Current research on mitochondria-associated membranes in cardiovascular diseases (Review)

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Abstract. The present study aimed to explore the role of mitochondria-associated membranes (MAMs) as a key interface between mitochondria and the endoplasmic reticulum (ER) and to evaluate their importance in maintaining the physiological functions of these two organelles. MAMs not only act as a structural bridge between mitochondria and the ER but also widely participate in the regulation of mitochondrial biosynthesis and function, Ca^{2+} signal transduction, lipid metabolism, oxidative stress response and autophagy. In addition, the specific protein composition of MAMs is increasingly being recognized as having a profound impact on their function, and these proteins play a central role in regulating intercellular communication. Recently, the scientific community has accumulated a large amount of evidence supporting MAMs as potential targets for cardiovascular disease treatment. The present review focuses on the fine structure and multifunctional properties of MAMs and their mechanisms in the occurrence and development of cardiovascular diseases. The goal is to explore the mechanism of MAMs, therapeutic intervention points directly related to cardiovascular diseases, and feasibility of incorporating MAMs into the diagnostic strategy and treatment plan of cardiovascular diseases to provide novel insights and theoretical support for clinical practice in this field. MAMs have great potential as therapeutic targets for various cardiovascular diseases. This finding not only deepens the understanding of the interaction between organelles but also opens up a promising research path for the development of new therapeutic strategies for cardiovascular diseases.

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Contents

1. Introduction

With the aging of the population and the transformation of lifestyles, cardiovascular and cerebrovascular diseases have become major public health problems threatening individuals' lives and health. Research data show that the prevalence of cardiovascular diseases is high (1). With the advancement of basic research and clinical practice, related therapies and research have achieved remarkable results. However, they still face numerous challenges, including in-depth analysis of pathological mechanisms, exploration of new therapeutic targets, and development of effective therapeutic strategies.

In cardiovascular research, mitochondria act as a 'power plant' of cells, converting chemical energy in organic matter into chemical energy in ATP through cellular respiration, such as oxidative phosphorylation, providing direct energy for cellular activities (2). This function has attracted considerable attention in recent years. Moreover, as the 'processing workshop' and 'logistics system' of cells, the endoplasmic reticulum (ER) is not only involved in protein synthesis, processing and transportation but is also responsible for lipid synthesis, metabolism and detoxification of foreign substances, which are essential for cell function maintenance (3). However,

studies on the relationship between mitochondria and the ER remain insufficient.

Electron microscopy revealed a narrow space of ~10-30 nm between mitochondria and the ER (4). Numerous protein interactions can occur in this space to promote the orderly progress of biochemical reactions. These proteins form the basis of the functions of mitochondria and the ER, and this specific space is also hypothesized to have special functions. It was mistaken for artifacts owing to technical limitations (5); however, in previous years, this structure has been objectively confirmed with the development of detection technology, and mitochondria-associated membranes (MAMs) may be this special place (6).

Research on MAMs as new targets for the treatment of cardiovascular diseases is increasing. Interference with specific protein complexes or lipid metabolism pathways in MAMs is expected to restore cell Ca^{2+} homeostasis, lipid metabolism balance and mitochondrial function and reduce apoptosis and myocardial injury (7). In addition, promoting MAM-mediated autophagy may help clear damaged organelles and proteins and maintain cell homeostasis and survival. Given the important role of MAMs in cardiovascular diseases, regulating their function may provide a new way to improve the prognosis and therapeutic effects of cardiovascular diseases.

Therefore, the present review aimed to elaborate on the concept of MAMs, explore their structural characteristics, comprehensively elaborate on the basic functions of MAMs based on the proteins in the structure of MAMs and their interaction with mitochondria and the ER, and highlight the application of MAMs in cardiovascular diseases. The present study contributed to the understanding of the relationship between MAMs and cardiovascular diseases and provided new ideas and directions for the study of cardiovascular diseases.

The present article is a literature review, with the following key words being used for literature search: i) MAMs, ii) Mitochondria and iii) ER. PubMed database (https://pubmed.ncbi.nlm.nih.gov/) was utilized and the screening methods were: i) Summarizing the content of the article by reading articles in the past 5 years and ii) eliminating articles that were inconsistent with key words.

2. Special position of MAMs

Before understanding MAMs, it is necessary to clarify that they are not immutable. Consistent with the highly dynamic characteristics of mitochondria, the distance between MAMs, mitochondria and the ER often changes according to the density and difference in ribosomes. When the ribosome density near the smooth ER is low, the distance between ribosomes and mitochondria is usually 10-15 nm. The rough ER has a large number of ribosomes attached to it, and the density of ribosomes is high; therefore, the distance between ribosomes and mitochondria can increase to 20-30 nm (8). This feature also indirectly indicates that MAMs have a relationship with mitochondria. The specific reasons for how ribosomes control the change in distance remain unknown, but it is sufficient to show that the special structure of MAMs plays a specific role in different types of organelles.

As a space shared by mitochondria and the ER, in recent years, increasing evidence has proven the close relationship between MAMs in mitochondria and the ER and it has gradually been found that MAMs are involved in numerous cellular functions. Since they can regulate functions closely related to mitochondria and the ER, such as mitochondrial dynamics, lipid homeostasis (9) and Ca^{2+} homeostasis and as the birthplace of numerous normal maintenance proteins that affect numerous functions, MAMs can be vividly described as central regulators. However, because of their unique location, the organelles related to MAMs confirmed by current research are limited to mitochondria and the ER. However, according to previous studies, it is not difficult to hypothesize that the ER, as a place for the initial processing of lipids and proteins in the Golgi apparatus, is known as the 'sorting station' or 'packaging workshop' of cells. It receives proteins and lipids from the ER and further processes, sorting and packaging, in which Golgi bodies modify proteins, such as through glycosylation, for specific functions. The Golgi apparatus transports these processed substances to specific parts of the cell, such as cell membranes, lysosomes and mitochondria, or secretes them outside the cell through exocytosis. The connection between the ER and Golgi apparatus is also very close, suggesting that MAMs can indirectly affect changes in the Golgi apparatus (10). Similarly, mitochondria must undergo quality control processes such as fission, fusion and autophagy, which are of great significance for cell metabolism, aging, disease development, and therapeutic response. The process of autophagy requires lysosomes to play the role of a 'scavenger'. To protect the integrity of mitochondrial function and stability of cells, and prevent damaged mitochondria from causing damage to cells, damaged mitochondria are specifically encapsulated in autophagosomes and fused with lysosomes to complete the degradation of mitochondrial-lysosomal complexes. This process is known as mitophagy. Similarly, it is assumed that mitophagy-related signals can be sent from MAMs, which are audited by mitochondria and executed by lysosomes. This hypothesis has not yet been confirmed; therefore, the specific mechanism of MAMs in various organelles remains unclear.

3. Function of MAM structure

The structure of mitochondrial-ER membrane contact sites is highly compatible with their function. Studies have shown that there are numerous resident proteins on MAMs, and the physiological functions of some of them have been elucidated. However, due to the wide variety of proteins on MAMs, there are some contradictions in the functional studies of different proteins, leaving a broad space for future research. Simultaneously, the effect of proteins on MAMs on mitochondria and the ER is bidirectional, which also increases the complexity of studying MAM function (Table I).

Maintenance of Ca^{2+} homeostasis. The maintenance of Ca^{2+} homeostasis as a key secondary messenger is crucial for cells. Numerous proteins on MAMs endow them with unique functional properties, and mitochondria play a key role in regulating Ca^{2+} homeostasis and cytoplasmic Ca^{2+} signaling. Calcium flux across the mitochondrial inner membrane is important for decoding cytoplasmic Ca^{2+} signals and increasing ATP production. Ca^{2+} ions enter mitochondria through the mitochondrial Ca^{2+} uniporter complex (mtCU).

Table I. Proteins related to MAMs.

Functional classification	Protein name	Functional description
Calcium homeostasis maintenance	Mitochondrial calcium uniporter complex	It contains the pore-forming subunit MCU and regulatory subunits, such as MICU1 and MICU2, which are responsible for Ca^2 entry into mitochondria and regulate mitochondrial calcium uptake. MICU sets the uptake threshold and regulates Ca^2 exchange on both sides of the intima through dimerization.
	Mfn protein	Mfn2 makes MAMs become a Ca_2 transfer hub and participates in the transport of Ca 2 between endoplasmic reticulum and mitochondria. The control effect of Mfn2 on Ca 2 concentration is controversial.
	DJ-1	It is expressed in various tissues, located in the cytoplasm and membrane gap, interacts with the IP3R3-Grp75-VDAC1 complex, regulates and maintains the stability of MAMs, and participates in mitophagy and homeostasis regulation.
	TDP-43	In physiology, it is mainly in the nucleus, and in pathology, it is abnormally aggregated. It is regulated by FUNDC1 and affects the stability of MAMs.
	CypD	Mitochondrial cyclophilin regulates the opening and closing of mPTP, and abnormal expression affects the structure and function of MAMs.
	FUNDC1	It is widely distributed, concentrated in the heart, regulates mitosis and mitochondrial dynamics, and its structural changes affect mitochondrial morphology through different pathways, which is critical for MAMs formation and disease occurrence.
	SERCA	Endoplasmic reticulum resides in the protein, actively pumps Ca^2 Ω into the ER to maintain normal ER Ca^2 Ω level, and mediates Ca2 Ω-related apoptosis.
	IP3R1-GRP75-VDAC1 complex	MAMs play a regulatory role, silencing GRP75 inhibits ER-mitochondrial calcium transport and reduces mitochondrial oxidative stress.
	ATAD3A	Endoplasmic reticulum-mitochondrial interaction regulators in MAMs prevent ISO-induced mitochondrial calcium accumulation and improve mitochondrial dysfunction and ER stress.
	Seipin	Endoplasmic reticulum proteins, located in MAMs, interact with Ca^2 storage regulators, control mitochondrial Ca^2 input, and regulate mitochondrial metabolism.
Lipid homeostasis maintenance	PS (phosphatidylserine)	The important enzymes of endoplasmic reticulum, mainly in MAMs, are transported to mitochondria and transformed into PE, and some PE return to endoplasmic reticulum and transform into PC, and then distribute other organelles.
	Acetyl-CoA cholesterol acyltransferase	It catalyzes cholesterol to form cholesterol ester, regulates cell membrane binding and cytoplasmic lipid storage, and is a marker of MAMs.
	MLCK	Phosphorylation of MLC enhances its ability to recruit actin filaments to form tight MAMs structure, which is involved in regulating lipid homeostasis.
	MLC	Under the action of MLCK, it is involved in the formation of tight MAMs structure and affects the storage and outflow of lipid cells.
	Scavenger receptor CD36	The upregulated expression of MAMs in metastasis-associated macrophages promotes the uptake of lipid-rich extracellular vesicles by macrophages, regulates lipid metabolism, drives M2 polarization, and promotes tumor metastasis.

Table I. Continued.

Functional classification	Protein name	Functional description
	ORP5 and ORP8	It is located or enriched in MAMs, regulates PS transfer, maintains the normal structure and function of mitochondria, or participates in seipin recruitment to MAM-LD contact sites, and mediates the occurrence and maintenance of LD.
Regulation of mitochondrial homeostasis	Mfn1 and Mfn2	Mfn2 and its heterodimer Mfn1 regulate mitochondrial outer membrane fusion. Mfn2 is important for mitochondrial morphology and function.
	Drp1	Motility-related protein 1, which is involved in mitochondrial fission, interacts with proteins such as FUNDC1 and is regulated by other proteins in MAMs.
	Mff	It is mainly located in the outer membrane of mitochondria, containing hydrophobic helix repeat sequence, transmembrane region and N-terminal GTPase domain. It interacts with Drp1 and plays a key role in mitochondrial division.
	LonP1	In cardiomyocytes, MAMs are proteins that connect endoplasmic reticulum and mitochondria. Deletion leads to decreased MAMs formation and mitochondrial breakage.
Regulate endoplasmic reticulum material exchange and stress	VAPs	It forms a protein complex with Mfn1/Mfn2, builds a physical connection between mitochondria and endoplasmic reticulum, and promotes rapid exchange of substances.
	ACAT	It plays an important role in the transport of cholesterol from endoplasmic reticulum to mitochondria, maintains membrane fluidity, prevents abnormal cholesterol metabolism, and protects endoplasmic reticulum integrity.
	Bap31	Endoplasmic reticulum stress-related proteins affect ERS-related path ways to ensure normal ERS.
	PERK	Participate in protein quality control, prevent protein misfolding and aggregation, eliminate misassembled proteins, and maintain endo plasmic reticulum function stability.
	Fis1	Mitochondrial fission protein 1 homologues, with the participation of MAMs, affect Drp1 recruitment, change mitochondrial morphology and function, and participate in mitochondrial fission and endoplasmic reticulum-induced apoptosis.

MAMs, mitochondria-associated membranes; MICU, mitochondrial Ca2+ uptake protein; Mfn, mitofusim; IP3R1, inositol 1,4,5-trisphosphate receptor type 3; GRP75, heat shock protein family A (Hsp70) member 9; VDAC1, voltage-dependent anion channel; FUNDC1, FUN14 domain-containing protein 1; SERCA, ATPase sarcoplasmic/endoplasmic reticulum Ca2+ transporting 2; ER, endoplasmic reticulum; MLCK, myosin light chain kinase; MLC, myosin light chain protein; ORP, oxysterol binding protein like; Drp1, recruiting dynamin-related protein 1; mff, mitochondrial fission factor; LonP1, lon peptidase 1, mitochondrial; VAPs, amine oxidase copper containing 3; ACAT, cholesterol acyltransferase; Bap31, B cell receptor-associated protein 31; (PERK), eukaryotic translation initiation factor 2 α kinase 3; Fis1, mitochondrial fission protein 1.

The mtCU is not only a Ca^{2+} channel, but it also decodes the dynamic Ca^{2+} signal by reducing mitochondrial Ca^{2+} uptake at rest and increasing uptake when the physiological level of Ca^{2+} increases. The large electrochemical gradient generated by the electron transport chain on the mitochondrial inner membrane drives mitochondrial Ca^{2+} uptake; therefore, the mtCU requires a regulatory mechanism to prevent continuous uptake and overload.

The mtCU is composed of multiple subunits, including the pore-forming subunit, mitochondrial calcium uptake 1 (MCU), and multiple regulatory subunits. The mitochondrial Ca^{2+} uptake protein (MICU), as the Ca^{2+} sensor of the MCU, sets the threshold for mitochondrial Ca^{2+} uptake and synergistically activates the MCU when the concentration of Ca^{2+} increases (11). The MICU regulates Ca^{2+} ion exchange on both sides of the intima through dimerization to further regulate

mitochondrial Ca^{2+} concentration. MICU1 and MICU2 are important members of the homologous protein family. They close the channel in a low-Ca^{2+} environment through the MCU complex and perform dimer rearrangement in a high-Ca^{2+} environment to activate the MCU channel, thereby achieving precise regulation of mitochondrial Ca^{2+} absorption (12).

In addition, the presence of mitofusim (Mfn) protein makes MAMs key hubs for Ca^{2+} ion transfer. When mitochondria absorb Ca^{2+} ions released from the ER to MAMs through Mfn (13), intracellular Ca^{2+} ions can enter the cytoplasm through the Inositol-1,4,5-triphosphate receptor (IP3R) or RyR channels. When the concentration of Ca^{2+} ions is low, the absorption rate of Ca^{2+} by mitochondria decreases. When the concentration of Ca^{2+} ions increases, the transfer rate of Ca^{2+} ions between mitochondria and the ER increases accordingly. Moreover, MAMs may also be involved in the regulation of this process, but how Mfn regulates the movement of Ca^{2+} ions in MAMs and the ER is inconclusive. Whether Mfn2 is an important target for controlling Ca^{2+} ion concentration in MAMs remains controversial (14).

In addition to the aforementioned important proteins, MAMs also contain DJ-1, TDP-43, cyclophilin D (CypD), and other proteins that are not directly involved in the structure of MAMs but are essential for their regulatory functions. At present, related research is gradually being carried out, among which the study of FUN14 domain-containing protein 1 (FUNDC1) is the clearest. FUNDC1 is widely distributed throughout the body, particularly in the heart (15). It consists of 155 amino acids, three transmembrane domains, and a typical N-terminal leucine zipper transcription regulator motif (5). This structure facilitates the binding of microtubule-associated protein 1 light chain 3 to regulate mitosis, which is more pronounced in hypoxic environments. This is mainly due to decreased Src kinase activity and phosphorylation of Tyr18, resulting in enhanced binding of microtubule-associated protein 1 light chain 3 to FUNDC1 (16). In addition, nuclear respiratory factor 1, a transcription factor, binds to promoter 186/176 of FUNDC1 and activates FUNDC1 (17).

In addition to mitosis, when lysine 10 in FUNDC1 is eliminated, mitochondria break, indicating that FUNDC1 has a regulatory effect on mitochondrial dynamics (18). By contrast, FUNDC1 regulates mitochondrial morphology. Inhibition of FUNDC1 in HeLa cells leads to increased mitochondrial fusion. By contrast, promoting FUNDC1 expression inhibits mitochondrial fusion. This function achieves mitochondrial fission by recruiting dynamin-related protein 1 (DRP1) to mitochondria (19). When the S13 residue in FUNDC1 is phosphorylated, the connection between FUNDC1 and DRP1 is weakened and the connection with optic atrophy protein 1 is enhanced, synergistically regulating mitochondrial dynamics (16). Thus, changes in FUNDC1 structure affect mitochondrial morphology through different pathways. Additionally, the upstream regulation of FUNDC1 and changes in FUNDC1 expression play key roles in controlling the formation of MAMs and the occurrence of different diseases.

Ca^{2+} ion flow is also regulated by the ER resident protein SERCA, which maintains normal ER Ca^{2+} levels by actively pumping Ca^{2+} from the intracellular space into the ER, and it also plays a crucial role in mediating Ca^{2+}-related apoptosis (20). In addition, the inositol 1,4,5-trisphosphate receptor type 3 (IP3R1)-heat shock protein family A (Hsp70) member 9 (GRP75)-voltage-dependent anion channel (VDAC1) complex is considered to play a regulatory role in MAMs. Silencing GRP75 can inhibit ER-mitochondrial Ca^{2+} transport and reduce mitochondrial oxidative stress, thereby preventing diabetes-induced atrial remodeling (21). Combot *et al* (22) reported that the ATPase family AAA domain-containing protein 3A (ATAD3A) is an important regulator of ER-mitochondrial interaction in MAMs. ATAD3A can prevent isoproterenol-induced mitochondrial Ca^{2+} accumulation and improve mitochondrial dysfunction and ER stress, thereby protecting cardiac function and reducing cardiac hypertrophy. In addition, studies have shown that the ER protein seipin is located in MAMs and can control the input of mitochondrial Ca^{2+} ions by interacting with Ca^{2+} storage regulators, such as SERCA2, IP3R, and VDAC1 in MAMs, thereby regulating the normal operation of mitochondrial metabolism (22).

Maintenance of lipid homeostasis. MAMs are closely associated with lipid homeostasis and interfere with lipid synthesis. The ER is the main synthesis site of intracellular lipids. Lipids need to be synthesized by the ER and delivered to other organelles, which requires the assistance of mitochondria. Therefore, MAMs are crucial for maintaining lipid homeostasis. In addition, MAMs are involved in the regulation of cholesterol metabolism. When lipid levels are high, MAMs promote cholesterol transport to the liver and accelerate its metabolism, whereas when lipid levels are low, MAMs inhibit cholesterol transport and help maintain intracellular cholesterol storage. Phosphatidylserine is an important enzyme in the ER that is mainly distributed on MAMs and transported to mitochondria for conversion into phosphatidylethanolamine (6). A small portion of PE is returned to the ER, converted into phosphatidylcholine, and distributed to other organelles. MAMs are also involved in the production of ceramides, regulation of cell proliferation, inflammation, differentiation and apoptosis (23,24). Acetyl-CoA cholesterol acyltransferase plays an important role in lipid homeostasis by catalyzing the formation of cholesterol esters and regulating cell membrane binding and cytoplasmic lipid storage. It is often used as a marker because of its abundance in MAMs. However, the mechanism of action of lipid transfer proteins in MAMs remains to be explored. Enzymes that maintain lipid homeostasis also play an important role in maintaining the integrity of the mitochondrial membrane, thereby strengthening the connection between the ER and mitochondria. MAMs involved in the regulation of lipid homeostasis are mainly composed of myosin light chain kinase and myosin light chain protein. Myosin light chain kinase is responsible for phosphorylating myosin light chain protein and enhancing its ability to recruit actin filaments to form a tight MAM structure. When the lipid level is high, the structure of MAMs is susceptible to interference, the stability decreases, and fatty acids are more likely to flow out of the cell; on the contrary, when the lipid level is low, the structure of MAMs is stable, which is beneficial to the storage of lipid in cells. Surprisingly, the expression of the scavenger receptor CD36 is upregulated in the MAMs of metastasis-associated macrophages. By promoting the uptake of lipid-rich extracellular vesicles by macrophages, it regulates macrophage lipid

metabolism and drives M2 polarization to reshape the tumor microenvironment and promote tumor metastasis (25).

Lipid droplets (LDs), the main organelles involved in cellular lipid storage, originate from the ER (26). The ER resident protein seipin in MAMs is a key regulator of LD biogenesis. Seipin mutations are closely related to imbalances in intracellular lipid metabolism and Ca^{2+} homeostasis (27). Guyard *et al* (28) found that oxysterol binding protein like (ORP)5 and ORP8 are also localized or even enriched in specific ER subdomains in contact with mitochondria, namely the MAM, and regulate the transfer of PS to maintain the normal structure and function of mitochondria, or are involved in the process of seipin recruitment to the MAM-LD contact site, mediating the occurrence and maintenance of LDs.

Regulating mitochondrial homeostasis. Mitochondria are a key source of power in mammalian cells and are essential for the regulation of cell metabolism, proliferation, survival and death (29-31). It generates energy mainly through key metabolic pathways, such as oxidative phosphorylation, tricarboxylic acid cycle, and fatty acid β-oxidation, and produces most of the cellular reactive oxygen species (ROS) through the electron transport chain.

MAMs mediate the exchange of different ions and metabolites and play a key role in regulating mitochondrial dynamics and Ca^{2+} homeostasis (32). Mitochondrial fission, fusion and apoptosis constitute a complex dynamic network. In this process, the Mfn2 protein and its heterodimer partner Mfn1 play a vital role, and they jointly regulate the fusion process of the mitochondrial outer membrane (33). MAMs are the initial sites of mitochondrial fission (34). Mitochondrial fission protein 1 (Fis1), mitochondrial fission factor and mitochondrial dynamics proteins preferentially accumulate in MAMs prior to mitochondrial fission (35). ATAD3A in MAMs can inhibit excessive activation of mitochondrial fission, which is helpful in maintaining the integrity of the mitochondrial ultrastructure (36). Mfn2 is another resident protein of MAMs that is present in the outer membrane of mitochondria and is essential for mitochondrial morphology and function. It is a key GTPase that is involved in mitochondrial fusion. It has been found that it has the opposite function (37). IP3R acts as a key Ca^{2+} outflow channel on the ER surface, mediating the flow of Ca^{2+} from the ER lumen to the cytoplasm. The Ca^{2+} homeostasis in mitochondria is controlled by the VDAC protein on the outer membrane of mitochondria, which controls the inflow and outflow of Ca^{2+} to maintain Ca^{2+} homeostasis. The two need to be connected by Grp75 in MAMs to maintain the structure of MAMs. The specific mechanism of the interaction between the three remains to be further studied (38). Other proteins such as DJ-1 are expressed in various tissues and are mainly located in the cytoplasm and membrane. Under oxidative stress, DJ-1 mainly regulates and maintains the stability of MAMs by interacting with the IP3R3-Grp75-VDAC1 complex, which can be transferred to the mitochondria to participate in mitophagy and regulate mitochondrial homeostasis (39). TDP-43 is a nucleic acid-binding protein encoded by *TARDBP*. It is mainly localized to the nucleus under physiological conditions, whereas abnormal aggregation occurs under pathological conditions. It has been recently reported that the mitophagy receptor FUNDC1 can regulate the structure and homeostasis of TDP-43 through its own expression differences and interaction with different proteins, and then participate in the quality control process of mitochondria and affect the stability of MAMs (40). CypD is a cyclophilin located in mitochondria, which can regulate the opening and closing of the mitochondrial permeability transition pore (mPTP). Abnormal CypD expression can affect the structure and function of MAMs, thereby interfering with disease development (41).

Ca^{2+} homeostasis affects mitochondrial dynamics. Mitochondrial Ca^{2+} and ROS synergistically regulate the opening of mPTPs. Excessive ROS production may lead to abnormal mitochondrial Ca^{2+} accumulation, which in turn affects mitochondrial function. Under oxidative stress conditions, MAMs produce a small increase in ROS, which maintains cell survival by reducing the ER-mitochondrial Ca^{2+} transfer (42,43). Excessive Ca^{2+} induces excessive production of mitochondrial ROS through MAM transfer (32). Inhibition of FUNDC1 and reduction in MAM formation can improve mitochondrial ROS overproduction (44). Ca^{2+} channel modulators in MAMs play a key role in the regulation of ROS. ERO1α and ERp44 are highly enriched enzymes in MAMs. ERO1α contains a redox domain responsible for catalyzing the formation and isomerization of disulfide bonds. It is mainly located in the ER and participates in oxidative folding of proteins, indirectly affecting the structure and function of MAMs. ERp44 also exhibits disulfide isomerase activity and can repair misfolded proteins. Although it is not directly localized to MAMs, it can circulate between the ER and Golgi apparatus, indirectly affecting MAM function (45). Similarly, INF2, an ER-localized protein, aggregates with Drp1 and initiates the initial mitochondrial fission process (45). ERO1α causes the separation of ERp44 and IP3R by oxidizing IP3R, thereby exacerbating the transfer of Ca^{2+} from the ER to mitochondria and leading to excessive ROS production (46).

It has been shown that mtDNA replication, mitochondrial transport, and mitochondrial fission occur in MAMs (9). Notably, MAMs have been recently regarded as the starting point of mitochondrial fission, where Drp1, Fis1 and Mff are present in large numbers to participate in this process (45). Mff is mainly located in the outer membrane of mitochondria and participates in the localization process. Its N-terminus also contains a GTPase domain that plays a critical role in mitochondrial division by interacting with Drp1 (47), thereby maintaining mitochondrial health and normal function. In cardiomyocytes, LonP1 connects the ER and mitochondria in MAMs, and its deletion leads to decreased MAM formation, which in turn causes mitochondrial rupture (45). Thus, MAMs play a role in the survival of mitochondria not only from their own proteins, but also through the ER, an organelle.

MAMs regulate ER material exchange and stress. As a key link between mitochondria and the ER, MAMs are essential for cell activity (48). MAMs are important platforms for substance exchange, allowing for the effective exchange of key molecules and substances, such as Ca^{2+} ions, phospholipids and cholesterol, between two organelles to maintain the normal function and metabolic stability of related organelles. MAMs form protein complexes through Mfn1/Mfn2 and amine oxidase copper containing 3 (VAP) to build a direct physical connection between mitochondria and the ER,

thereby promoting the rapid exchange of Ca^{2+} ions, phospholipids and other metabolites. MAMs are rich in cholesterol acyltransferase and play an important role in cholesterol transport from the ER to mitochondria. After synthesis of the ER, it is transported to other organelles, such as mitochondria, through lipid rafts to meet the structural and functional requirements of target organelles, maintain fluidity between mitochondria and the ER membrane, prevent metabolic abnormalities of cholesterol, and protect the integrity of the ER. In this process, MAMs may be involved in the formation and maintenance of lipid rafts, which are of great significance for maintaining their function (49,50). MAMs are also important for the regulation of ER stress (ERS) (51). MAMs are rich in the Ca^{2+} release channel protein IP3R as the receptor of IP3 in the ER and have the pore protein VDAC1 of the mitochondrial outer membrane, which is connected to form a complex through the molecular chaperone GRP75, thereby promoting Ca^{2+} ion signal transmission between the ER and mitochondria to maintain the balance and stability of Ca^{2+} ions (52), which is crucial for the regulation of ERS. Because Ca^{2+} fluctuations can activate the unfolded protein response, and proteins in the ER must be correctly folded to perform corresponding functions, MAMs participate in the quality control process of proteins through their own proteins, such as eukaryotic translation initiation factor 2α kinase 3 (PERK), to prevent misfolding of proteins and excessive aggregation of misfolded proteins, while removing misassembled proteins to maintain the stability of ER function. There are also some ERS-related proteins on MAMs (53), such as B cell receptor-associated protein 31 (BAP31) and Mfn2, which can directly or indirectly affect the related pathways of ERS and ensure the normal progress of ERS.

In addition to these functions, MAMs participate in the regulation of autophagy, apoptosis, and numerous other biological processes. For example, MAMs affect cell apoptosis and signal transduction through specific proteins (53), such as IP3R, VDAC1 and PERK, and thus play a key role in maintaining the stability of the intracellular environment and coordination between organelles. For example, Fis1 and BAP31 are resident proteins on MAMs. Fis1 has an effect on the recruitment of Drp1 under the participation of MAMs, as well as the morphological and functional changes in mitochondria, which have an important impact on mitochondrial fission, and participates in ER-induced apoptosis (54), thereby maintaining cell homeostasis.

In summary, MAMs play a vital role in cells. As a bridge between the ER and mitochondria, they are involved in several cellular physiological and pathological processes. MAM dysfunction is also associated with various diseases, including neurodegenerative (53), cardiovascular and metabolic diseases (55). Therefore, studying MAMs is of great significance for the diagnosis and treatment of cardiovascular diseases (Fig. 1).

4. MAMs and cardiovascular diseases

Diabetic cardiomyopathy (DCM). DCM is a unique complication of diabetes and a major cause of death. Its pathological features include cardiomyocyte hypertrophy, interstitial fibrosis and impaired coronary microvascular perfusion (56). DCM usually has no clinical symptoms in the early stages; however, patients generally show abnormal cardiac diastolic function. Subsequently, in the absence of dyslipidemia, hypertension, or coronary heart disease, cardiac diastolic or systolic dysfunction occurs, which eventually leads to heart failure (HF) and is one of the main causes of death in patients with diabetes (57). Studies have shown that, compared with non-diabetic patients of the same age, the incidence of HF in male patients with diabetes increased by 2.4 times, whereas that in female patients increased by 5 times. However, owing to the lack of large amount of data on different populations with diabetes, the incidence of DCM remains unclear. Other studies have reported that the prevalence of diastolic dysfunction in patients with type 2 diabetes is high, reaching 40-60% (58,59). Presently, it is considered that comorbid factors such as chronic systemic hypertension and vascular atherosclerosis (AS) can promote the occurrence of cardiovascular diseases in patients with diabetes, but insulin resistance and hyperglycemia are undoubtedly the basis and core of the occurrence and development of DCM (60). The potential molecular mechanism underlying DCM is not fully understood and involves multiple factors and complex pathophysiological processes, including oxidative stress, neurohormone activation, Ca^{2+} homeostasis damage and mitochondrial damage (16). Abnormal glucose and lipid metabolism can lead to inflammatory responses, oxidative stress and ERS, which promote each other and form a vicious circle, leading to myocardial death, hypertrophy, fibrosis, microcirculation disorders, and ultimately, HF (61). Energy metabolism remodeling is the core hub connecting diabetes and HF. As the most energy-consuming organ of the human body, the heart has very little energy reserve and requires a continuous ATP supply to maintain normal operation. In diabetic HF, the two core energy 'reactors' of the heart are disordered and toxic; one is the imbalance of fatty acid oxidation and utilization; the supply and uptake of fatty acids in cardiomyocytes are increased, but the ability of mitochondrial oxidation and utilization is decreased, resulting in myocardial lipid accumulation and lipotoxic substances; second, the glucose supply and uptake of cardiomyocytes are increased, but the aerobic oxidative phosphorylation of myocardium is decreased, anaerobic glycolysis is increased, and glucotoxic substances are produced (62-64). Additionally, DCM cardiomyocytes lose the ability to randomly select substrates and rely on fatty acid utilization to supply energy. This contradiction forces the heart to compensate for high energy consumption, high oxygen consumption, low supply, and low efficiency. Long-term overload eventually causes the myocardium to enter a state of decompensation and failure (65).

In previous years, studies have indicated that MAMs play an important role in DCM. In a mouse model of type 2 diabetes, the connection between the ER and mitochondria was enhanced in the early stages (66,67). Wu *et al* (68) confirmed this in high glucose-treated mouse cardiomyocytes and mice carrying the insulin 2 gene; however, the specific mechanism has not been elucidated. Changes in FUNDC1 levels in cardiac tissues of patients with diabetes are significant. Decreased FUNDC1 expression inhibits abnormal cardiac tissue in patients with diabetes, which may be closely related to the Ca^{2+} transfer function of MAMs. Wang *et al* (69) detected mitochondrial Ca^{2+} overload in patients with high

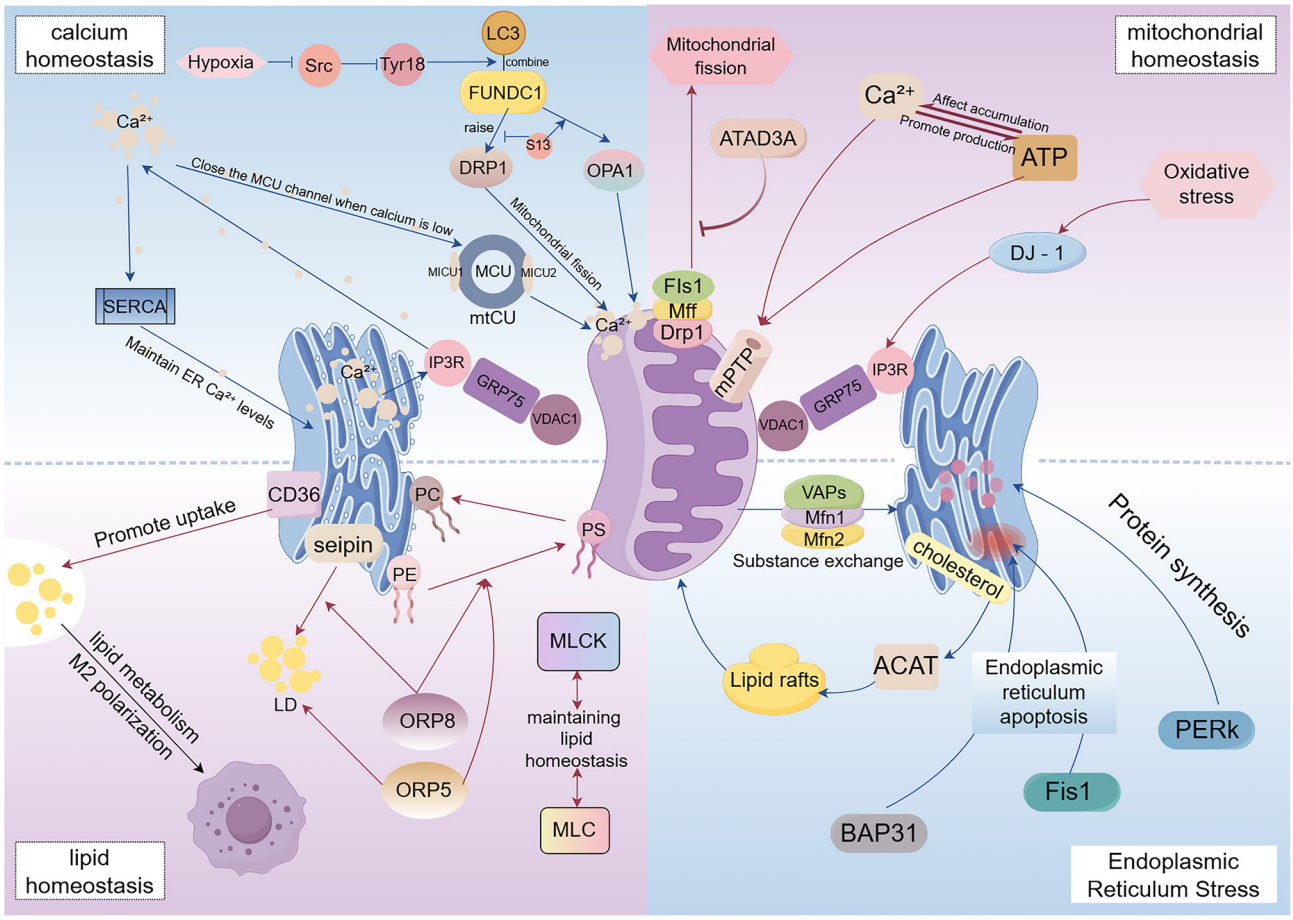

Figure 1. Summary diagram of the functions created by the structure of MAMs. MAMs, mitochondria-associated membranes; FUNDC1, FUN14 domain-containing protein 1; Drp1, recruiting dynamin-related protein 1; MICU, mitochondrial Ca^{2+} uptake protein; MCU, mitochondrial calcium uptake 1; MTCU, mitochondrial Ca^{2+} uniporter complex; SERCA, ATPase sarcoplasmic/endoplasmic reticulum Ca^{2+} transporting 2; IP3R1, inositol 1,4,5-trisphosphate receptor type 3; GRP75, heat shock protein family A (Hsp70) member 9; VDAC1, voltage-dependent anion channel; mff, mitochondrial fission factor; DJ-1, parkinsonism associated deglycase; VAPs, amine oxidase copper containing 3; Mfn, mitofusim; ACAT, cholesterol acyltransferase; PERK, eukaryotic translation initiation factor 2 α kinase 3; Fis1, mitochondrial fission protein 1; Bap31, B cell receptor-associated protein 31; MLCK, myosin light chain kinase; MLC, myosin light chain protein; ORP, oxysterol binding protein like; KLF4, KLF transcription factor 4.

glucose levels. Under normal circumstances, MAMs ensure the stability of mitochondrial and ER contact points and play an important role in maintaining intracellular Ca^{2+} balance and lipid metabolism. In the case of diabetes, when the level of FUNDC1 increases, it interacts with IP3R on MAMs, promotes MAM formation, increases Ca^{2+} concentration in mitochondria, hinders the normal energy metabolism function of mitochondria, and affects the production process and redox state of cardiomyocytes, thus affecting the function of the whole heart. In response to this situation, Xie *et al* (70) found that metformin improved cardiac structure by reducing FUNDC1 levels by inactivating AMPK, suggesting that MAMs are potential targets for metformin to improve blood vessels. FUNDC1 interacts with IP3R2 to promote Ca^{2+} transfer in DCM. When glucose concentration increases, the activation of FUNDC1 promotes the binding of cyclic AMP response element-binding protein to the Fis1 promoter, thereby promoting MAM formation. Thus, FUNDC1 has a maintenance effect on MAMs. Inhibition of FUNDC1 leads to the formation of a large number of MAMs, changes in mitochondrial morphology and function, initiation of apoptotic procedures, and abnormal death of numerous mitochondria, resulting in reduced mitochondrial synthesis and failure of the respiratory chain to operate normally. In response to this problem, Ding *et al* (71) reduced the formation of MAMs using ferulic acid and metformin, enhanced the expression of FUNDC1, and successfully ameliorated the symptoms of cardiomyopathy caused by diabetes.

In the context of DCM, the function of phosphofurin acidic cluster sorting protein 2 (PACS-2) has also received significant attention. As a multifunctional sorting protein that plays a role in MAMs, PACS-2 plays a key role in maintaining the homeostasis of mitochondria, ER and lysosomes (72). For patients with diabetes, the decreased level of PACS-2 in MAMs *in vivo* may lead to the destruction of the structure and function of MAMs, which may be related to the IP3R-Grp75-VDAC1 complex regulating Ca^{2+} homeostasis and mitochondrial autophagy dysfunction (73). The significant decrease in the complex IP3R-VDAC1 detected in the subjects confirmed this conclusion (66). In a diabetic mouse model, SIRT3 inhibited the excessive proximity of Mito-ER and increased ROS by limiting the formation of abnormal MAMs, while reducing the levels of the pro-apoptotic protein Bax, activating caspase 3, and increasing the level of the anti-apoptotic protein Bcl2,

thereby inhibiting apoptosis. SIRT3 can also promote the deacetylation of VDAC1 and reduce the enhancement of the interaction between IP3R, GRP75 and VDAC1 in MAMs, thereby reducing the formation of MAMs and protecting neurons from damage (74). Salin *et al* (75) found that under high glucose conditions, the upregulation of phosphofurin acidic cluster sorting protein 2 (*PACS2)* promotes the formation of MAMs, while reducing mitochondrial biosynthesis and oxidative phosphorylation, and driving mitochondrial apoptosis, which is crucial in the molecular pathogenesis of DCM. Basic helix loop helix ARNT like 1 (*Bmal1)* plays a key role in heart health, and changes in its expression directly affect the heart function. Downregulation of *Bmal1* aggravates cardiac hypertrophy and DCM, whereas its upregulation improves symptoms. *Bmal1* reduces mitochondrial Ca^{2+} overload and apoptosis in MAMs by regulating the Bcl2/IP3R pathway, thereby providing a new direction for DCM treatment (76).

AS. AS is a progressive chronic vascular disease. It refers to a lesion on the inner wall of large and medium arteries. It mainly manifests as lipid deposition in the intima of the artery and gradually accumulates to form atherosclerotic plaques, eventually leading to stenosis or occlusion of the arterial lumen. It is an important branch of cardiovascular and cerebrovascular diseases. The common risk factors for AS include hypertension, smoking, hyperlipidemia, diabetes and obesity (77). AS mortality, morbidity and disability rates are high and show a trend toward a younger age. One reason why AS has these characteristics is that plaques are more likely to rupture during the evolution of the disease, resulting in more dangerous clinical events secondary to thrombosis, such as stroke and acute coronary syndrome. Currently, clinical diagnosis mainly relies on ultrasound, magnetic resonance imaging and CT imaging, and early identification and prognostic judgment are still lacking (78). Widely used clinical treatment methods include best medical treatment (BMT) and surgical treatment, but long-term BMT treatment undoubtedly increases the liver burden for patients and may also cause adverse reactions such as gastrointestinal discomfort and cardiac rhythm disorders (79). Surgical treatment may lead to postoperative bleeding, recurrence, and other consequences in patients with a high preoperative status. Therefore, in recent years, the diagnosis, treatment and late detection of thrombotic plaques in AS have gradually become the focus of global AS prevention and treatment.

Inflammation is generally considered to be a key factor in all stages of AS, involving macrophages, lymphocytes, dendritic cells, endothelial cells, vascular smooth muscle cells, and various cytokines and adhesion factors. Oxidized low-density lipoprotein triggers NF-κB through the CD36 receptor, thereby triggering an inflammatory response that eventually leads to vascular wall destruction and thrombosis (80). In recent years, the role of immune factors in AS progression has attracted attention, and researchers have explored AS treatment strategies that target the immune response. Nanomedicine has shown potential in the diagnosis and treatment of AS, but it also faces biosafety challenges (78). The effect of gut microbiota on cardiovascular diseases provides a new approach for the targeted treatment of AS. Intestinal flora may be involved in the development of AS by affecting the inflammatory response and endothelial cell function, as well as being associated with changes in blood pressure. The gut and oral microbes found in atherosclerotic plaques, as well as the association between plaque stability and *Roseburia* fecal levels, further confirmed this hypothesis (81).

A number of studies have shown that MAMs can crosstalk with inflammation in cardiovascular diseases, including in the field of AS (82-85). For example, studies have shown that oxidized low-density lipoprotein can increase the expression of MAM-related PACS-2 protein in cells, thereby mediating MAM formation by promoting ER-mitochondrial contact (85). Chen *et al* (85) found that PACS-2 is an essential factor for normal mitophagy in vascular smooth muscle cells. Its downregulation inhibits mitophagy and reduces the assembly of the inflammasome NLR family pyrin domain containing 3 (NLRP3), which in turn enhances cell death (85). In addition, MAMs, as a platform for the assembly of the inflammasome NLRP3, can also affect the release of the chronic inflammatory factors IL-1β and IL-18 (82). The dissociation of hexokinase 2 and VDAC triggers the activation of IP3R, which mediates the production of ER-mitochondrial Ca^{2+} current, leading to VDAC oligomerization and the formation of NLRP3 inflammasome complex (86). Therefore, targeting MAM formation or NLRP3 and its upstream steps is a potential strategy for treating AS.

From the current research status, Mfn2 protein is also a promising therapeutic target for AS. Studies have confirmed that Mfn2 can inhibit calcification of blood vessels in AS by activating the RAS-RAF-ERK1/2 pathway (87). Yimai granules regulate mitophagy mediated by the PTEN induced kinase 1 (Pink1)-Mfn2-Parkin pathway through miRNA-125a-5p and regulate pro-inflammatory factors and blood lipids to inhibit AS (88). In addition to miRNA-125a-5p, MiR-93 acts on Mfn2 protein to regulate the proliferation and migration of smooth muscle cells (89). The ER resident protein RTN4 has the potential to regulate MAM formation, and NUS1 dehydrodolichyl diphosphate synthase subunit (Nogo-B) is an important member of this family. Nogo-B is highly expressed in vascular endothelial cells and smooth muscle cells (7). Clinical studies have shown that Nogo-B expression is upregulated in human atherosclerotic plaques. Zhang *et al* (90) further explored its mechanism of action, proving that Nogo-B mediates inflammation by triggering mitochondrial ROS production and p38-p65 signaling, thereby affecting the normal function of vascular endothelial cells.

Phosphorylation of the Ca^{2+} channel IP3R directly affects the recruitment of Ca^{2+} from the ER to the cytoplasm and regulates platelet activation and aggregation in AS. Artesunate induces the phosphorylation of IP3R by increasing cAMP content in platelets and indirectly downregulating the recruitment of Ca^{2+} ions in platelets, platelet aggregation and thrombosis, thereby improving the prognosis of patients with cardiovascular disease (91). Targeting the Ca^{2+} ion flow during platelet activation is an effective treatment approach. The relationship between the mitophagy downstream mediator DJ-1 and AS can be observed in the regulation of vascular smooth muscle cell surface conversion and plaque stability. The underlying mechanism is that DJ-1 inhibits the KLF transcription factor 4 pathway, thereby affecting the phenotypic transformation of Lamin A/C (VSMC) (92). In addition,

downregulation of DJ-1 significantly increases plaque vulnerability by affecting matrix proteins and metalloproteinases. Thus, DJ-1 also plays an important role in plaque stability (92).

HF. HF, the end stage of various cardiovascular diseases, is a complex clinical syndrome. As the heart cannot pump enough blood and oxygen to support the metabolic needs of other organs, it often manifests clinically as dyspnea, lower-limb edema and fatigue. Owing to the rapid increase in morbidity and mortality rates, it has become a serious public health problem.

A total of ~64 million individuals worldwide suffer from HF, and this number is increasing annually owing to factors such as an aging population (41). According to statistics from the European Society of Cardiology, >15 million/~1 billion individuals have HF (23). In addition, the National Hospital Discharge Survey in the United States showed that the number of patients over 65 years of age diagnosed with congestive HF increased by 48.5% from 1970 to 1985. Epidemiological studies in China have found that ~8.9 million individuals are currently affected, an increase of 44% compared with that in 2000 (24,25). According to research, the prevalence of HF in China has exceeded 2-3% (35). It can be observed that HF has become a serious public health problem, despite the diversity of current treatments. However, hospitalization and mortality rates remain high (14).

Currently, it is considered that the pathophysiological mechanism of HF is extremely complex. It is generally considered that myocardial cell mitochondria, one of the main areas of cell aerobic respiration and energy metabolism, are widely involved in cell proliferation, differentiation, apoptosis, information transmission, energy metabolism, and other pathophysiological processes. Their dysfunction is closely associated with the occurrence and development of HF (93). It is necessary to conduct more in-depth and detailed prevention and control studies in this field.

Patients with myocardial infarction (MI), myocardial injury, and even necrosis are prone to HF. By examining mice after MI, it was found that the SR Ca^{2+} of MAMs was damaged through the RyR2 channel, resulting in a large accumulation of Ca^{2+} in mitochondria, which changed mitochondrial activity and increased the probability of MI. In addition, FUNDC1 can affect the connections between SR Ca^{2+} channels. Under normal conditions, FUNDC1 interacts with FBXL2 to degrade IP3R3, thereby maintaining balanced mitochondrial mass. However, the lack of FUNDC1 in mice fed a high-fat diet disrupted this balance (68,94), causing myocardial cell remodeling and HF. The Sig-IR pathway is also present in mice fed a high-fat diet (95). Under normal conditions, Sig-IR prevents the death of mice by inhibiting the destruction of myocardial cells caused by oxidative stress, whereas the Sig-IR pathway in mice fed a high-fat diet is reversed by mitochondrial Ca^{2+} overload.

Mfn2 also plays an important role in mice with HF. The upregulation of Mfn2 reverses the production of ROS and depolarization of mitochondria, thus avoiding changes in the hypertrophic phenotypes of cardiomyocytes (96). This was also confirmed by the decrease in Mfn2 levels in mice with HF (97). The expression levels of Fis1 and DRP1 in mice with HF after myocardial ischemia-reperfusion were downregulated by drugs, while the expression level of Mfn2 was upregulated; this effectively prevented abnormal division and loss of mitochondria and protected myocardial function. During this process, the expression of Mfn1 increased (98).

BAP31 is a membrane protein on MAMs that is involved in apoptosis and autophagy (99). The BAP31-Fis1 complex is involved in the regulation of Ca^{2+} release from the ER, thereby activating mitochondria and leading to apoptosis. There is a close relationship between PACS2 and BAP31. When PACS2 concentration decreases, BAP31 is cleaved into p20, resulting in the release of Ca^{2+} from the ER. Studies have shown that myocardial injury is aggravated after reduced PACS2 concentration. This result suggests that BAP31 on MAMs is associated with HF (100).

In addition, decreased FUNDC1 expression has been detected in both patients with HF and mouse cardiomyocytes (101,102). Further studies have shown that FUNDC1 mainly damages mitochondrial function and cardiomyocytes. There is an inevitable link between mitochondrial dysfunction and MAM destruction (102). Similar to metformin, α-lipoic acid reduces the phenotypic changes in cardiomyocytes by inhibiting FUNDC1 (103). In addition, FUNDC1 can induce mitochondrial autophagy, rapidly induce apoptosis, and lead to MI (104).

Myocardial hypertrophy is an independent risk factor for cardiovascular diseases and is closely associated with the development of HF. Treatment of rats with myocardial hypertrophy with difluoro-methyl-ornithine showed that difluoro-methyl-ornithine downregulated the expression of GRP75, VDAC1 and CypD in MAMs, improved myocardial hypertrophy, and regulated apoptosis. The present study also showed that MAMs pathway may play a key role in myocardial hypertrophy (105). Luan *et al* (106) evaluated protein expression in cardiomyocytes of rats with TAC-induced cardiac hypertrophy and found that genes encoding MAM-related proteins were preferentially expressed in cardiac hypertrophy samples. Notably, Fis1, Hspa9, Mfn 1, and Mfn2 expression increased 2 weeks after TAC treatment but decreased at 8 and 11 weeks (HF period). These two experiments showed that different proteins in MAMs have different regulatory effects on the development of cardiac hypertrophy.

Myocardial ischemia reperfusion. Ischemic heart disease is one of the four leading causes of death worldwide with a high mortality rate (107) and prevalence in men. In addition, with increasing age, the incidence of ischemic heart disease shows an increasing trend annually (108). Ischemic heart disease includes the pathological process of myocardial ischemia, and myocardial ischemia-reperfusion is generally the main treatment plan for restoring the blood supply after MI. If the blood supply to the coronary artery of the heart cannot be restored in time, the myocardium will die due to ischemia, hypoxia, necrosis, formation of fibrous scars on the myocardium, and finally, HF. However, this treatment inevitably causes the original ischemic heart to undergo inflammatory reactions and myocardial damage. Myocardial ischemia-reperfusion injury increases mortality associated with MI and the difficulty of perfusion therapy (109). Animal experiments confirmed that in early ischemia-reperfusion, myocardial cells change from edema to inflammation, and the

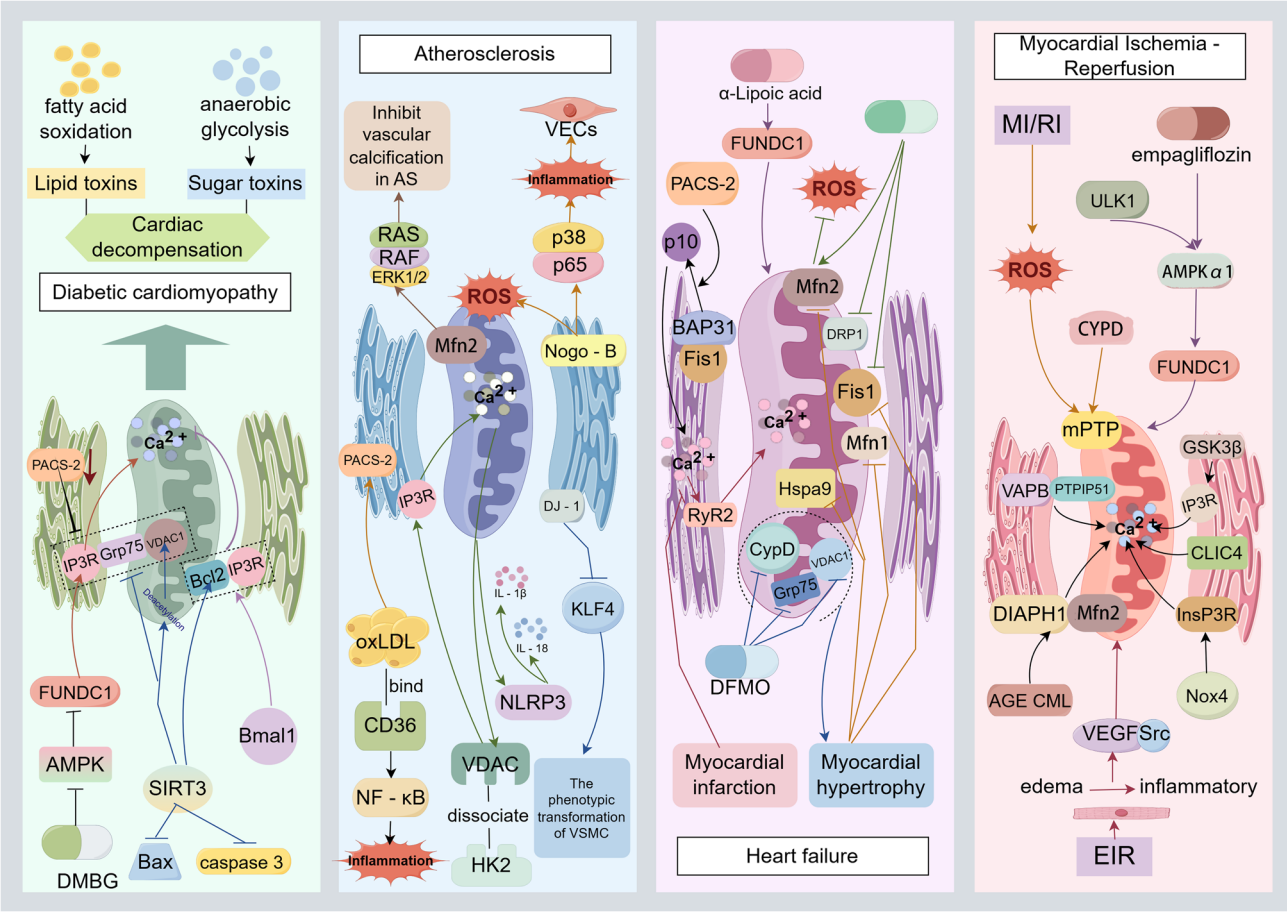

Figure 2. Mechanistic diagram of MAMs in cardiovascular diseases. MAMs, mitochondria-associated membranes; PACS2, phosphofurin acidic cluster sorting protein 2; IP3R1, inositol 1,4,5-trisphosphate receptor type 3; GRP75, heat shock protein family A (Hsp70) member 9; VDAC1, voltage-dependent anion channel; FUNDC1, FUN14 domain-containing protein 1; Bmal1,basic helix loop helix ARNT like 1; SIRT, sirtuin; Mfn, mitofusim; Nogo-B, NUS1 dehydrodolichyl diphosphate synthase subunit; DJ-1, parkinsonism associated deglycase; KLF4, KLF transcription factor 4; NLRP3, NLR family pyrin domain containing 3; Bap31, B cell receptor-associated protein 31; Fis1, mitochondrial fission protein 1; VAP, amine oxidase copper containing 3; CLIC4, chloride intracellular channel 4; Nox4, NADPH oxidase 4.

phosphorylation levels of VEGF and Src are increased (110). Myocardial necrosis and dissolution, increased mitochondrial damage, and oxidative stress-induced autophagosome accumulation were correspondingly increased. Sirt1 may play an important role in autophagosome clearance by upregulating Rab7 in MI/R (1,111). In addition, MI/R can affect a series of organelles, such as the ER and mitochondrial stress response, resulting in ROS aggregation. The mPTP is opened, and matrix-resident CypD is responsible for regulating the mPTP, which ultimately damages cardiomyocytes and leads to HF (112).

Mitochondrial Ca^{2+} overload is observed during myocardial ischemia-reperfusion, and MAMs are used as a medium for Ca^{2+} transport. When mitochondria and the ER are separated due to certain factors, such as the destruction of protein tyrosine phosphatase interacting protein 51-vesicular associated membrane protein-associated protein B, it leads to Ca^{2+} ion transport and energy metabolism disorders (112). The role of MAMs in myocardial ischemia-reperfusion has been previously confirmed (86). Gomez *et al* (113) found that during ischemia-reperfusion, increased activity of glycogen synthase kinase-3β in the SR/ER and MAM, which is localized in the heart, interacts specifically with the IP3Rs Ca^{2+} channel complex and increases the phosphorylation level of IP3Rs, which promotes the transfer of Ca^{2+} from the SR/ER to mitochondria, thereby triggering Ca^{2+} overload in the cytoplasm and mitochondria. Kirshenbaum *et al* (114) found that the interaction between cytoplasmic recombination diaphanous homologue 1 and Mfn2 leads to a direct correlation between the shortening the mito-ER distance. Activation of AGE carboxymethyl lysine in the heart may increase the interaction between diaphanous homologue 1 and Mfn2, shorten the mito-ER distance, lead to abnormal Ca^{2+} metabolism, and render the heart more vulnerable to damage during I/R injury. Researchers have used Cl-intracellular channel protein as a specific Cl-channel in myocardial cell MAM, which can regulate Ca^{2+} homeostasis, mitochondrial membrane potential balance and oxidative stress, thereby protecting the heart from ischemic reperfusion injury (115). Second, Nox4 enhances the Akt-dependent phosphorylation of InsP3R (a Ca^{2+} release channel) and reduces the activity of InsP3R on the ER by reducing the contact between the ER and mitochondria in cardiomyocytes and ischemic mouse hearts, thereby avoiding excessive accumulation of Ca^{2+} ions in mitochondria. It has a significant protective effect on the heart from mPT-dependent cell necrosis during ischemia-reperfusion injury (43).

Table II. Application of MAMs in cardiovascular diseases.

Disease	First author/s, year	Achievement	(Refs.)
Diabetic cardiomyopathy	Tan *et al*, 2020	Abnormal glucose and lipid metabolism cause inflammatory response, oxidative stress and endoplasmic reticulum stress, leading to heart failure.	(61)
	Chong *et al*, 2017	Remodeling of energy metabolism is the 'promoter' of myocardial injury.	(62)
	Opie *et al*, 2009	The imbalance of fatty acid oxidation and utilization in cardiomyocytes leads to the production of lipotoxic substances.	(63)
	Kolwicz *et al*, 2013	The imbalance of glucose oxidation and utilization in cardiomyocytes leads to the production of glucotoxic substances.	(64)
	Wu *et al*, 2019	Mitochondrial calcium overload in patients with high glucose leads to mitochondrial dysfunction.	(68)
	Xie *et al*, 2011	Metformin can inactivate AMPK and reduce FUNDC1 to improve cardiac structure.	(70)
	Wang *et al*, 2021	The reduction of FUNDC1 leads to cardiac tissue abnormalities in diabetic patients by affecting intracellular calcium balance and lipid metabolism.	(69)
	Meng *et al*, 2023	The IP3R-Grp75-VDAC1 complex regulates calcium homeostasis and mitophagy dysfunction. The decreased level of PACS-2 on MAMs in diabetic patients affects the function of MAMs.	(73)
	Tubbs *et al*, 2018	The significant decrease of IP3R-VDAC1 complex in patients with diabetic cardiomyopathy can be detected by experiments.	(66)
	Chang *et al*, 2023	SIRT3 inhibits apoptosis, promotes the deacetylation of VDAC1 and reduces its interaction with MAM, thereby reducing the formation of MAMs.	(74)
	Salin *et al*, 2023	Under the action of high glucose, the up-regulation of PACS2 promotes the formation of MAMs, reduces mitochondrial biosynthesis and oxidative phosphorylation, and drives mitochondrial apoptosis.	(75)
	Zhang *et al*, 2023	Downregulation of Bmal1 expression exacerbates cardiac hypertrophy and Diabetic cardiomyopathy, while up-regulation helps to improve symptoms by regulating the Bcl2/IP3R pathway to maintain the homeostasis of MAMs.	(76)
Atherosclerosis	Chen *et al*, 2024	The downregulation of PACS-2 protein inhibits mitophagy and reduces the assembly of inflammasome NLRP3, which in turn enhances cell death.	(85)
	Moulis *et al*, 2019	As a platform for the assembly of inflammasome NLRP3, MAMs can also affect the release of chronic inflammatory factors IL-1β and IL-18.	(82)
	Baik *et al*, 2023	The dissociation of hexokinase 2 and VDAC triggers the activation of IP3R, which leads to VDAC oligomerization and the formation of NLRP3 inflammasome complex.	(86)
	Zhang *et al*, 2022	Studies have confirmed that Mfn2 can inhibit vascular calcification in atherosclerosis by activating RAS-RAF-ERK1/2 pathway.	(87)
	Kong *et al*, 2024	Yimai Granule regulates mitophagy mediated by Pink1-Mfn2-Parkin pathway through miRNA-125a-5p, and regulates pro-inflammatory factors and blood lipids to inhibit atherosclerosis.	(88)
	Feng *et al*, 2019	MiR-93 has also been shown to act on Mfn2 protein to regulate the proliferation and migration of smooth muscle cells.	(89)
	Yang *et al*, 2019	The protein Nogo-B has the potential to regulate the formation of MAMs, mainly expressed in vascular endothelial cells and smooth muscle cells.	(7)

Table II. Continued.

Disease	First author/s, year	Achievement	(Refs.)
	Zhang *et al*, 2023	It is proved that Nogo-B mediates inflammation as a trigger of mitochondrial ROS production and p38-p65 signal, thus affecting the normal function of vascular endothelial cells.	(90)
	Yoon *et al*, 2022	Artesunate induces IP3R phosphorylation by increasing cAMP content in platelets, which indirectly improves the prognosis of patients with cardiovascular disease.	(91)
	Wang *et al*, 2021	DJ-1 affects the phenotypic transformation of VSMC by inhibiting the KLF4 pathway, and its down-regulation can also significantly increase plaque vulnerability.	(92)
Heart failure	Li *et al*, 2022	Mitochondrial dysfunction in cardiomyocytes is closely related to the occurrence and development of heart failure.	(93)
	Zhou *et al*, 2019	The lack of FUNDC1 in mice with high-fat diet breaks the balance between FUNDC1 and FBXL2.	(94)
	Wang *et al*, 2018	Sig-IR pathway was reversed by mitochondrial Ca^{2+} overload in mice fed with high-fat diet.	(95)
	Xu *et al*, 2021	The upregulation of Mfn2 reversed ROS production and mitochondrial depolarization.	(96)
	Dong *et al*, 2022	The downregulation of FIS1, DRP1 and Mfn2 expression levels can protect myocardial function.	(98)
	Zhao *et al*, 2021	DFMO can down-regulate the expression of GRP75, VDAC1 and CypD in MAMs, improve myocardial hypertrophy and regulate apoptosis.	(105)
	Luan *et al*, 2023	The genes of MAMs-related proteins are preferentially expressed in cardiac hypertrophy samples.	(106)
	Ding *et al*, 2024	The reduction of PACS2 will lead to the cleavage of BAP31 into p20, which will aggravate myocardial injury.	(100)
Myocardial ischemia reperfusion	Huang *et al*, 2023	Sirt1 plays an important role in autophagosome clearance by up-regulating Rab7 in MI/R.	(111)
	Gong *et al*, 2021	MI/RI can cause the accumulation of reactive oxygen species, make mPTP open, and ultimately damage myocardial cells and lead to heart failure.	(112)
	Gomez *et al*, 2015	The activity of GSK3β increases and interacts with the Ca^{2+} channel complex of IP3Rs to promote the transfer of calcium, thereby triggering calcium overload.	(113)
	Ponnalagu *et al*, 2022	CLIC4 can regulate Ca^{2+} homeostasis, mitochondrial membrane potential balance and oxidative stress, thereby protecting the heart from ischemic reperfusion injury.	(115)
	Beretta *et al*, 2020	Nox4 can avoid excessive accumulation of calcium ions in mitochondria and protect the heart from ischemia-reperfusion injury.	(43)
	Cai *et al*, 2022	FUNDC1 can reduce MI/R injury, but can also interact with other MAMs proteins to promote Ca^{2+} transfer.	(116)

MAMs, mitochondria-associated membranes; MCU, mitochondrial calcium uptake 1; FUNDC1, FUN14 domain-containing protein 1;PACS2, phosphofurin acidic cluster sorting protein 2; IP3R1, inositol 1,4,5-trisphosphate receptor type 3; GRP75, heat shock protein family A (Hsp70) member 9; VDAC1, voltage-dependent anion channel; Bmal1, basic helix loop helix ARNT like 1; NLRP3, NLR family pyrin domain containing 3; SIRT, sirtuin; Nogo-B, NUS1 dehydrodolichyl diphosphate synthase subunit; Mfn, mitofusim; Pink1, PTEN induced kinase 1; ROS, reactive oxygen species; VSMC, lamin A/C; KLF 4, KLF transcription factor 4; FBXL2, F-Box and leucine rich repeat protein 2; Fis1, mitochondrial fission protein 1; Drp1, recruiting dynamin-related protein 1; CypD, cyclophilin D; BAP31, B cell receptor-associated protein 31; GSK3β, glycogen synthase kinase 3 beta; CLIC4, chloride intracellular channel 4; Nox4, NADPH oxidase 4.

There are also numerous autophagy-related proteins in MAMs, such as the mitophagy receptor FUNDC1. Studies have shown that empagliflozin can activate AMPKα1 and enhance FUNDC1-dependent mitophagy after ULK1 phosphorylation. Mitochondrial autophagy clears damaged mitochondria and ultimately reduces MI/R injury; however, FUNDC1 also interacts with other MAM proteins to promote Ca^{2+} transfer. Therefore, it is certain that FUNDC1 is a double-edged sword in I/R injury (11,116)(Table II).

Therefore, MAMs play an important role in myocardial ischemia-reperfusion injury, and their dysfunction may lead to Ca^{2+} ion transport disorders, energy metabolism disorders and organelle dysfunction, which aggravates myocardial injury. This therapeutic strategy for MAMs may provide a new therapeutic approach for myocardial ischemia-reperfusion injury (Fig. 2).

5. Outlook

As a special connection area between the ER and mitochondria, the MAM determines the two important organelles in cells, mitochondria and the ER, and shows excellent therapeutic potential in cardiovascular and other diseases. However, how it affects the activity and function of mitochondria and the ER requires further exploration. Molecular targets related to heart diseases in MAMs provide a theoretical basis for the development of new drugs for the treatment of heart diseases. To translate the research results of MAMs into clinical applications, clinical trials should be conducted; the effectiveness and safety of MAM-related drugs in the treatment of heart disease should be verified; and interdisciplinary cooperation in biology, medicine, pharmacy, and other fields should be strengthened to jointly promote the progress of MAMs in the field of heart disease research. There are only a few clinical studies on how MAMs can improve diseases. Therefore, the performance and function of MAMs under different disease conditions must be extensively studied. With an in-depth study of the role of MAMs in heart disease, development of more effective treatments for heart diseases in the future is expected. However, research in this field still faces numerous challenges, such as the complex regulatory mechanisms of MAMs, diversity of heart diseases, and difficulty in clinical transformation. Therefore, it is necessary to work together to promote the research and application of MAMs in the field of heart disease treatment. However, based on the existing literature, MAMs have far-reaching therapeutic significance in diseases, and the role of MAMs in heart diseases has broad research prospects and clinical application potential. In-depth research and exploration are expected to provide new strategies and ideas for the treatment of heart diseases. In-depth research on MAMs may reveal the key mechanisms of certain diseases.

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Availability of data and materials

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Authors' contributions

JZ conceptualized the study, performed the methodology, wrote the first draft of the manuscript, and wrote, reviewed and edited the manuscript. JT conceptualized the study, wrote the first draft of the manuscript, and wrote, reviewed and edited the manuscript. ZZ wrote the first draft of the manuscript, and wrote, reviewed and edited the manuscript. WP performed visualization (Fig. 1), and wrote, reviewed and edited the manuscript. YX performed visualization (Fig. 2), wrote figure legends and assisted in writing and editing the manuscript. YG prepared Table I and assisted in writing and editing the manuscript. JG prepared Table II and assisted in writing and editing the manuscript. CJ and LD translated the manuscript from Chinese, edited the language and assisted in writing and editing the manuscript. CT and GZ wrote, reviewed and edited the manuscript. Data authentication is not applicable. All authors read and approved the final version of the manuscript.

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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