (Ero1) (136) and 66-kDa isoform of the growth factor adaptor Shc (p66Shc) (137), play pivotal roles in redox signaling between mitochondria and the ER, thereby regulating ROS production (Table I). Ero1α, localized at the MAM (138), facilitates Ca^{2+} influx by activating the mitochondrial calcium uniporter (MCU) (139). During early stages of ER stress, Ero1α interacts with PKR-like endoplasmic reticulum kinase (PERK), a PKR-like ER kinase, forming the Ero1-PERK complex that coordinates mitochondrial fusion, enhances ER-mitochondria interactions, restores mitochondrial bioenergetics and modulates intracellular ROS levels (140). PERK functions as a MAM-anchoring protein, promoting the formation of MAMs through oligomerization (141) and transmitting ROS signals to mitochondria (142). Furthermore, the Ero1-PERK complex reduces ER Ca^{2+} levels and promotes ER-to-mitochondria Ca^{2+} flux (143). Conversely, the absence of PERK impairs Ero1α-mediated IP_3R oxidation, thereby disturbing mitochondrial redox homeostasis (144). Similarly, under oxidative stress, activated protein kinase C β (PKCβ) phosphorylates p66Shc at Ser36, triggering its translocation to mitochondria or the MAMs, where it contributes to ROS generation (137,145). Although ROS derived from p66Shc may support short-term cellular repair responses (146), persistent activation can lead to the onset and progression of various cardiovascular diseases (147). NADPH oxidase (Nox), particularly the Nox1, Nox2 and Nox4 isoforms (148), is a major contributor to ROS production in myocardial I/R injury. Nox4 localizes to MAMs, where its expression increases under stress conditions. It functions as an endoplasmic reticulum-localized source of ROS, maintaining basal IP_3R oxidation necessary for OXPHOS and regulating redox signaling within the ER under stress conditions (149). At these sites, Nox4 facilitates Akt-mediated phosphorylation of IP_3R, which inhibits Ca^{2+}

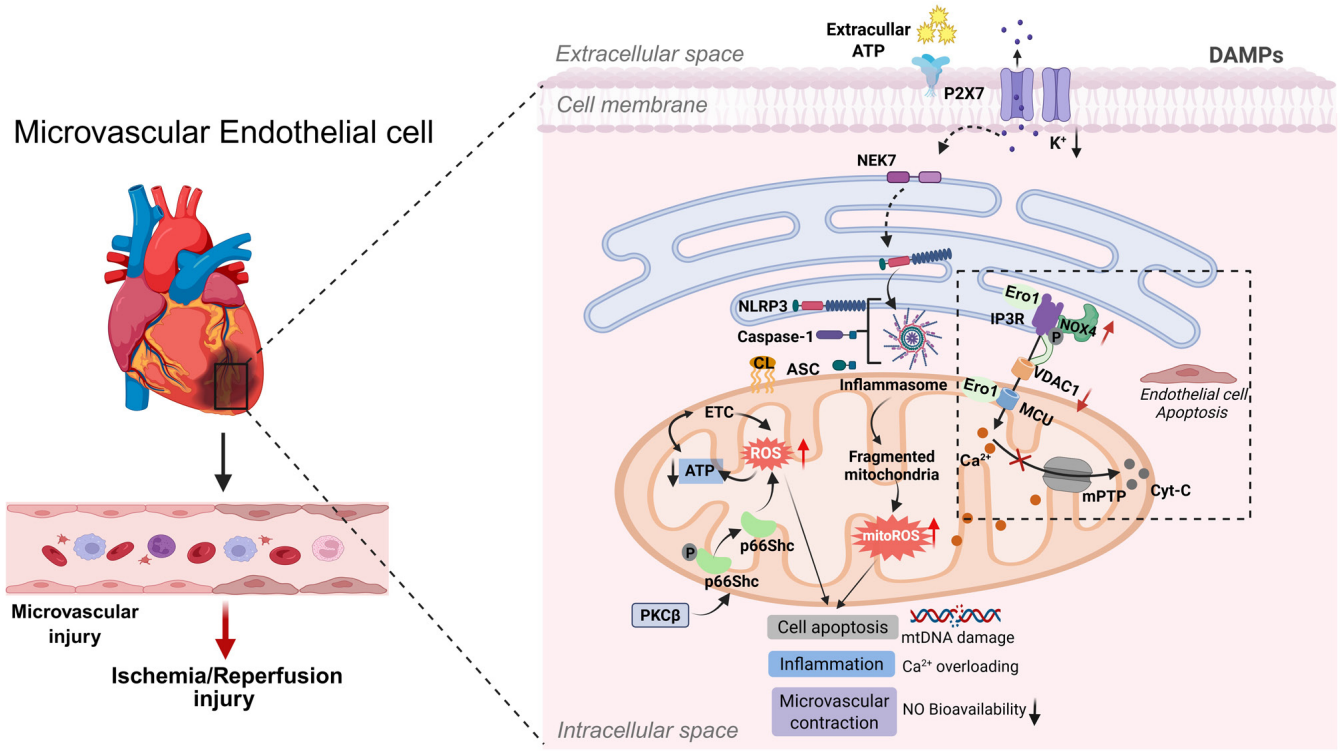

Figure 2. MAMs mediate the regulation of oxidative stress during the pathological process of cardiac microvascular I/R injury. Following cardiac microvascular ischemia, excessive Ca^{2+} transfer from the ER to the mitochondria induces calcium overload, leading to elevated mROS production. Excessive ROS stimulation further releases apoptosis-related proteins into the cytoplasm and activates the apoptotic cascade. During cardiac ischemia-reperfusion, necrotic cardiomyocytes release ATP, which binds to P2X7 receptors on neighboring non-ischemic cardiomyocytes. This interaction induces potassium ion (K^+) efflux, lowering cytoplasmic K^+ concentration. The resulting hypokalemic state activates NEK7, promoting inflammasome assembly and NLRP3 activation. Nox4 is increased at the MAM during cellular stress, where it encourages Akt-mediated phosphorylation of IP_3R to prevent calcium transfer and subsequent mPTP-dependent cell death. Furthermore, MAMs are currently the only known assembly platform for the NLRP3 inflammasome and are important mediators of oxidative damage. Structural proteins within MAMs, such as Ero1 and p66Shc, play a direct role in redox crosstalk between the mitochondria and ER, further exacerbating ROS generation. MAM, Mitochondria-associated endoplasmic reticulum membrane; I/R, ischemia-reperfusion; ER mROS, mitochondrial ROS; ROS, reactive oxygen species; NEK7, NIMA-related kinase 7; mtDNA; mitochondrial DNA; IP_3R, 1,4,5-trisphosphate receptors; NLRP3, pyrin domain-containing receptor 3; mPTP, mitochondrial permeability transition pore; Ero1, endoplasmic reticulum oxidoreductase 1; p66Shc, 66-kDa isoform of the growth factor adaptor Shc.

transfer to mitochondria and prevents mPTP-dependent cell death. This localized redox signaling underlies the protective role of Nox4 in reducing necrosis in both cardiomyocytes and intact hearts following I/R injury (149) (Fig. 2).

A number of therapeutic strategies have been reported to alleviate oxidative stress and protect cardiac function. ENPP2 regulates redox balance and mitochondrial activity, reducing hypoxia/reoxygenation injury in CMECs (150). Liproxstatin-1, a ferroptosis inhibitor, protects the myocardium by downregulating VDAC1 and restoring GPX4 (151). In a pressure-overload mouse model, ginkgolide A (GA) reduced oxidative stress and increased NO bioavailability in the heart (152). Glucagon-like peptide-1 (GLP-1) analogs, such as liraglutide, have demonstrated cardioprotective effects in clinical trials by lowering oxidative stress and vascular inflammation, preventing eNOS uncoupling and preserving endothelial function (153). Histone deacetylase 7-derived peptides promote angiogenesis and limit oxidative stress in hind limb ischemia, preserving endothelial integrity (154). Naringin (Nar) improves cardiac microvascular function, potentially by facilitating NADH ubiquinone oxidoreductase core subunit S1 (NDUFS1) translocation to mitochondria, reducing ROS and protecting endothelial cells (155). Furthermore, PSS-carrying nanoparticles minimize oxidative stress and reverse coronary microcirculatory dysfunction (156).

Regulation of ROS production and mitigation of oxidative damage constitute the primary mechanisms by which MAMs modulate cellular functions during oxidative stress responses (157). Importantly, MAM-induced mitochondrial oxidative stress does not occur in isolation; elevated ROS levels drive a shift in mitochondrial dynamics from fusion toward fission. These fragmented mitochondria become major sources of apoptotic signals and excessive mROS generation (158). Excessive ROS stimulation further amplifies mitochondrial dysfunction, leading to swelling, loss of cristae structure and rupture of the outer membrane, ultimately releasing apoptosis-related proteins into the cytoplasm and activating the apoptotic cascade (159). Further research on how MAM-inflammasome crosstalk contributes to oxidative stress is essential for elucidating the mechanisms underlying cardiac microvascular I/R injury and developing effective therapeutic strategies.

5. Mitophagy and mitochondria-associated membranes

Mitophagy, the selective autophagic degradation of damaged mitochondria, is essential for maintaining cellular homeostasis

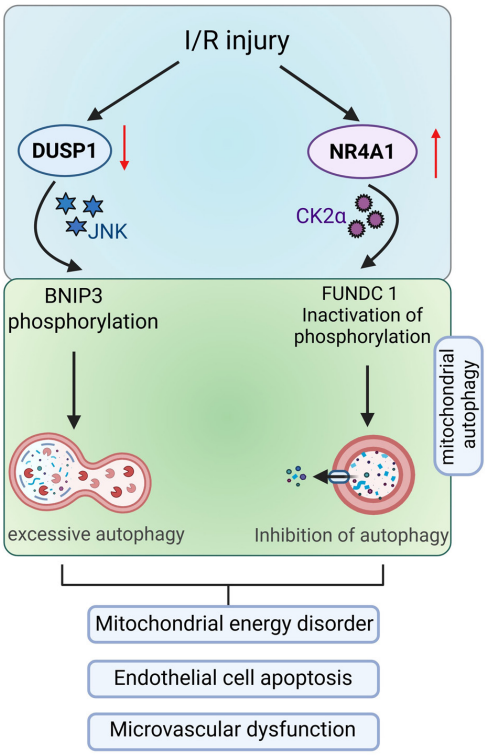

Figure 3. During I/R injury, DUSP1 and NR4A1 play distinct roles in the activation of mitophagy: DUSP1 induces mitophagy by promoting BNIP3 phosphorylation, whereas NR4A1 suppresses mitophagy through inhibition of FUNDC1 activity. These alterations contribute to mitochondrial energy disorder, ultimately leading to endothelial cell apoptosis and microvascular dysfunction. I/R, ischemia-reperfusion; DUSP1, dual-specificity phosphatase 1; NR4A1, nuclear receptor 4A1; FUNDC1, FUN14 domain-containing protein 1; BNIP3, BCL2/adenovirus E1B 19 kDa interacting protein 3.

and regulating energy metabolism. It has emerged as a potential therapeutic target for limiting I/R injury (160) and protecting the microvasculature (48). MAMs play a central role in this process by functioning as specialized subdomains where both initiation and progression of mitophagy occur. The pathway proceeds through different stages: initiation, phagophore elongation, autophagosome closure, lysosomal fusion and degradation and is regulated by a set of autophagy-related genes and proteins (161). Mitophagy signaling depends on receptor proteins at the OMM, including FUNDC1, BCL2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3), Nip3-like protein X (Nix) and mitochondrial E3 ubiquitin protein ligase 1 (Mul1), as well as the E3 ubiquitin ligase Parkin (162). Upstream regulation is closely associated with mitochondrial dynamics. Mitochondrial fission, often a prerequisite for mitophagy, is regulated by proteins such as MFF, whose activity is influenced by DUSP1 (72) and NR4A1 (73). In CMECs, NR4A1 inhibits mitophagy by suppressing FUNDC1 (73), whereas DUSP1 promotes it through BNIP3 phosphorylation (Fig. 3).

Numerous key autophagic proteins, including ATG5/14 (163) and mTORC2 (164), are enriched at MAMs, highlighting the crucial role of these contact sites as central hubs for autophagy regulation (Table I). The autophagosome marker ATG14 interacts with STX17 and localizes to MAMs to facilitate autophagosome formation (165). Similarly, PTEN-induced putative kinase 1 (PINK1)/Parkin and Beclin-1 are concentrated at these sites (166), promoting the formation of autophagosomes and aiding in the identification and removal of damaged mitochondria (166). In the PINK1/Parkin pathway, PINK1 accumulates on damaged mitochondria, where it recruits Parkin and initiates the ubiquitination of OMM proteins such as MFN2 and VDAC. This process triggers p97-dependent disassembly of MFN2 complexes from the OMM, thereby marking the damaged mitochondria for degradation (167). Upon mitophagic activation, PINK1 translocates to the MAM and promotes the generation of phosphatidylinositol 3-phosphate (PI3P) (168) by recruiting Beclin1, a key component of the class III PI3-kinase complex. PI3P, a lipid signaling molecule primarily enriched in the ER but also present at MAMs, serves as a critical signal for autophagosome initiation. Gp78, a MAM-resident ubiquitin ligase, also contributes to Parkin-independent mitophagy (169). Mitophagy mediated by the PINK1/Parkin signaling pathway plays a pivotal role in protecting against myocardial injury induced by I/R (170) (Fig. 4).

Beclin1, which is also enriched at MAMs, enhances autophagic flux and regulates ER-mitochondria interactions, functioning as a protective factor against I/R injury (171). The serine residue at position 15 of Beclin1 can be phosphorylated by Unc-51-like autophagy-activating kinase 1 (ULK1) (172), a kinase involved in mitophagy (173) and this modification is essential for Beclin1's association with MAMs during the mitophagic process. Localization of Beclin1 at MAMs ensures that autophagosome formation occurs in proximity to damaged mitochondria, facilitating their efficient sequestration and degradation (171). Furthermore, studies have shown that Beclin1-driven autophagy suppresses caspase-4-mediated apoptosis, thereby protecting microvascular endothelial cells from I/R-induced injury (174).

During reperfusion, BNIP3 levels increase and FUNDC1 expression decreases (175). This is paradoxical, as FUNDC1 is recognized as a critical mediator of protective mitophagy under hypoxic conditions. FUNDC1 facilitates the removal of damaged mitochondria by interacting with LC3 (176) (Fig. 4). Activation of FUNDC1 is regulated by multiple key post-translational modifications that act cooperatively to modulate its function. These include phosphoglycerate mutase family member 5 family member 5 (PGAM5)-mediated dephosphorylation at Ser13 (177), ULK1-mediated phosphorylation at Ser17 (178) and MARCH5-mediated ubiquitination at Lys119, all of which play crucial roles in controlling mitochondrial dynamics and mitophagy. Under hypoxic conditions, the ER-resident deubiquitinase USP19 accumulates at MAMs, where it interacts and deubiquitinates FUNDC1. This interaction leads to mitochondrial fission and counteracts the MARCH5-FUNDC1 signaling pathway (179). Under normoxic conditions, MARCH5 facilitates the degradation of excess FUNDC1, thereby preventing uncontrolled mitochondrial fission. The resulting fragmented mitochondria subsequently recruit the ULK1 complex to initiate mitophagy (68). Furthermore, FUNDC1 activates the mitochondrial unfolded protein response (UPR^{mt}) to preserve mitochondrial quality control during reperfusion injury (180). However, during reperfusion, increased RIPK3 phosphorylation of FUNDC1, impairs mitophagy and heightens susceptibility to cell death (181). Collectively, these findings underscore the

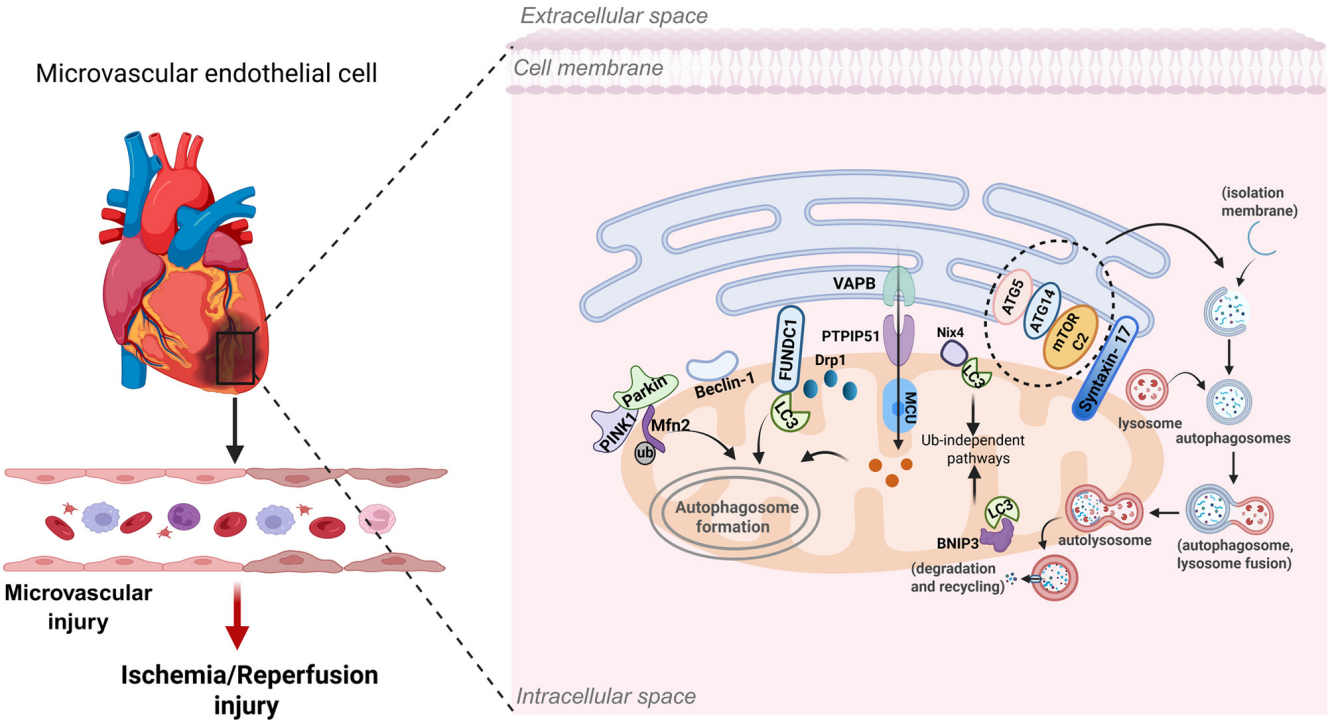

Figure 4. MAMs play a critical role in regulating mitophagy during microvascular I/R injury. The mechanism targets of autophagosome markers (ATG) 5/14 and mTOR2 are key inducers of autophagy. For example, STX 17, located on the autophagosome outer membrane can bind to ATG14 and transfer it to MAM until autophagosome is complete. Under ischemic and hypoxic conditions, PINK1 accumulates on the damaged OMM and recruits Parkin from the cytosol, which then ubiquitinates OMM proteins such as MFN2 and VDAC to promote mitophagy. As a mitochondrial membrane protein, FUNDC1 interacts with LC3 during hypoxic stress to facilitate mitochondrial mitophagy. It also recruits Drp1 to MAMs and stimulates the elimination of defective mitochondria. In addition, Beclin1, an upstream regulator of mitophagy, protects the microvascular against I/R injury. MAM, mitochondria-associated endoplasmic reticulum membrane; I/R, ischemia-reperfusion; STX 17, syntaxin 17; ATG14, autophagy related 14; OMM, outer mitochondrial membrane; MFN2, mitofusin-2; VDAC, voltage-dependent anion channel; Drp1, dynamin-related protein 1

pivotal role of FUNDC1 in the pathogenesis of I/R injury. Its context-dependent function is shown in divergent therapeutic observations. For instance, the AMP-activated protein kinase α1(AMPKα1)/ULK1/FUNDC1 axis is required to maintain endothelial homeostasis during I/R injury and empagliflozin may exert protective effects through this pathway (182). Melatonin protects against cardiac I/R injury by suppressing FUNDC1-dependent mitophagy in platelets, reducing energy production, platelet hyperactivity and thrombotic complications (183). These findings emphasize that FUNDC1 activity is not uniformly beneficial but is shaped by the cellular and pathological context. Pharmacological studies further support the dual role of mitophagy. Shenlian extract attenuates I/R injury by inhibiting the PINK1/Parkin pathway and reducing mitophagy (184), whereas the mitophagy inducer UA improves overall mitochondrial quality control and confers protection (185). These results suggest that therapeutic strategies should not aim to universally enhance or inhibit mitophagy, but rather focus on fine-tuning specific pathways, including those involving FUNDC1.

Crosstalk among various mitophagy adaptors ultimately determines the net effect of mitophagy. Fission of damaged mitochondria into smaller fragments facilitates their elimination through mitophagy (186). Autophagy and fission occur simultaneously, forming a coordinated response (187). Moderate mitophagy limits excessive fragmentation induced by pathological fission (175,188,189). Thus, fission is both a prerequisite for mitophagy activation and, when excessive, a process that can be counterbalanced by appropriately regulated mitophagy. Taken together, these findings underscore that mitophagy exerts both protective and detrimental roles depending on the signaling context. The precise contribution of specific adaptors in endothelial cells and their interactions with fission machinery remain unclear. Therefore, the controlled regulation of mitophagy represents a key area of investigation for mitigating microvascular I/R injury.

6. Ca^{2+} overloading and mitochondria-associated membranes

Mitochondrial Ca^{2+} overload is a major driver of mitochondrial dysfunction, leading to endothelial impairment and cardiomyocyte death and represents a key contributor to I/R injury (190,191). MAMs function as specialized platforms that tightly regulate intracellular Ca^{2+} homeostasis during I/R (192). For instance, disruption of MAM integrity has been shown to protect endothelial cells against I/R damage (193), underscoring their dual role in both facilitating signaling and promoting injury under pathological conditions. Ca^{2+} transfer between the ER and mitochondria occurs through a coordinated sequence of steps mediated by MAM-associated complexes. First, Ca^{2+} is released from the ER into the cytosol via ryanodine receptors (RyR) and inositol IP_3R) (194)). Second, Ca^{2+} crosses the OMM through the VDAC, the

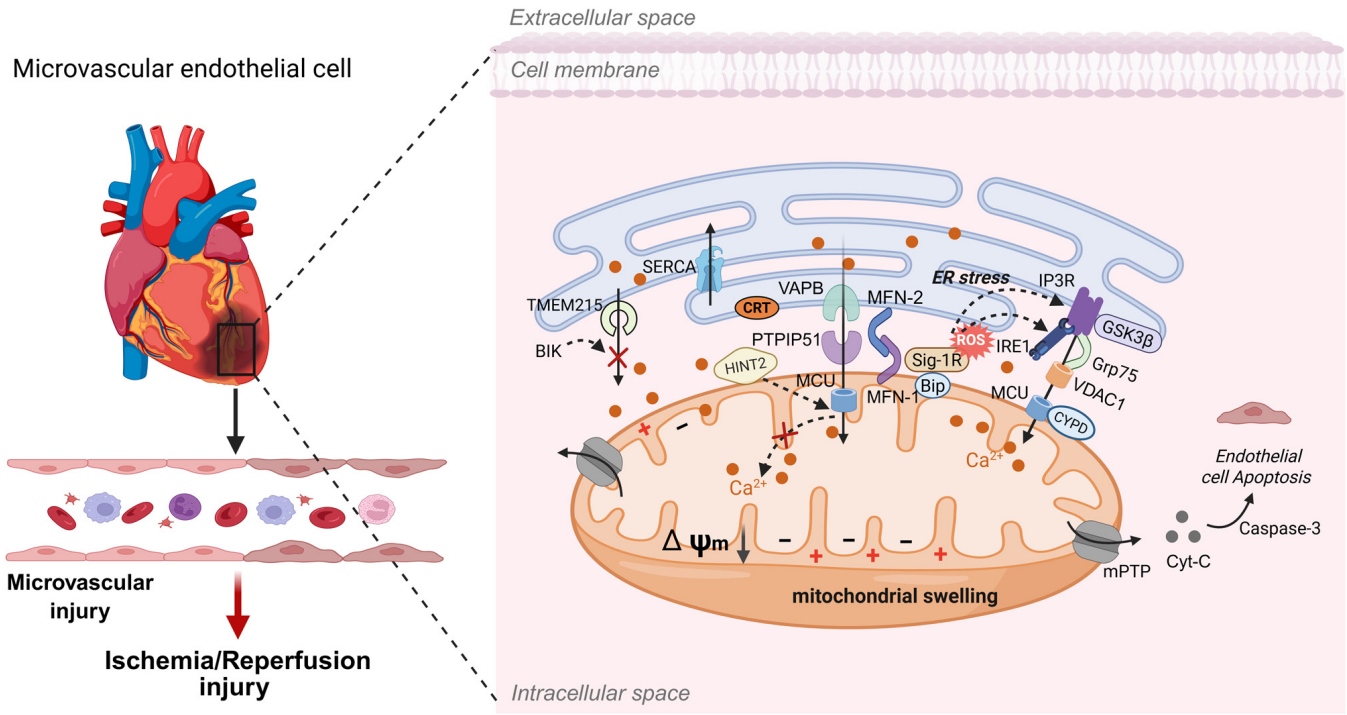

Figure 5. MAMs regulate calcium homeostasis during microvascular I/R. During hypoxia/reoxygenation, an increased interaction of the CYPD-VDAC1-GRP75-IP_3R1 Ca^{2+} complex leads to mitochondrial Ca^{2+} overload and cardiomyocyte mortality. The activity of SERCA and CRT, responsible for Ca^{2+} reuptake into the endoplasmic reticulum and Ca^{2+} storage in the ER, is inhibited. The complex of VAPB-PTPIP51-MCU mediates the transport of Ca^{2+} from the endoplasmic reticulum to mitochondria. GSK-3β can be recruited to the MAM, where it regulates IP_3R1-mediated calcium release. This regulation promotes mitochondrial Ca^{2+} accumulation and induces the opening of the mPTP. Sig-1R is a specific chaperone localized at MAMs and is functionally associated with the IP_3R-GRP75-VDAC-MCU calcium signaling axis. Therapeutically, TMEM215 protects endothelial cells by inhibiting BIK. Similarly, HINT2 protects CMECs during ischemia by directly inhibiting the MCU complex, reducing mitochondrial Ca^{2+} overload and preserving cardiac function. MAM, mitochondria-associated endoplasmic reticulum membrane; I/R, ischemia-reperfusion; CYPD, cyclophilin D; VDAC1, voltage-dependent anion channel 1; GRP75, glucose-regulated protein 75; IP_3R, 1,4,5-trisphosphate receptors; SERCA, sarco/endoplasmic reticulum Ca^{2+} ATPase; CRT, calreticulin; ER, endoplasmic reticulum; VAPB, vesicle-associated membrane protein-associated protein-B; PTPIP51, protein tyrosine phosphatase-interacting protein-51; MCU, mitochondrial calcium uniporter; GSK-3β, glycogen synthase kinase-3β; mPTP, mitochondrial permeability transition pore; Sig-1R, σ-1 receptor; TMEM215, transmembrane protein 215; BIK, Bcl-2-interacting killer; HINT2, histidine triad nucleotide-binding protein 2; CMECs, cardiac microvascular endothelial cells.

primary conduit for ions and metabolites. Finally, Ca^{2+} enters the mitochondrial matrix through the mitochondrial calcium uniporter (MCU) complex. Excessive MCU activity is a key determinant of Ca^{2+} overload and subsequent mitochondrial injury (195,196).

The IP_3R is a calcium channel located on the ER membrane and is regulated by the MAM-anchoring protein inositol-requiring enzyme 1 (IRE1). The presence of IRE1 at MAMs is critical for IP_3R function, as IRE1 acts as a scaffold that directly interacts with IP_3R within MAMs to modulate ER-mitochondria Ca^{2+} transfer and sustain cellular energy homeostasis (197,198). SERCA, the primary ER calcium pump, is equally important for maintaining calcium homeostasis by sequestering Ca^{2+} into the ER, maintaining low cytoplasmic concentrations. Experimental evidence shows that inhibiting IP_3R or increasing SERCA expression protects against I/R-induced microcirculatory dysfunction (199). These protective effects occur through the reduction of mitochondrial calcium overload and prevention of mPTP-mediated necrosis. Pharmacological interventions further support this concept: dapagliflozin (DAPA) alleviates cytosolic Ca^{2+} overload by preventing oxidation and inactivation of SERCA2. This action appears to involve inhibition of XO activity, limiting oxidative stress and preserving SERCA2 function (200).

VDAC, an outer mitochondrial membrane protein (117), demonstrates high permeability to Ca^{2+} and mediates its transfer across the IMS, thereby enabling Ca^{2+} influx into the IMM (201,202). Within the MAM, IP_3R and VDAC do not interact directly, but are functionally connected via the glucose-regulated protein 75 (GRP75) linker protein. The transfer of Ca^{2+} between the ER and mitochondria is mediated by the VDAC1/GRP75/IP_3R1 complex (203). Within this assembly, GRP75 functions as a molecular bridge, tethering IP_3R1 on the ER to VDAC1 on the OMM. This complex forms local high-Ca^{2+} microdomains that strongly promote mitochondrial Ca^{2+} uptake (203). Moreover, Ca^{2+} transfer depends on the MCU (204), forming a coordinated complex known as the IP_3R-Grp75-VDAC-MCU calcium regulatory axis. In this system, VDAC works in concert with the MCU to regulate Ca^{2+} influx into mitochondria (205). While essential for physiological signaling, excessive activity of this complex contributes to pathology.

Several molecular regulators modulate this process. Glycogen synthase kinase-3β (GSK-3β) and the Sigma-1 receptor (Sig-1R) are key MAM-associated proteins that alleviate ER stress and reduce Ca^{2+} uptake, conferring cardioprotection during I/R (206,207). GSK-3β, an enzyme responsible for phosphorylating and inactivating glycogen

Table II. Proteins in the MAM associated with calcium homeostasis.

Protein	Function	(Refs.)
IP_3R	Releases Ca^{2+} from the ER into the mitochondria, which in turn affects oxidative metabolism and energy production.	(194)
IRE1	MAM-anchoring protein IRE1 interacts with IP_3R within MAMs to modulate ER-mitochondria Ca^{2+} transfer.	(197,198)
SERCA	Overexpression of SERCA in CMECs reverses MFN2/OPA1 downregulation, increases mitochondrial fusion and improves microvascular integrity by restoring Ca^{2+} homeostasis.	(109)
	The primary ER calcium pump, is equally important for maintaining calcium homeostasis by sequestering Ca^{2+} into the ER.	(199)
VDAC	Mitochondrial fragmentation promotes the polymerization of VDAC1 and displaces HK2 from VDAC1. These changes result in the opening of the mPTP and exacerbate cardiac microvascular I/R injury.	(63)
	Inhibition of VDAC1 and VDAC2 in the OMM significantly reduces NLRP3 inflammasome activation, caspase-1 cleavage, and IL-1β production.	(127)
	Demonstrates high permeability to Ca^{2+} and mediates its transfer across the IMS, thereby enabling Ca^{2+} influx into the IMM.	(201,202)
MCU	Ca^{2+} enters the mitochondrial matrix through the (MCU) complex. Excessive MCU activity is a key determinant of Ca^{2+} overload and subsequent mitochondrial injury.	(195,196)
CypD	A key regulator of the mPTP located in the matrix. During H/R, increased interactions within the CypD-VDAC1-GRP75-IP_3R1 super-complex drive mitochondrial Ca^{2+} overload and cardiomyocyte death.	(126)
GSK-3β	Can be recruited to the MAM, where it regulates IP_3R1-mediated calcium release.	(208,209)
Sig-1R	Sig-1R is a specific chaperone localized at MAMs.	(207)
	Sig-1R stabilizes MAM structure through its interactions with VDAC1 and IP_3R.	
	Under conditions of elevated ROS, Sig-1R also interacts with reactive oxygen species, thereby activating and stabilizing IRE1.	(210)
VAPB	The OMM protein PTPIP51 and the ER protein VAPB form a structural bridge between the two organelles.	(213)
	Disruption of this complex promotes mitophagy.	
PTPIP51	Overexpression of PTPIP51 strengthens the physical connection between ER and mitochondrial, enhances ER-mitochondria coupling, and increases mitochondrial Ca^{2+} uptake through MCU activation.	(214,215)
CRT	Plays a key role in buffering and storage with its high Ca^{2+}-binding capacity.	(216)

MAM, mitochondria-associated endoplasmic reticulum membrane; IP_3R, inositol 1,4,5-trisphosphate receptor; ER, endoplasmic reticulum; IRE1, inositol-requiring enzyme 1; SERCA, sarco/endoplasmic reticulum Ca^{2+} ATPase; MFN2, mitofusin-2; OPA1, optic atrophy 1; VDAC1, voltage-dependent anion channel 1; VDAC2, voltage-dependent anion channel 2; HK2, hexokinase 2; NLRP3, pyrin domain-containing receptor 3; caspase-1, cysteinyl aspartate specific proteinase-1; IL-1β, interleukin-1 beta; IMS, intermembrane space; IMM, inner mitochondrial membrane; mPTP, mitochondrial permeability transition pore; MCU, mitochondrial calcium uniporter; CypD, cyclophilin D; GRP75, glucose-regulated protein 75; GSK-3β, glycogen synthase kinase-3β; Sig-1R, σ-1 receptor; VAPB, vesicle-associated membrane protein-associated protein-B; PTPIP51, protein tyrosine phosphatase-interacting protein-51; CRT, calreticulin

synthase (208,209), can be recruited to the MAM, where it regulates IP_3R1-mediated calcium release. This regulation promotes mitochondrial Ca^{2+} accumulation and induces the opening of the mPTP. As a result, inhibition of GSK-3β has been suggested to exert cardioprotective effects during I/R injury (206). The Sig-1R is a specific chaperone localized at MAMs (207). Overexpression of Sig-1R enhances ER-to-mitochondria Ca^{2+} flux and through its interactions with ankyrin and the ER chaperone BiP. Under physiological conditions, Sig-1R remains bound to BiP; however, under ER stress or following ER Ca^{2+}depletion, Sig-1R dissociates from BiP and binds to IP_3R instead. This interaction stabilizes IP_3R, preventing its degradation and restoring efficient Ca^{2+} transfer from the ER to mitochondria (207). Moreover, Sig-1R stabilizes MAM structure through its interactions with VDAC1 and IP_3R and provides cardioprotective benefits by mitigating MAM-mediated Ca^{2+} overload and ER stress (207). Under conditions of elevated ROS, Sig-1R also interacts with reactive oxygen species, thereby activating and stabilizing IRE1 (210).

Cyclophilin D (CypD), a key regulator of the mPTP located in the matrix. During H/R, increased interactions within the CypD-VDAC1-GRP75-IP_3R1 super-complex drive

Table III. Role of regulating MAM-related molecules in microvascular I/R injury.

Protein	Function	(Refs.)
MARCH5	Protects endothelial cells against hypoxia-induced injury via Akt/eNOS signaling.	(37)
RIPK3	Exacerbates hypoxia-induced microvascular damage by upregulating IP_3R expression, leading to Ca^{2+} overload and oxidative damage.	(38)
	Increased RIPK3 phosphorylation of FUNDC1 impairs mitophagy and heightens susceptibility to cell death	(181)
Malat1	Preserves microvascular function after myocardial infarction by regulating mitochondrial dynamics through the miR-26b-5p/MFN1 axis.	(39)
BI1	Preserves mitochondrial integrity under I/R conditions by reducing F-actin-mediated fission, suppressing XO activity, and limiting ROS production, ultimately maintaining endothelial viability and barrier function.	(84)
	BI1 is also associated with microvascular protection in I/R injury viarepressing Syk-Nox2-Drp1-mitochondrial fission pathways.	(85)
LonP1	Loss of cardiac-specific LonP1 is associated with ER stress and impaired intercellular connections.	(110)
MFN2	Restores microcirculatory perfusion and cellular junction functions by increasing the endothelial progenitor cell marker expression and maintaining the balance of MMP-3 and TIMP-1.	(113,114)
ENPP2	Regulates redox balance and mitochondrial activity, reducing hypoxia/reoxygenation injury in CMECs.	(150)
TMEM215	Protects endothelial cells by inhibiting BIK and reducing pathological Ca^{2+} flux.	(218)
HINT2	Protects cardiac function during ischemia by directly inhibiting the MCU complex, reducing mitochondrial Ca^{2+} overload.	(219)

MAM, mitochondria-associated endoplasmic reticulum membrane; I/R, ischemia-reperfusion; MARCH5, mitochondrial E3 ubiquitin ligase; eNOS, endothelial nitric-oxide synthase; IP_3R, inositol 1,4,5-trisphosphate receptor; RIPK3, receptor-interacting protein kinase 3; FUNDC1, FUN14 domain-containing protein 1; MFN1, mitofusin-1; BI1, Bax inhibitor-1; Syk, spleen tyrosine kinase; Nox2, NADPH oxidases 2; Drp1, dynamin-related protein 1; XO, Xanthine Oxidase; LonP1, Lon peptidase 1; MFN2, mitofusin-2; MMP-3, matrix metalloproteinase-3; TIMP-1, tissue inhibitor of metalloproteinases 1; ENPP2, ectonucleotide pyrophosphatase/phosphodiesterase 2; TMEM215, transmembrane protein 215; BIK, Bcl-2-interacting killer; HINT2, histidine triad nucleotide-binding protein 2; MCU, mitochondrial calcium uniporter.

mitochondrial Ca^{2+} overload and cardiomyocyte death (126). Genetic ablation of CypD protects against I/R-induced necrosis by limiting this aberrant Ca^{2+} transfer (211,212). Similarly, deletion of the *PPIF* gene (encoding CypD), or knockdown of IP_3R1 or GRP75, reduces H/R-induced Ca^{2+} overload and cell death (211). Pharmacological interventions also provide protection; melatonin attenuates oxidative stress and reduces CMEC mortality by inhibiting IP_3R-VDAC-mediated mitochondrial Ca^{2+} influx, increasing endothelial resistance to oxidative damage (77).

MAM tethering is also regulated by the OMM protein PTPIP51 and the ER protein vesicle-associated membrane protein-associated protein-B (VAPB), which form a structural bridge between the two organelles (213). Overexpression of PTPIP51 strengthens this physical connection, enhances ER-mitochondria coupling and increases mitochondrial Ca^{2+} uptake through MCU activation (214,215). However, pharmacological or genetic inhibition of MCU abolishes this effect and protects cardiomyocytes from apoptosis (211). The ER chaperone calreticulin (CRT), with its high Ca^{2+}-binding capacity, also plays a key role in buffering and storage. Upregulation of CRT restores Ca^{2+} homeostasis by improving ER Ca^{2+} reserves (216) (Fig. 5). Collectively, MAM-associated proteins regulate calcium transport through distinct and highly coordinated mechanisms (Table II).

Therapeutically, pinacidil has been shown to preserve CRT expression, reduce endothelial Ca^{2+} overload and prevent mitochondrial apoptosis in CMECs, ultimately improving microvascular density, increasing blood flow, reducing infarct size and attenuating the no-reflow phenomenon following I/R injury (217). Other protective mechanisms involve ER-transmembrane proteins such as transmembrane protein 215 (TMEM215), which protect endothelial cells by inhibiting BCL-2-interacting killer (BIK). Since BIK promotes ER-to-mitochondria Ca^{2+} transfer, its suppression by TMEM215 reduces pathological Ca^{2+} flux and supports cell survival during reperfusion (218).

Other targets act more directly on calcium-handling machinery. For example, Li *et al* (219) demonstrated that histidine triad nucleotide-binding protein 2 (HINT2) protects CMECs during ischemia by directly inhibiting the MCU complex, reducing mitochondrial Ca^{2+} overload and preserving cardiac function. Regulating MAM-associated molecules plays a critical role in microvascular ischemia/reperfusion injury (Table III). Similarly, acetylcholine has been shown to protect endothelial cells by destabilizing ER-mitochondrial

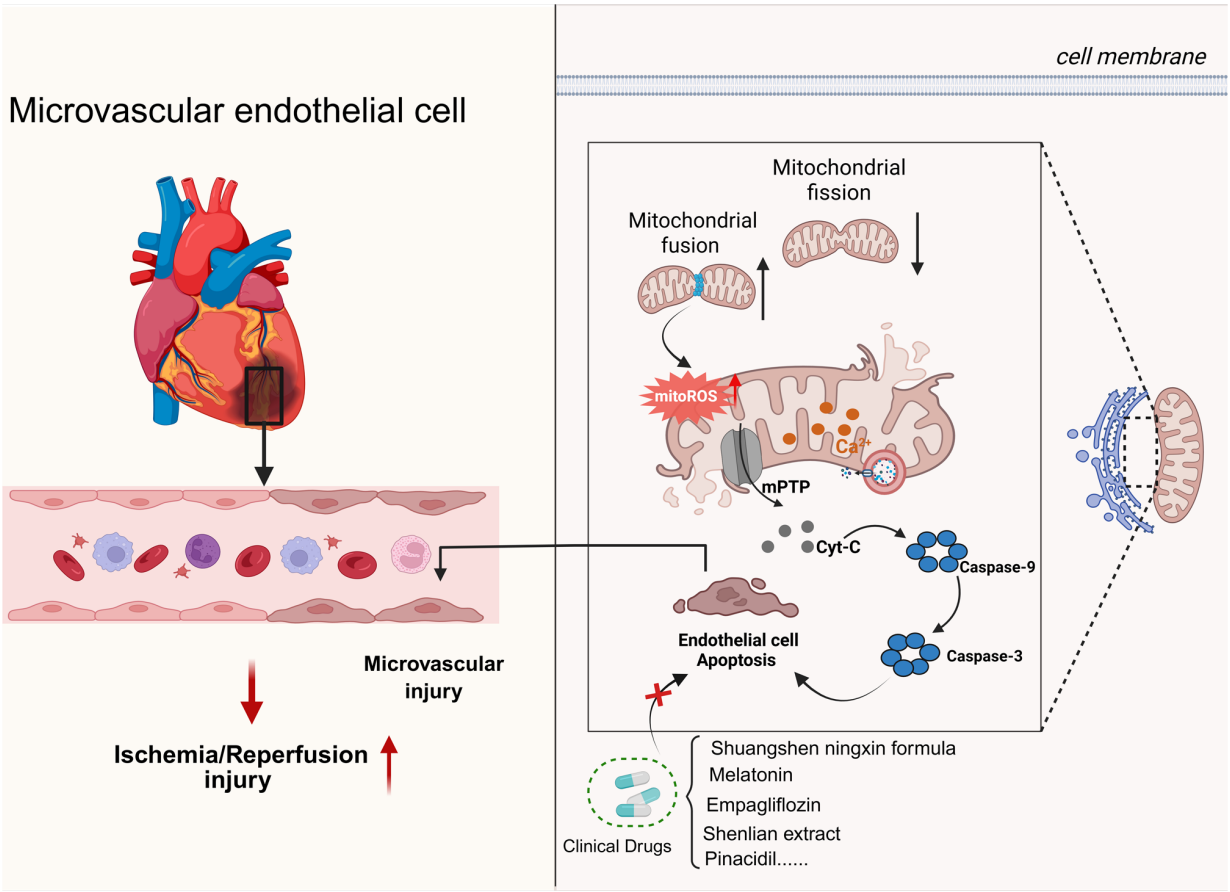

Figure 6. Mitochondrial dysfunction plays a central role in the apoptosis of endothelial cells during cardiac microvascular I/R injury. Specifically, ischemia/reperfusion induces mitochondrial oxidative stress and structural remodeling in microvascular endothelial cells, characterized by excessive mitochondrial fission, impaired fusion and overproduction of mROS. These alterations facilitate the opening of the mPTP and calcium overload, leading to the release of Cyt-C, the activation of caspase-9 and caspase-3 and ultimately, endothelial apoptosis and microvascular damage. Furthermore, potential therapeutic interventions, such as the Shuangshen Ningxin formula, melatonin, empagliflozin, Shenlian extract and pinacidil have been shown to mitigate mROS generation, stabilize mPTP function and restore mitochondrial dynamics, thereby protecting endothelial cells and alleviating cardiac microvascular I/R injury. I/R, ischemia-reperfusion; m/mitoROS, mitochondrial reactive oxygen species; mPTP, mitochondrial permeability transition pore; Cyt-C, cytochrome *c*.

contacts and reducing intracellular and mitochondrial Ca^{2+} overload (193).

Inhibiting ER-to-mitochondria Ca^{2+} transfer in endothelial cells improves cardiac microcirculation, enhances perfusion, reduces microvascular obstruction and limits inflammatory cell infiltration. An important mechanism underlying this protection is the preservation of mitochondrial morphology and function (198). In conclusion, MAMs represent a critical hub in the pathogenesis of microvascular I/R injury. Dysregulated Ca^{2+} transport through MAMs not only disrupts mitochondrial homeostasis but also increases ROS production and activates cell death pathways. A deeper understanding of MAM-regulated Ca^{2+} signaling may provide novel therapeutic opportunities to mitigate cardiac microvascular dysfunction during reperfusion.

7. Conclusions

Damage to this microvascular network during I/R can result in interstitial hemorrhage and edema (220). The MAM functions as a pivotal signaling hub that orchestrates mitochondrial dynamics, oxidative stress responses, mitophagy and calcium homeostasis. Importantly, these mitochondrial alterations do not occur in isolation but are intricately interconnected (Fig. 6). Core MAM-associated proteins such as Drp1, MFN2, FUNDC1, Ero1α, IP_3R, VDAC1 and Sig-1R play essential roles in maintaining normal microvascular physiology. By integrating these key MAM components, molecular mechanisms and signaling pathways, advances in understanding cardiac microvascular I/R injury have provided new perspectives for addressing clinical conditions such as the no-reflow phenomenon and microvascular angina (Fig. 7).

Moreover, several pharmacological agents, including empagliflozin, Shuangshen Ningxin Pill and melatonin, have been shown to exert protective effects against microvascular I/R injury through MAM-related mechanisms (Table IV). However, most of the current evidence remains confined to cellular and animal models. Future research, focusing on the safety, controllability and efficacy of MAM-targeted interventions at the human microvascular level may enable the development of more effective therapeutic strategies.

Despite these advances, the inherent complexity and dynamic nature of MAMs present major challenges to further investigation. Our current understanding of MAMs remains limited, particularly regarding how their morphology,

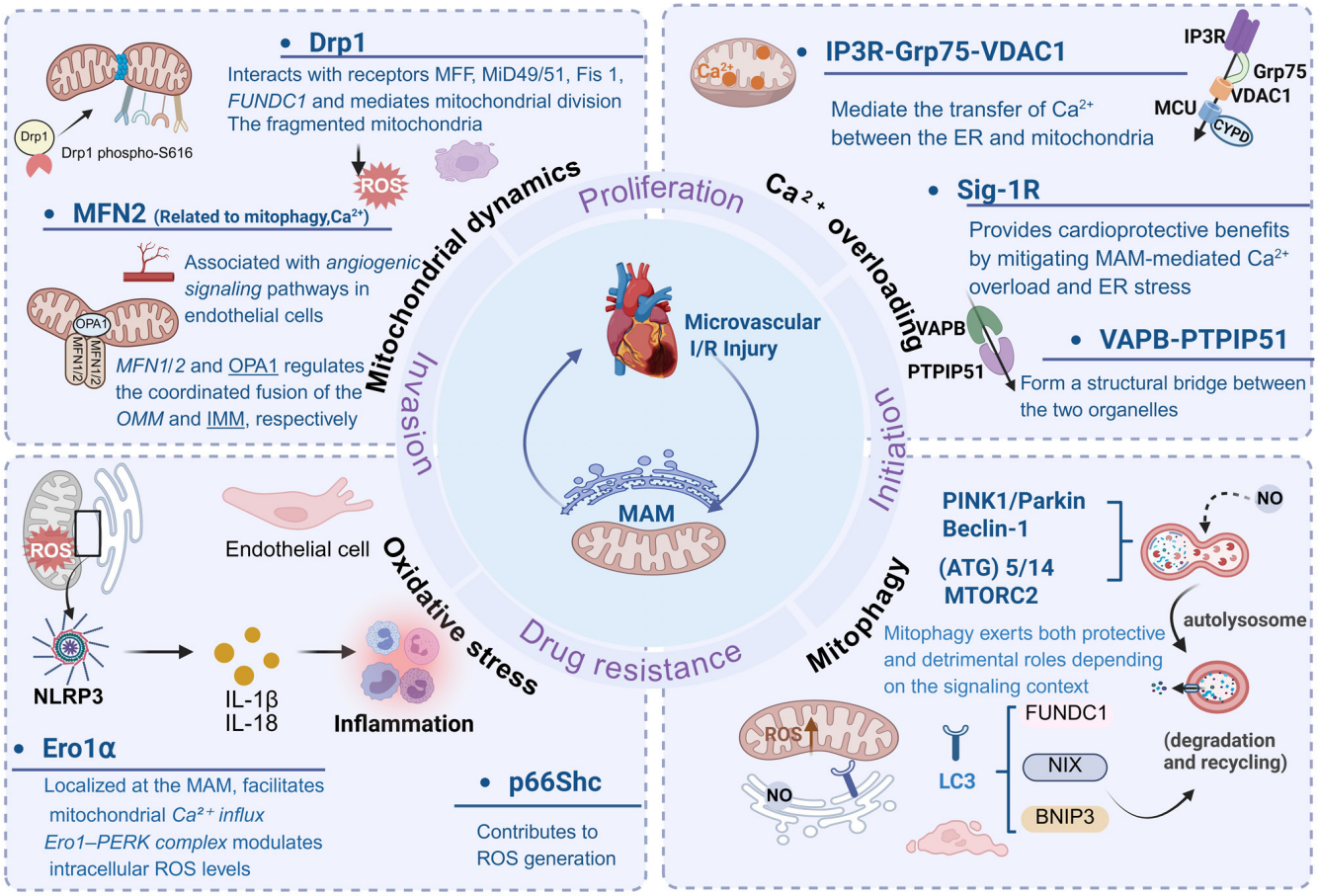

Figure 7. MAMs play a central role in maintaining mitochondrial homeostasis during cardiac microvascular I/R injury. MAMs function as structural and signaling hubs that coordinate mitochondrial dynamics, oxidative stress, mitophagy and Ca^{2+} homeostasis. Specifically, the Drp1 and MFN1/2-OPA1 complexes mediate mitochondrial fission and fusion. MFN1 and MFN2 are not only central to mitochondrial structure but are also closely associated with angiogenic signaling pathways in vascular endothelial cells. MAM-localized p66Shc and Ero1α contribute to reactive oxygen species (ROS) generation and Ca^{2+} influx, activating NLRP3 inflammasome-mediated inflammatory cascades. The IP_3R-Grp75-VDAC1 complex regulates Ca^{2+} transfer between the endoplasmic reticulum and mitochondria, while Sig-1R and VAPB-PTPIP51 tethers stabilize inter-organelle communication and prevent Ca^{2+} overload. Additionally, MAMs serve as key platforms for PINK1/Parkin- and LC3-dependent mitophagy, mediated through FUNDC1, NIX and BNIP3. Dysregulation of these pathways leads to excessive ROS accumulation, Ca^{2+} imbalance and mitochondrial dysfunction, ultimately contributing to endothelial apoptosis and impaired microvascular repair following cardiac ischemia-reperfusion (I/R) injury. MAM, mitochondria-associated endoplasmic reticulum membrane; I/R, ischemia-reperfusion; MFN1, mitofusin-1; MFN2, mitofusin-2; OPA1, optic atrophy 1.

inter-organelle distance, membrane thickness and number of contact sites influence cellular energy metabolism and contribute to disease pathogenesis. Beyond serving as a structural bridge between mitochondria and the ER, the bidirectional regulatory mechanisms by which MAMs coordinate organelle function remain incompletely understood, for instance, the role of MAM-localized MFN2. It also remains unclear whether MAMs show conserved structural and functional features across different cardiovascular cell types, how their formation can be selectively modulated for therapeutic benefit and whether they might serve as early biomarkers of microvascular injury. Furthermore, the temporal dynamics, spatial organization and hierarchical signaling networks that govern MAM remodeling in endothelial cells under stress conditions are still poorly characterized.

8. Future perspectives

Future research should aim to develop multiscale integrative models of MAMs to elucidate the causal relationships between their dynamic remodeling and microvascular pathological responses. Employing advanced *in vivo* multi-omics and imaging technologies, such as the Split-GFP contact sensor (221,222) and serial block-face scanning electron microscopy (223), may provide deeper insights into their structural and functional characteristics. Given the involvement of MAMs in key cellular processes, including energy metabolism, inflammation and cell death, their dysregulation likely contributes to the pathogenesis of cardiovascular, metabolic and neurological disorders. Therefore, clarifying the molecular mechanisms underlying MAM function could not only enhance our understanding of cardiovascular microcirculatory pathology but also reveal broadly applicable therapeutic targets for multiple diseases. However, pharmacological strategies targeting MAMs alone may be limited by individual metabolic variations and comorbid conditions; thus, future investigations should emphasize combinatorial regulatory approaches, such as dual-target therapies that modulate both MAMs and mitochondrial metabolism.

Table IV. Role of MAM-targeted drugs in cardiac microvascular ischemia-reperfusion injury.

Name	Target	Models	(Refs.)
Shuangshen Ningxin formula	Alleviates cardiac microvascular I/R injury by improving mitochondrial function through the regulation of the NR4A1/MFF/Drp1 pathway.	Rat cardiac microvascular I/R injury	(83)
Melatonin	Exerts protective effects against cardiac microvascular I/R injury by promoting inhibitory phosphorylation of Drp1 at Ser637, suppressing fission.	Mouse cardiac microvascular I/R injury H/R cardiac microvascular endothelial cells (CMEC)	(63) (78)
	Attenuates cardiac microvascular injury by targeting the mitochondrial fission-VDAC1-HK2-mPTP-mitophagy cascade. Attenuates oxidative stress and reduces CMEC mortality by inhibiting IP_3R-VDAC-mediated mitochondrial Ca^{2+} influx. Protects against cardiac I/R injury by inhibition of the PPAR/FUNDC1/mitophagy pathway.	H/R CMECs Mouse I/R injury	(183)
Empagliflozin	Protects against microvascular I/R injury by suppressing mitochondrial fission via through the inactivation of the DNA-PKcs/Fis1 pathway.	Mouse cardiac microvascular I/R injury	(87)
	Exerts protective effects through activating AMPKα1/ULK1/FUNDC1 axis.	Mouse cardiac microvascular I/R injury	(182)
HCA (2'Hydroxycinnamaldehyde)	Pretreatment with HCA reduces Drp1 expression and improves microvascular function during reperfusion.	Rat cardiac microvascular I/R injury H_2O_2-Induced H9C2 Cells	(88)
Liproxstatin-1	Protects the myocardium by downregulating VDAC1 and restoring GPX4.	Mouse I/R injury	(151)
Ginkgolide A	Reduces oxidative stress and increased NO bioavailability in the heart.	Mouse with pressure overload	(152)
Naringin	Improves cardiac microvascular function, potentially by facilitating NDUFS1 translocation to mitochondria and reducing ROS.	Rat cardiac microvascular I/R injury	(155)
Shenlian extract	Attenuates I/R injury by inhibiting the PINK1/Parkin pathway and reducing mitophagy.	Rat cardiac microvascular I/R injury	(184)
Urolithin A	Mitophagy inducer, improves overall mitochondrial quality control and confers protection.	H/R human umbilical vein endothelial cells (HUVECs)	(185)
Acetylcholine	Protects endothelial cells by destabilizing ER-mitochondrial contacts, and reducing the intracellular and mitochondrial Ca^{2+} overload.	H/R HUVECs	(193)
Dapagliflozin	Reduces cardiac microvascular damage and endothelial dysfunction through inhibition of the XO-SERCA2-CaMKII-cofilin pathway.	Mouse cardiac microvascular I/R injury H/R human coronary artery endothelial cells (HCAECs)	(200)
Pinacidil	Preserves CRT expression, reduces endothelial Ca^{2+} overload, and prevents mitochondrial apoptosis in CMECs.	Mouse cardiac microvascular I/R injury	(217)

MAM, mitochondria-associated endoplasmic reticulum membrane; I/R, ischemia-reperfusion; H/R, hypoxia/reoxygenation; NR4A1, nuclear receptor 4A1; MFF, mitochondrial fission factor; Drp1, dynamin-related protein 1; VDAC1, voltage-dependent anion channel 1; HK2, hexokinase 2; mPTP, mitochondrial permeability transition pore; IP_3R, inositol 1,4,5-trisphosphate receptor; PPAR, peroxisome proliferator-activated receptor; FUNDC1, FUN14 domain-containing protein 1; DNA-PKcs, DNA-dependent protein kinase; Fis1, mitochondrial fission protein 1; AMPKα1, AMP-activated protein kinase alpha1; ULK1, Unc-51-like autophagy-activating kinase 1.

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Authors' contributions

YW and B F conceived the idea for the present review and drafted the manuscript. YtW and ZS created the figures and contributed to the writing of the manuscript. HY, WC and CZ reviewed and modified the manuscript and screened literature. ZL provided valuable guidance and analysis during the present review. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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