Mitochondrial-endoplasmic reticulum crosstalk: Molecular mechanisms and implications for cardiovascular disease (Review)

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Received January 22, 2025; Accepted July 14, 2025

DOI: 10.3892/mmr.2025.13640

Abstract. Cardiovascular disease (CVD), which includes conditions such as coronary heart disease, hypertension, heart failure and diabetes cardiomyopathy, is a major cause of mortality among middle-aged and elderly populations worldwide; however, there is a concerning trend of individuals of increasingly younger ages being affected. Despite extensive research and numerous treatments available, CVD remains a major health threat for middle-aged and elderly individuals due to its complex causes and the effect of environmental and lifestyle factors. In recent years, the structural and functional abnormalities of mitochondria and endoplasmic reticulum (ER) organelles have been associated with CVD. In addition to the intrinsic role of organelles, the interaction between organelles, particularly the homeostasis imbalance between the mitochondria and the ER through the interaction of the mitochondria-associated ER membrane (MAM), serves a key role in CVD, such as ischemia-reperfusion, diabetic cardiomyopathy and heart failure. The main mechanism involves regulating lipid transport, calcium homeostasis, mitochondrial function, cell survival and death, as well as signal transduction. The present review summarized recent advancements in MAM research, elucidated key mechanisms that influence MAM homeostasis, highlighted its significance in cardiovascular health and disease and explored its potential as a therapeutic target for CVD, thereby providing a theoretical foundation for future research.

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Key words: cardiovascular disease, mitochondria, mitochondria-associated endoplasmic reticulum membrane, endoplasmic reticulum

Contents

1. Introduction

The mitochondria are double-layered membrane organelles composed of outer and inner membranes (foldable into cristae), an inner membrane gap, matrix and mitochondrial DNA. They mainly participate in energy metabolism, redox processes, calcium ion (Ca^{2+}) concentration regulation, cell apoptosis and other cellular processes and serve a crucial role in maintaining cellular homeostasis (1). The outer mitochondrial membrane (OMM) encloses the organelle, whereas the inner mitochondrial membrane (IMM) forms intricate structures known as cristae. The inner membrane cristae are involved in a wide range of processes, including the electron transport chain, ATP synthase, protein transport, metabolite exchange, protein translation and degradation (2). Protons and electrons can be distributed asymmetrically on both sides of the membrane, resulting in a change in the membrane potential and energy generation, thereby completing the cell energy conversion. Mitochondria are highly dynamic organelles intrinsically linked to their function. There are several levels of mitochondrial dynamics within a single mitochondrion, among multiple mitochondria and between mitochondria and other organelles (3). Mitochondria interact with other cellular structures through contact points that facilitate the transfer of ions, lipids, proteins or metabolites and regulate mitochondrial dynamics, quality control and mitochondrial DNA replication (4). The formation of mitochondrial contact points is responsive to cellular and metabolic states, which fine-tune the mitochondrial output in numerous aspects. Crosstalk between organelles are essential for numerous intracellular functions, with the mitochondrial-endoplasmic reticulum (ER) axis exemplifying a paradigmatic inter-organelle system (5,6). The ER and mitochondria are physically interconnected, as demonstrated by electron tomography, which reveals that these organelles are adjoined by tethers and electron-dense structures (7,8). Further research has revealed a protein complex that connects these organelles (9).

Organelle dynamics, including mitochondrial fission/fusion and ER-mitochondrial tethering, are critical for maintaining cellular homeostasis through regulated oxidative phosphorylation, ATP production, calcium storage and reactive oxygen species. Mitochondrial dysfunction disrupts oxidative phosphorylation and calcium handling, whilst ER stress induces protein misfolding, exacerbating oxidative stress and apoptosis. Emerging evidence highlights that ER-mitochondrial interorganellar communication, particularly via inositol 1,4,5-triphosphate receptor (IP3R) type 1- voltage-dependent anion channel-1 (VDAC1)-glucose-regulated protein 75 (Grp75) complexes, directly modulates calcium flux and apoptotic thresholds in cardiovascular disease (CVD) pathogenesis (10-12).

Mitochondria-associated ER membranes (MAMs) are crucial communication centers that facilitate the exchange of ions, lipids, metabolites and signaling molecules (13). MAMs are maintained by interactions between complementary tethering molecules located on their surfaces. Several tethering proteins, such as VDAC1, Grp75 and mitofusin-1/2, are crucial for the establishment and regulation of this complex intracellular communication network and serve essential roles in these interactions (14). Cellular physiology is coordinated by the swift exchange of molecules between organelles at specialized organelle-organelle contact sites (15). Numerous studies have demonstrated that MAMs serve essential roles in calcium homeostasis, lipid synthesis and transport and mitochondrial functions and homeostasis (16-18). Additionally, these sites act as signaling hubs for intracellular stress responses such as oxidative stress, energy stress and stimulus signals (19). Moreover, MAMs are considered pivotal sites for transmitting stress signals between the ER and mitochondria. The cell fate also depends on these contact sites for the decision between autophagy and apoptosis (20,21).

The interaction between organelles is a rapidly emerging field that could allow the identification of key proteins, help describe new regulatory pathways and clarify their significance in CVD (22). Recent research findings suggest that the pathogenic factors of CVD may interfere with the interactions between mitochondria and other organelles and the lack of specific functional proteins or interactions involved in mitochondrial-organelle connections will lead to several pathological changes in different tissues (23,24). Understanding MAM proteins and their influence on cellular physiological and pathological processes may help reveal their diagnostic and therapeutic potential. Therefore, the present review summarizes and discusses research progress on the interaction between mitochondria and ER in CVD, specifically focusing on the functional role and characteristics of MAM proteins in CVD.

2. MAMs and their function

Mitochondria are intimately juxtaposed to the ER and their membrane contacts range from 10-50 nm in width, referred to as MAMs or mitochondria-ER contacts (25). It has been observed that MAMs exist in a wide range of species, from yeast to mammals. They facilitate inter-organelle communication, help cells detect extracellular signals and respond to stressful stimuli (26).

MAMs are integral to numerous cellular processes such as lipid transport and synthesis, calcium exchange, mitochondrial function and apoptosis/survival (26-28), facilitated by protein complexes that exhibit both tethering capabilities and specialized functions (29). MAM-localized proteins have been categorized into three groups: i) MAM-specific proteins, (such as the IP3R1-VDAC1-Grp75 complex, which directly mediates ER-mitochondria calcium flux); ii) dual-organelle proteins [such as phosphofurin acidic cluster sorting protein 2 (PACS-2), regulating lipid transfer and mitophagy]; and iii) transient translocators [such as σ-1 receptor (Sig-1R), dynamically adjusting MAM organization under stress] (30,31). Among these, six core protein complexes structurally organize MAMs to mediate ER-mitochondria crosstalk: i) The IP3R1-VDAC1-Grp75 axis, critical for calcium signaling; ii) the vesicle-associated membrane protein-associated protein B (VAPB)-protein tyrosine phosphatase interacting protein 51 (PTPIP51) complex, integral to the formation and stability of MAMs; iii) mitofusin 2 (Mfn2), governing MAM structure and functional homeostasis; iv) PACS-2, which binds to beclin 1 (BECN1) and mediates its relocation to the MAM, facilitating MAM formation and mitophagy; v) Sig-1R, which acts as a Ca^{2+}-sensitive, ligand-operated chaperone; and vi) mitochondrial contact site and cristae organizing system (MICOS), which is evolutionarily conserved, connecting these inner membrane domains by forming and stabilizing crista junctions (Fig. 1).

IP3R1-VDAC1-Grp75 complex. In the context of the MAM, the most extensively studied protein complexes related to the ER and mitochondria that act as molecular tethers include IP3R1, VDAC1 and Grp75 (32). Structurally, IP3Rs serve as crucial Ca^{2+} efflux channels on the ER membrane, facilitating the transfer of Ca^{2+} from the ER lumen to the cytoplasm (33). Voltage-dependent anion channels (VDACs) are ion channels located on the OMM that regulate the passage of metabolites and ions across the mitochondrial membranes. Grp75 bridges IP3Rs and VDACs, thereby maintaining the architecture of MAMs (34).

The VDAC1/Grp75/IP3R1 complex mediates at least part of the Ca^{2+} transfer from the ER to mitochondria under physiological conditions. MAMs expand during mitosis, which is associated with improved Ca^{2+} coupling between the two organelles (35). The increase or decrease in these three proteins enhances or weakens MAM formation, thereby affecting intracellular calcium homeostasis. Elevated levels or activity of IP3Rs are frequently observed under several pathological conditions of CVD, including atherosclerosis, hypertension, heart failure, ischemic dilated cardiomyopathy and myocardial hypertrophy (36-38). VDACs enhance connectivity between the ER and mitochondria, thereby facilitating the influx of Ca^{2+} into the mitochondria. VDAC1 knockdown or inhibition was reported to disturb the connection of ER-mitochondria (39). Moreover, silencing Grp75 disrupted the IP3R-VDAC interaction, whilst higher Grp75 levels enhanced it (40,41). Furthermore, the IP3R1-GRP75-VDAC1 complex is crucial for effective Ca^{2+} transfer, mitochondrial morphology and dynamics regulation (42). A previous study identified DJ-1 (19.9 kDa), a crucial mediator in PTEN induced kinase 1/parkin-dependent mitophagy, interacting closely

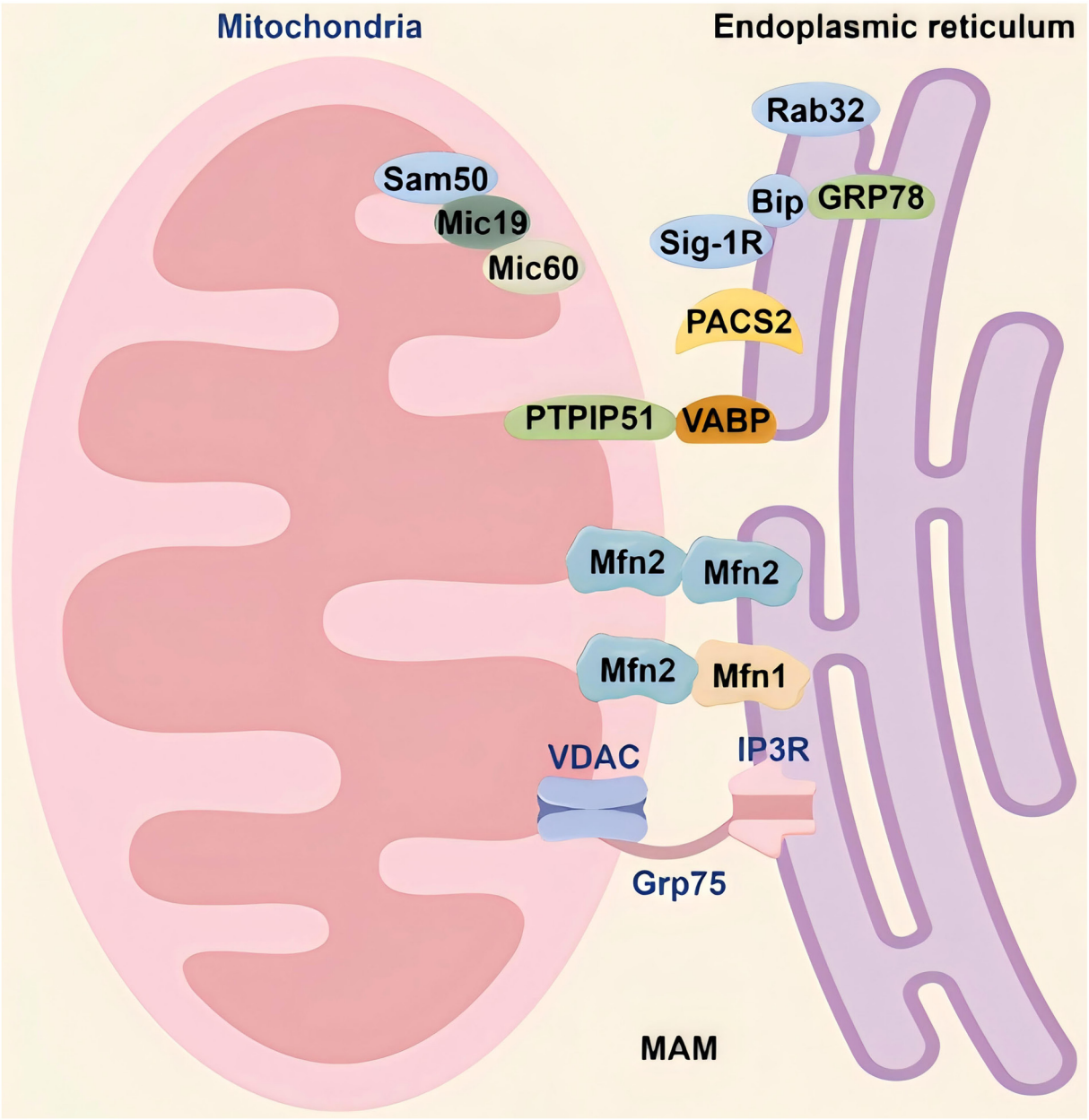

Figure 1. Representation of proteins and protein complexes involved in the crosstalk between the ER and mitochondria in MAMs. There are mainly six protein/protein complexes located in MAMs, including IP3R1-VDAC1-Grp75, VAPB-PTPIP51, Mfn2, PACS-2, Sig-1R, Rab32 and MICOS. ER, endoplasmic reticulum; MAM, mitochondria-associated ER membrane; IP3R1, inositol 1,4,5-triphosphate receptor type 1; VDAC1, voltage-dependent anion channel-1; Grp75, glucose-regulated protein 75; VAPB, vesicle-associated membrane protein-associated protein B; PTPIP51, protein tyrosine phosphatase interacting protein 51; Mfn2, mitofusin 2; PACS-2, phosphofurin acidic cluster sorting protein 2; Sig-1R, σ-1 receptor; MICOS, mitochondrial contact site and cristae organizing system; Sam, sorting and assembly machinery.

with the IP3R3-Grp75-VDAC1 complex. The ablation of DJ-1 destabilized this complex, disrupting Ca^{2+} signaling and weakening the association between the ER and mitochondria, compromising the functional integrity of MAMs (43,44).

VAPB-PTPIP51 complex. The VAPB-PTPIP51 complex is another important component of MAMs. The membrane protein VAPB is located in the ER membrane, whilst the membrane protein PTPIP51 is located in the OMM. Together, VAPB and PTPIP51 are integral to the formation and stability of MAMs (45). Emerging evidence reveals that VAPB molecules can rapidly enter and exit MAMs within seconds, allowing MAM to dynamically reshape according to the intracellular and extracellular environment to precisely regulate cellular metabolic demands. This demonstrates the critical role of VAPB diffusion kinetics in maintaining MAMs homeostasis (46). Oxysterol-binding protein-related protein 5 is found at the interface and interacts with OMM protein PTPIP51, thereby serving a role in mitochondrial function (47). Following ischemic stroke, the expression of VAPB-PTPIP51 is downregulated, which damages the MAMs structure, potentially exacerbating cerebral ischemia-reperfusion injury by inhibiting the phosphatidylinositol 3-kinase pathway and activating autophagy (48). Nucleoporin 358, a nucleoporin resident in the annulate lamellae, can interact with the VAPB-PTPIP51 complex, thereby suppressing the mTORC2/Akt/glycogen

synthase kinase-3β (GSK3β) signaling pathway activation and disrupting the MAMs (49). The VAPB-PTPIP51 tethers also serve a crucial role in the regulation of autophagy by mediating the transfer of Ca^{2+} from ER stores to the mitochondria (50). Additionally, neuronal protein α-synuclein interacts with the VAPB, thereby disrupting MAMs and Ca^{2+} homeostasis, as well as mitochondrial ATP production (51).

Mfn2. Mfn2-mediated MAM structure and functional homeostasis are crucial for coordinating vital cellular homeostatic processes. There are three main mechanisms by which the mitochondrial dynamics protein Mfn2 affects MAMs are as follows: i) It directly affects the linkage of MAMs; ii) it promotes oligomerization; and iii) it facilitates the formation of complexes with other proteins, thereby affecting MAMs linkages (52,53). Splicing of Mfn2 produces ER-specific variants ERMIT2 and ERMIN2. ERMIN2 regulates the morphology of the ER, whereas ERMIT2 associates with Mfn2 and engages with mitochondrial mitofusins to facilitate the tethering of the ER to mitochondria. This interaction promotes enhanced mitochondrial Ca^{2+} uptake and phospholipid transfer (54). The substantial expression of dimethylarginine dimethylaminohydrolase-1 in dopaminergic neurons of the substantia nigra may confer neuroprotective effects by sustaining the formation of MAMs and preserving mitochondrial function through oligomerization of Mfn2 (55). Mfn2 not only mediates MAM formation but also regulates mitochondria-ER interactions by binding to Diaphanous-1, modulating MAM proximity and ischemia-reperfusion injury susceptibility (56). Knocking out Mfn2 reduces the interaction between the ER and mitochondria via the VAPB-PTPIP51 tethering complex, whilst overexpressing Mfn2 increases the interaction (57). PDZ-domain-containing protein synaptojanin-2 binding protein (SYNJ2BP) maintains mitochondrial Zn^{2+} homeostasis in nucleus pulposus cells during intervertebral disc degeneration by stabilizing MAM contacts via Mfn2 and facilitating the formation of the NOD-like receptor X1-the zinc transporter solute carrier family 39 member 7 complex (58). Mfn2 regulates protein kinase RNA-like endoplasmic reticulum kinase (PERK) and inositol-requiring enzyme 1 axis signaling and maintains MAM integrity. Its deficiency disrupts MAM structure, inducing ER stress, mitochondrial ROS accumulation and apoptosis in cisplatin nephropathy (59). Exposure to Di-(2-ethylhexyl) phthalate induces the downregulation of Mfn2, which impairs MAMs by inhibiting Mfn2-PERK interaction (60). Conversely, skeletal muscle-specific knockdown of the mitochondrial fusion mediator optic atrophy 1 (OPA1) upregulates Mfn2 but impairs MAM formation through activating transcription factor 4-dependent mechanisms (61).

PACS-2. PACS-2 is crucial for MAM formation (62) and mitigates diabetic renal tubular injury by stabilizing MAM (63). Mechanistically, PACS-2 recruits BECN1 to MAMs, enhancing mitophagosome assembly and mitophagy (64). Hyperglycemia upregulates mitogen-activated protein kinase 1 (MAPK1), which reduces PACS-2 levels, whilst MAPK1 inhibition restores PACS-2 expression to preserve MAM integrity and prevent mitochondrial fragmentation (65). In atherosclerosis, atherogenic lipids augment PACS-2-dependent MAM contacts, whereas PACS-2 knockdown disrupts MAMs, impairing mitophagy and increasing vascular smooth muscle cell (VSMC) apoptosis (66).

Sig-1R. Sig-1R, an ER-resident MAM protein, prevents ferroptosis by acting as a Ca^{2+}-sensitive chaperone that dissociates from binding immunoglobulin protein (BiP) upon ER Ca^{2+} depletion or ligand binding, thereby amplifying mitochondrial Ca^{2+} signaling via IP3Rs (67). In acute lung injury, the ER chaperone BiP/glucose-regulated protein 78 (GRP78), a critical component of MAM, is a novel determinant of endothelial cell (EC) dysfunction (68). Sig-1R- is associated with BiP/GRP78 in MAM and is recognized as a versatile modulator of cellular homeostasis (69). Sig-1R exerts its anti-inflammatory effect only when dissociated from BiP/GRP78, thereby confirming that the suppression of EC inflammation mediated by BiP/GRP78 knockdown or inactivation is facilitated by Sig-1R (70). Moreover, a previous study reported that sig-1R suppression via CGI1746 protected against cisplatin-induced acute kidney injury by impairing MAM Ca^{2+} transfer, increasing mitochondrial ROS and promoting polyunsaturated lipid accumulation (71).

Rab32. Rab32 is a small GTPase located in the ER and mitochondria, where it regulates ER Ca^{2+} handling in the ER and disrupts calnexin enrichment on MAM without affecting the ER distribution of protein-disulfide isomerase or Mfn2. Furthermore, Rab32 influences the targeting of protein kinase A to mitochondrial and ER membranes, thereby regulating the phosphorylation of Bcl-2 agonist of cell death and dynamin-related protein 1 (Drp1) (72). Moreover, Rab32 modulates the positioning of the Ca^{2+} regulatory transmembrane protein calnexin to MAM (72). Thioredoxin-related transmembrane protein 1 is selectively degraded via a Rab32-dependent process with the long isoform of reticulon-3 (RTN3L) acting as a Rab32 effector. Together, Rab32 and RTN3L promote autophagic degradation of the mitochondrial-proximal ER membranes (73). Proteins in the Rab32 subfamily, including Rab32A, Rab32B, Rab29 and Rab38, serve an evolutionarily conserved role in interacting with Drp1, which is essential for mitochondrial dynamics and dependent on their localization in the ER and MAM (74).

MICOS complex. The outer mitochondria membrane links the mitochondria to other organelles, whereas the inner membrane consists of a boundary region and a folded crista. The MICOS system, which is evolutionarily conserved, connects these inner membrane domains by forming and stabilizing crista junctions. Moreover, MICOS creates contact sites between the inner and outer membranes through interactions with outer membrane proteins (75). Mitochondrial contact site and cristae organizing system complex (Mic)19 forms the sorting and assembly machinery (Sam) 50-Mic19-Mic60 axis by interacting with Sam50 (the outer membrane protein) and Mic60 (the inner membrane protein), linking the *S*-adenosylmethionine and MICOS complexes to the MIB super complex that connects the mitochondrial outer and inner membranes (76). As a key MICOS subunit, Mic19 also regulates ER-mitochondria contacts via the EMC2/SLC25A46/Mic19 pathway, with disruptions potentially leading to nonalcoholic steatohepatitis and liver fibrosis (77).

ER and mitochondria are key sites for membrane biogenesis in eukaryotes, facilitating lipid exchange through membrane contact sites (78,79). In yeast, this process is mediated by the endoplasmic reticulum-mitochondria encounter structure (ERMES) (9,80), a complex composed of at least four proteins: The mitochondrial outer membrane proteins (Mdm10 and Mdm34), the ER membrane component (Mmm1) and the cytoplasmic protein (Mdm12). ERMES forms ~25 bridge-like complexes at contact sites, each featuring three synaptotagmin-like domains in a zig-zag pattern (79). These ER-mitochondrial contact sites are essential for importing hydrophobic mitochondrial precursor proteins into the IMM through the ER- syndrome of undifferentiated recurrent fever pathway. ERMES, in conjunction with translocase of outer mitochondrial membrane 70 (Tom 70), Djp1 and Lam6, form two parallel, partially redundant pathways for ER-to-mitochondrial transport. Disruption of these contact sites results in several mitochondrial inner membrane protein precursors becoming trapped in the ER membrane, leading to mitochondrial dysfunction (81). Djp1, a chaperone involved in the mitochondrial import of ER-resident proteins, is located near the ER exit sites (ERES)-ERMES region, suggesting a potential link between the proximity of ERES and ERMES and mitochondrial protein import. Besides lipid transport, ERMES facilitates protein transfer from the ER to mitochondria, overlapping with the function of the Tom70-Djp1/Lam6 contact site (82). To date, ERMES components have only been identified in fungi, to the best of the authors' knowledge (83). Further investigations are required to determine whether these proteins are involved in lipid transfer in other species.

3. Characteristics of MAMs in CVD

Ischemia/hypoxia-reperfusion. MAMs critically regulate pathological processes in ischemic heart disease through coordinated control of calcium homeostasis, mitochondrial dynamics and metabolic signaling. The IP3R1-GRP75-VDAC1 complex serves as a central hub: GRP75 mediates ER-mitochondrial tethering, enabling VDAC1-dependent calcium flux that modulates apoptosis and glycolytic adaptation under hypoxia. Experimental ablation of GRP75 disrupts this coupling, exacerbating calcium overload and impairing adaptive stress responses in cardiomyocytes (84). GRP75-mediated ER-mitochondrial interactions via the IP3R1-VDAC1 complex are essential for Ca^{2+} homeostasis and ER stress adaptation in cardiomyocyte hypoxia-ischemia. Targeting GRP75 regulates Ca^{2+} flux, glycolysis and cell survival (38). In pulmonary hypertension, downregulation of OPA1/Mfn2 impairs mitochondrial fusion, accelerating right ventricular (RV) hypertrophy via reactive oxygen species overproduction, whereas their overexpression preserves mitochondrial integrity and attenuates maladaptive remodeling (85). Diaphanous related formin 1 (DIAPH1)-Mfn2 interaction governs MAM architecture by regulating ER-mitochondrial proximity, as synthetic linkers disrupting this interaction negate the silencing of the DIAPH1 cardioprotective effects during ischemia (86). CypD-VDAC1/GRP75/IP3R1 complex dynamics further fine-tune calcium transfer, with hypoxia-reoxygenation enhancing CypD binding to amplify mitochondrial calcium overload, making this complex a therapeutic target for reperfusion injury (87). Finally, Pacs2 deficiency disrupts MAM-mediated mitophagy and energy metabolism, exacerbating RV dysfunction in hypobaric hypoxia, whilst Pacs2 overexpression restores calcium flux and mitophagic flux, highlighting its role as a metabolic checkpoint (88).

Myocardial hypertrophy. ATPase family AAA-domain containing protein 3A (ATAD3A), which is located in the MAM, maintains ER-mitochondrial contact homeostasis, prevents mitochondrial Ca^{2+} overload and protects the mitochondrial bioenergetics from ER stress. It is a substrate of sirtuin 3 and its acetylation at K134 disrupts its oligomerization. ATAD3A monomer interacts with the IP3R1-GRP75-VDAC1 complex, leading to mitochondrial Ca^{2+} overload and dysfunction in myocardial hypertrophy (29). A nonselective cation channel, transient receptor potential vanilloid type 1, enhances the formation of MAMs and maintains mitochondrial function through the AMP/APK/Mfn2 pathway, reducing myocardial hypertrophy caused by pressure overload in cardiomyocytes (Fig. 2) (89).

Cardiotoxicity. Sorafenib (SOR), a first-line drug for the treatment of advanced hepatocellular carcinoma, induces cardiac dysfunction via mitochondrial Ca^{2+} overload, activating calcium/calmodulin dependent protein kinase II δ (CaMKIIδ) and the receptor interacting protein 3 (RIP3)/mixed lineage kinase domain-like protein (MLKL) cascade, with excessive MAM formation and tight ER-mitochondria contact serving as the key pathogenic mechanisms (90). SOR also downregulates Mfn2 expression. Lowering Mfn2 enhances SOR-induced MAM biosynthesis and mitochondrial MAM binding in cardiomyocytes. Furthermore, SOR inactivates mTOR, activated transcription factor EB and promotes mitochondrial phagocytosis and Mfn2 degradation. Sorafenib triggers necroptosis through the Mfn2-MAM-Ca^{2+}-CaMKIIδ pathway, but Mfn2 overexpression prevents cardiac dysfunction and necroptosis caused by sorafenib by blocking the MAM-CaMKIIδ-RIP3/MLKL pathway (90). Upon tunicamycin treatment, the oxidoreductase ER oxidoreductase 1 α (ERO1α) has been reported to form a covalent bond with the protein kinase PERK, which requires the C-terminal active site of ERO1α and cysteine 216 of PERK. This interaction oxidizes MAMs and regulates mitochondrial dynamics, enhancing ER-mitochondria Ca^{2+} flux to maintain bioenergetics and reduce oxidative stress (91). MAMs initiate autophagy and form autophagosomes, whilst FUN14 domain containing 1 (FUNDC1) acts as a tethering protein. Overexpression of FUNDC1 is reported to restore autophagosome biogenesis by maintaining the MAM structure and aiding in the formation of the autophagy-related (ATG)5-ATG12/ATG16L1 complex without affecting mitophagy (92). FUNDC1 also reduces doxorubicin (DOX)-induced oxidative stress and cardiomyocyte death through autophagy. Therefore, FUNDC1-mediated MAMs provide cardio-protection against DOX-induced cardiotoxicity by restoring autophagosome biogenesis (Fig. 2).

Coronary artery disease. In patients with coronary heart disease, the mitochondria exhibit increased oxygen consumption, higher ATP production and tighter connections with the ER, thereby forming MAMs. This Ca^{2+} transfer through

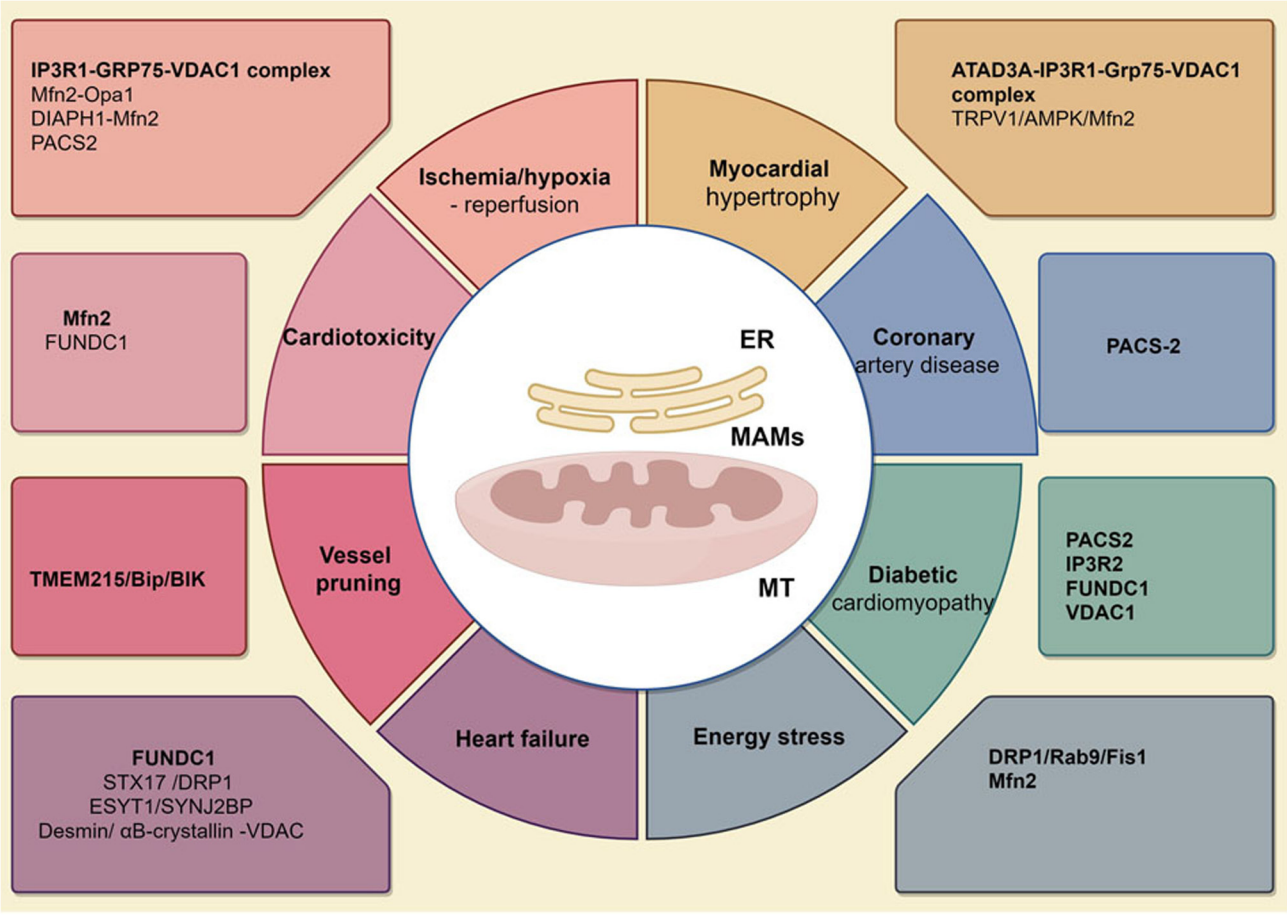

Figure 2. Effect of MAMs homeostasis imbalance on CVD. The association between the signaling pathways of MAMs homeostasis imbalance and different types of cardiovascular diseases, including myocardial hypertrophy, coronary heart disease and diabetic cardiomyopathy. MAM, mitochondria-associated endoplasmic reticulum membrane; CVD, cardiovascular disease; ER, endoplasmic reticulum; PACS-2, phosphofurin acidic cluster sorting protein 2; IP3R2, inositol 1,4,5-trisphosphate receptor type 2; FUNDC1, FUN14 domain containing 1; VDAC1, voltage-dependent anion channel 1; DRP1, dynamin-related protein 1; Rab9, Ras-related protein Rab-9A; Fis1, fission 1 protein; Mfn2, mitofusin 2; TMEM215, transmembrane protein 215; Opa1, optic atrophy 1; DIAPH1, Diaphanous-1.

MAMs sustains mitochondrial hyperactivity and is dependent on the inactivation of GSK3β (93). Moulis *et al* (66) reported that PACS-2 accumulates at MAM sites in VSMCs exposed to oxidized low-density lipoprotein. PACS-2 enhances MAM contacts and its deletion disrupts these connections, leading to impaired mitophagosome formation and enhanced VSMC apoptosis. Further research by Assis *et al* (94) reported that Pravastatin reduces ER-mitochondrial interactions, leading to increased mitochondrial branching. Moreover, Pravastatin upregulated the expression of the mitochondrial dynamics regulators fission 1 protein (Fis1) and Mfn2 in bone marrow-derived macrophage from $Ldlr^{-/-}$ mice. Mendelian randomization-transcriptomic analysis further identified MAM-related KLRC1/SOCS2 as protective AS resistance genes with reduced expression in atherosclerotic plaques (Fig. 2) (95).

Heart failure. FUNDC1, a conserved OMM protein, interacts with IP3R2 to regulate ER Ca^{2+} transfer to the mitochondria and the cytosol. Disruption of this interaction leads to reduced Ca^{2+} levels, causing abnormal mitochondrial dysfunction and heart failure. The FUNDC1/MAMs/cyclic AMP response element-binding protein/Fis1 signaling pathway is notably suppressed in patients with heart failure (96). Syntaxin 17 (STX17), a SNARE protein essential for autophagosome maturation, localizes to MAMs and dynamically modulates obesity-induced pathologies: Elevated STX17 levels in obese individuals and high-fat diet (HFD)-fed mice have been associated with exacerbated cardiac remodeling and oxidative stress, whereas STX17-knockout attenuates mitochondrial damage and improves cardiac function in these models. Mechanistically, STX17 drives MAM formation in obesity via parkin-mediated MCUb ubiquitination/degradation, enhancing MCU-dependent mitochondrial calcium influx (97), while STX17 recruitment of cyclin-dependent kinase-1 through its SNARE domain phosphorylates DRP1 at Ser616 to promote stress-induced mitophagy. Cardiac-specific STX17-ablation reduces p(S616)-DRP1 levels in MAMs, causing mitochondrial dysfunction and contractile deficits, whereas STX17 overexpression enhances DRP1-dependent mitophagy to protect against aortic constriction-induced injury (98). The ER-resident SMP domain protein extended synaptotagmin 1 (ESYT1) complexes with SYNJ2BP on the OMM to stabilize MERCs; ESYT1 or SYNJ2BP deficiency disrupts MERC integrity, impairs ER-mitochondria calcium flux and alters mitochondrial lipid homeostasis (such as

reduced cardiolipin and phosphatidylethanolamine levels), effects rescued by exogenous ESYT1 or artificial MAM tethers (99). In metabolic syndrome-induced endothelial dysfunction, lipid accumulation in cardiomyocytes induces MAM disruption, mitochondrial dysfunction and cardiac remodeling through caveolae/CAV1-mediated signaling, which triggers apoptosis and maladaptive remodeling (100). Desmin and αB-crystallin in SR-MAMs interact with VDAC, MICOS complex component Mic60 and ATP synthase, suggesting roles in mitochondrial quality control and cell survival (Fig. 2) (101).

Diabetic cardiomyopathy. Under high glucose conditions, the formation of MAMs is markedly increased through the involvement of PACS2, IP3R2, FUNDC1 and VDAC1 in H9c2 cardiomyoblasts. This increase in MAMs coincides with decreased mitochondrial biogenesis, fusion and oxidative phosphorylation. However, ferulic acid has been reported to effectively counteract changes in MAM formation and the associated cellular dysfunction (102). IP3R1-GRP75-VDAC1 complex mediates ER-mitochondrial calcium dysregulation, driving atrial remodeling and atrial fibrillation in type 2 diabetes mellitus via exacerbated oxidative stress. GRP75 ablation attenuates these pathological processes in diabetic rat and cell models, identifying this complex as a therapeutic target for diabetes-associated atrial fibrillation (103).

Vessel pruning. Transmembrane protein 215 (TMEM215) is a two-pass protein located in the ER. Knockdown of TMEM215 in endothelial cells triggers apoptosis. TMEM215 interacts with chaperone-BiP and facilitates its interaction with the pro-apoptotic protein BCL-2 interacting killer (BIK). Reducing TMEM215 levels increases the number and proximity of mitochondria-associated ER membranes, leading to enhanced mitochondrial Ca^{2+} influx. It also reduces the distance between MAMs, leading to a higher mitochondrial Ca^{2+} influx. TMEM215, induced by shear stress through enhancer of zeste homolog 2 downregulation, safeguards endothelial cells from BIK-induced mitochondrial apoptosis via Ca^{2+} influx during vessel pruning (Fig. 2) (104).

Energy stress. During the chronic phase of HFD consumption, DRP1 is phosphorylated at Ser616, localizes to MAMs and interacts with Rab9 and Fis1. By contrast, during the acute phase, DRP1 regulates mitophagy independently of MAMs (105). Under energy stress, AMPK translocated from the cytosol to MAMs and mitochondria during mitochondrial fission, where it directly interacts with Mfn2. *Mfn2*$^{-/-}$ mouse embryonic fibroblasts (MEFs) have been reported to exhibit notably reduced autophagic ability under energy stress compared with wildtype MEFs, but re-expressing Mfn2 restored their autophagy. Furthermore, *Mfn2*$^{-/-}$ cells were reported to have a markedly lower abundance of MAMs compared to control (17).

Other CVDs. Stromal interaction molecules (STIMs) are SR Ca^{2+} sensors that initiate store-operated Ca^{2+} entry (SOCE) in several cells. STIM2, which is located in MAMs, interacts with IP3Rs, VDAC, MCU and Mfn2. Studies indicate that in neonatal rat ventricular cardiomyocytes, STIM2.1, the primary variant that inhibits Orai1-driven SOCE, potentially regulates mitochondrial Ca^{2+} uptake through the STIM2-IP3Rs-VDAC-MCU and Mfn2 complexes (17). In rat hearts and skeletal muscle, MAMs are reported to be halved over the lifespan, with early thickening of the clefts. Proteomic analysis has linked aging signatures with disrupted ER-mitochondria communication, affecting metabolism, Ca^{2+} balance, organelle dynamics and autophagy. Decreased levels of proteins such as VDAC1, SAMM50, MTX1 and MIC60 may contribute to age-related MAM dysfunction (106).

4. Conclusions and future perspectives

The emerging evidence emphasizes that the MAM is a key hub for cellular homeostasis, integrating lipid metabolism, calcium signaling (IP3R-VDAC1-Grp75 complex) and mitochondrial dynamics (MFN2-mediated binding and Drp1-regulated fission) (16). The existing research results indicate that MAM dysfunction serves a key role in the pathogenesis of CVD, particularly through mechanisms involving ER mitochondrial calcium overload and lipid toxicity induced membrane remodeling (107,108).

There are still three limitations of the present review: i) The complexity of MAM regulatory networks: Current models inadequately capture the multi-layered regulation of MAM integrity. Whilst canonical pathways (such as Sig-1R-mediated ER stress modulation) have been characterized, systemic interconnections between MAM signaling nodes remain poorly defined; ii) Causal inference in MAM-CVD relationships: Despite robust associative data linking MAM disruption with CVD phenotypes, causal validation remains elusive. The need for cell-type-specific MAM editing tools (such as CRISPRa/i in human induced cardiomyocytes) to dissect tissue-specific patho-mechanisms; and iii) Translational barriers in MAM-targeted therapeutics: The MAM simultaneously participates in pathways such as calcium signaling (IP3R-VDAC1-GRP75), lipid metabolism (Sig-1R-ER stress) and mitochondrial dynamics (MFN2-mediated mitochondrial anchoring). Targeting a single node may trigger compensatory feedback.

The future directions of MAMs in CVD include: i) Dynamic MAM profiling, with implementation of live-cell super-resolution imaging (such as lattice light-sheet microscopy) to resolve MAM remodeling kinetics during CVDs; ii) multi-omic integration, with the combining of spatial lipidomics with proximity-dependent biotinylation (BioID2) to construct disease-specific MAM interaction networks; and iii) organoid models, where patient-derived cardiac organoids are developed with engineered MAM architectures to test genotype-specific therapies.

In conclusion, while the present MAM research provides potential for CVD treatment, bridging molecular mechanisms to clinical applications requires addressing methodological heterogeneity, refining causal inference frameworks and innovating organelle-specific delivery platforms. The present review highlighted the urgency of establishing standardized MAM assessment protocols to accelerate therapeutic discovery.

Acknowledgements

The figures were made by Figdraw (www.figdraw.com).

Funding

The present study was funded by the National Natural Science Foundation of China (grant no. 82100475), Sichuan Science and Technology Program (grant no. 2023NSFSC0617) and Chengdu Women's and Children's Central Hospital Talent Program (grant nos. YC2021003 and YC2022002).

Availability of data and materials

Not applicable.

Authors' contributions

SX and YL contributed to conceptualization. SX, YL and XG contributed to the methodology. The formal analysis, investigation and preparation of the original draft was performed by YL and XG. The review and editing of the manuscript, acquisition of funding and supervision was performed by SX. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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