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Review article

The roles of mitochondria-associated membranes in mitochondrial quality control under endoplasmic reticulum stress

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ABSTRACT

The endoplasmic reticulum (ER) and mitochondria are two important organelles in cells. Mitochondria-associated membranes (MAMs) are lipid raft-like domains formed in the ER membranes that are in close apposition to mitochondria. They play an important role in signal transmission between these two essential organelles. When cells are exposed to internal or external stressful stimuli, the ER will activate an adaptive response called the ER stress response, which has a significant effect on mitochondrial function. Mitochondrial quality control is an important mechanism to ensure the functional integrity of mitochondria and the effect of ER stress on mitochondrial quality control through MAMs is of great significance. Therefore, in this review, we introduce ER stress and mitochondrial quality control, and discuss how ER stress signals are transmitted to mitochondria through MAMs. We then review the important roles of MAMs in mitochondrial quality control under ER stress.

1. Introduction

The endoplasmic reticulum (ER) has a network structure consisting of rough ER (rER) and smooth ER (sER) and plays important roles in the synthesis of proteins and lipids and the storage of Ca^{2+}. Under stress conditions, such as starvation or hypoxia, ER homeostasis can be interrupted, which is termed ER stress. When ER stress occurs, ER protein folding and Ca^{2+} storage abilities are perturbed, leading to unfolded or misfolded proteins accumulating in the ER and Ca^{2+} release from the ER, resulting in activation of the ER unfolded protein response (UPR^{er}) and Ca^{2+} signal transmission. This can initiate pro-survival or pro-death responses, which determine cell fate [1]. Mitochondria are composed of inner and outer mitochondrial membranes, the inner mitochondrial membrane space (IMS) and the mitochondrial matrix. Mitochondria are the location for the intracellular tricarboxylic acid cycle and oxidative phosphorylation, and are the 'power stations' of cells. In addition to providing energy, mitochondria are also involved in cell differentiation, cell signaling, and apoptosis [2–4]. Mitochondria have a self-functioning security mechanism, namely mitochondrial quality control (MQC). Mitochondria have three levels of quality control. When cells are under mild stress, mitochondria can maintain mitochondrial protein homeostasis and structural integrity to ensure correct function at molecular and organellar levels. Cells can also initiate mitochondrial apoptosis to ensure MQC when the stress is too severe [5–7]. Accumulating evidence indicates that ER and mitochondrial functions are highly connected physiologically and pathologically. Under stress conditions, cells can coordinate ER and mitochondrial functions to restore cellular homeostasis. Many studies have shown that ER stress has an effect on mitochondrial function, but the detailed mechanism underlying this effect has not been established. It has long been known that ER membranes can be in close enough proximity to mitochondria to form lipid raft-like domains called mitochondria-associated membranes (MAMs). MAMs contain many proteins that physically connect the ER and mitochondria and that play important roles in lipid synthesis and Ca^{2+} transfer from the ER to mitochondria [8]. There is no doubt that MAMs are especially important for the transfer of stress signals from the ER to mitochondria and may play an important role in regulating MQC under ER stress (Figs. 1 and 2).

2. Two major features of ER stress

The ER is mainly responsible for proteins synthesis and folding, lipid synthesis and Ca2+ storage in cells. ER requires a strict steady environment to function properly. Stimuli, like starvation, hypoxia, can break down the homeostasis of intracellular environment, leading to dis-function of the ER, resulting in ER stress [1]. ER stress is an adaptive response, which has two major features including UPR^{er} and Ca2+ homeostasis perturbation.

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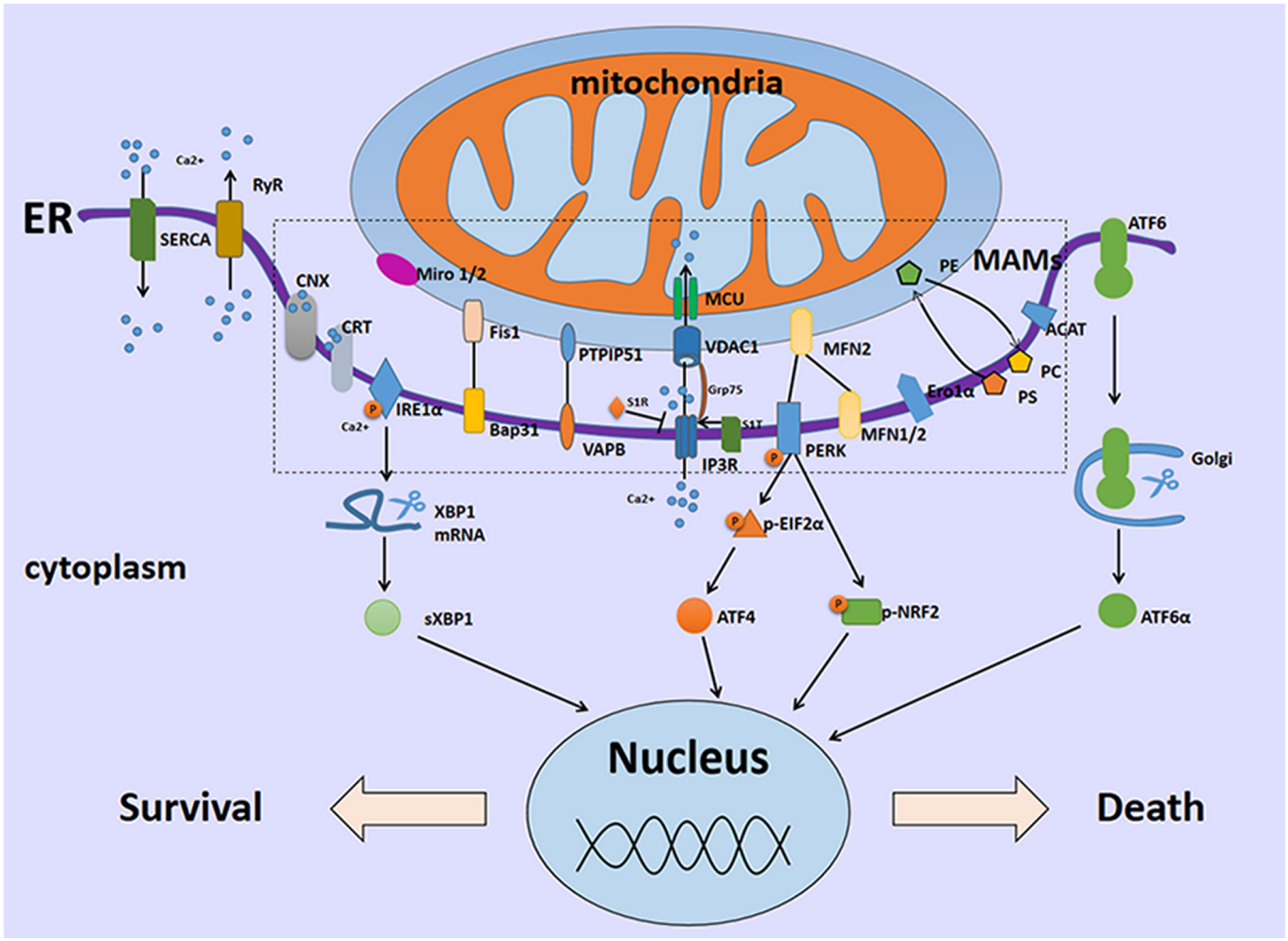

Fig. 1. Mitochondria-associated membranes (MAMs) and ER stress.
MAM-connected proteins include B cell receptor associated protein 31 (Bap31), mitochondrial fission 1 (fis1), tyrosine phosphatase-interacting protein 51 (PTPIP51), vesicle-associated protein (VAPB), PERK, and mitochondrial fusion protein 2 (MFN2). In addition, inositol 1, 4, 5-trisphosphate receptor (IP3R) is linked to voltage-dependent anion channel 1 (VDAC1) through glucose-regulated protein 75 (Grp75), which constitute the Ca^{2+} channels between the ER and mitochondria. MAMs also contain many chaperones, such as calnexin (CNX), calreticulin (CRT) and sigma 1 receptor (S1R), which play an important role in Ca^{2+} buffering. MAMs are also important sites for lipid synthesis and shuttling. Phosphatidylserine (PS) is synthesized in the ER and enters the IMS though MAMs to generate phosphatidylethanolamine (PE), which can go back to the ER where it will be converted to phosphatidylcholine (PC). Cholesterol acyltransferase (ACAT) is enriched in MAMs and can catalyze the generation of cholesteryl esters. The Miro GTPase 1/2 (miro1/2) is present in the OMM and can regulate mitochondrial movement. Two major features of ER stress include the endoplasmic reticulum unfolded protein response and unbalanced Ca^{2+} homeostasis. PERK can phosphorylate EIF2α to induce the activating transcription factor, ATF4. It can also phosphorylate nuclear transcription factor 2 (NRF2), activating its transcriptional function. Phosphorylation of IRE1α activates its RNase activity, which can cleave the X-box binding protein 1 (XBP1) mRNA into a tight form that can encode stable sXBP1. Activated ATF6 can dissociate from the ER and translocate to the Golgi where it can be cleaved by a protease into its active form. These transcription factors can translocate to the nucleus to up-regulate expression of genes that determine cell fate. The maintenance of Ca^{2+} homeostasis in the ER mainly depends on the endoplasmic reticulum Ca^{2+} ATPase (SERCA) and Ca^{2+} release channels [Ryanodine receptor (RyR) and inositol 1,4,5-triphate receptor (IP3R)]. When ER stress occurs, SERCA activity is inhibited and RyR and IP3R are activated, leading to Ca^{2+} homeostasis imbalance.

2.1. UPR^{er}

The UPR^{er} is an adaptive response that is activated under stress when nascent peptide cannot be folded or is misfolded, leading accumulation of non-functional proteins in the ER [9]. PERK, IRE1α and ATF6 are three transmembrane proteins in the ER. Under normal conditions, they bind to the chaperone, Bip, and remain in an inactive state. When ER stress occurs, Bip can sense the unfolded/misfolded proteins and dissociates from these three transmembrane proteins resulting to their activation [10]. Activated PERK can phosphorylate nuclear transcription factor 2 (NRF2) and the eukaryotic initiation factor 2 (EIF2α) [11,12]. Phosphorylated NRF2 can translocate to the nucleus to up-regulate redox-related proteins to ensure redox homeostasis [13]. Phosphorylated EIF2α can inhibit global mRNA translation, which reduces ER protein folding load and selectively up-regulates activating transcription factor 4 (ATF4) expression. ATF4 is a double-edged sword, which not only promotes the expression of anti-apoptotic proteins, but also increases the expression of pro-apoptotic proteins by up-regulating CHOP [14]. Phosphorylation of IRE1α activates its RNase activity, which can cleave the X-box binding protein 1 (XBP1) mRNA into a tight form that can encode stable sXBP1 [15]. sXBP1 is a transcription factor that can up-regulate genes related to ER chaperones and ER-associated degradation (ERAD) [16]. In addition, the RNase activity of IRE1 can degrade many RNA substrates reducing the protein folding load in the ER. This process is also known as regulatory IRE1-dependent degradation (RIDD) [17]. After activation, ATF6 can dissociate from the ER and translocate to the Golgi where it can be cleaved by a protease into an activated form. This can then transfer to the nucleus and up-

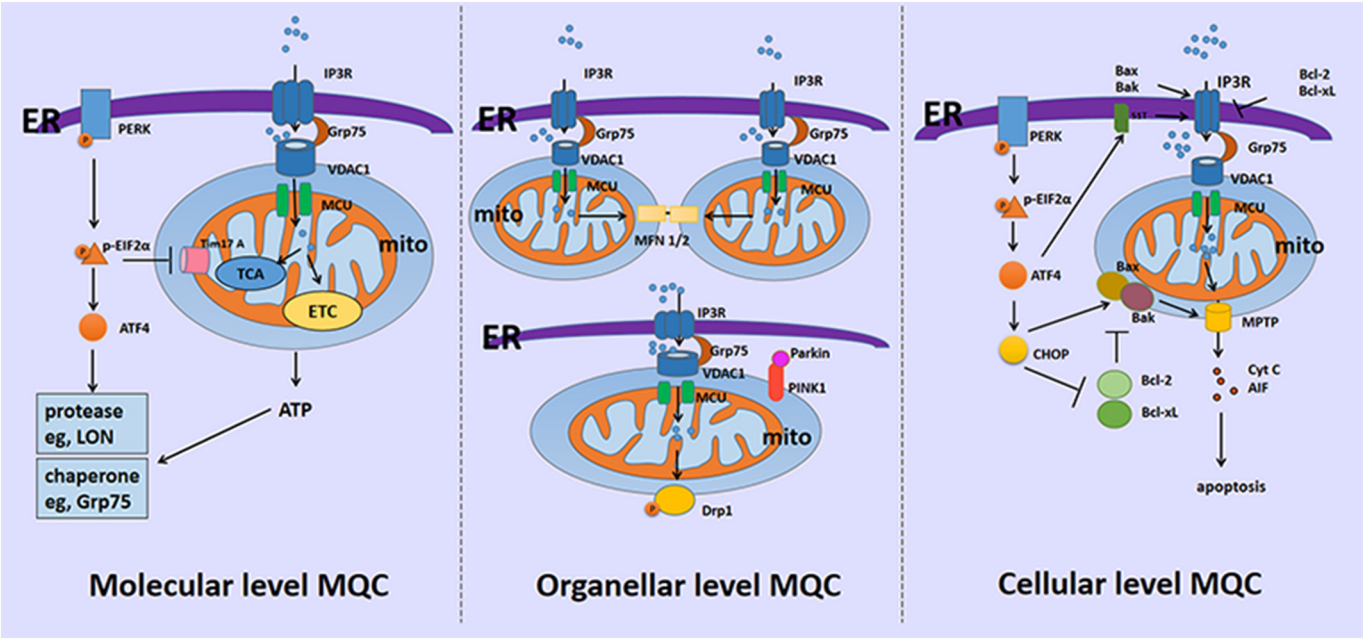

Fig. 2. The roles of mitochondria-associated membranes (MAMs) in mitochondrial quality control (MQC) under ER stress.
At molecular level MQC, the PERK/EIFα/ATF4 axis can decrease mitochondrial protein import and increase expression of mitochondrial proteases and chaperones. MAMs can increase ATP production by moderately increasing mitochondrial Ca^{2+} concentration to provide energy for the protease and chaperone functions. At organellar level MQC, moderately increased Ca^{2+} can promote mitochondrial fusion and ensure mitochondrial functional integrity. When stress is increased, the impaired part of mitochondria can be removed by mitochondrial division and mitophagy. When the stress is too severe, Ca^{2+} overload can lead to the mitochondrial permeability transport pore (mPTP) opening, resulting in the release of pro-apoptotic factors (Cyt C and apoptosis-inducing factor), initiating programmed cell death. This ensures MQC at the cellular level. PERK/EIFα/ATF4 can up-regulate SERCA1 truncation (S1T) to aggravate Ca^{2+} leakage, which amplifies the apoptotic effect, and up-regulates CHOP expression and promotes mPTP opening. CHOP can decrease anti-apoptotic protein Bcl-2 and Bcl-xL expression which can inhibit IP3R activity and increase levels of pro-apoptotic proteins Bax/Bak. This can increase IP3R activity, contributing to mitochondrial Ca^{2+} overload and amplification of the apoptotic signal.

regulate expression of genes such as BIP, protein disulfide bond isomerase (PDI) and CHOP [18]. In conclusion, under ER stress, UPR^{er} activates three pathways, initiates a series of adaptive responses, activates pro-survival or pro-apoptotic genes and ultimately determines cell fate.

2.2. Perturbed Ca^{2+} homeostasis under ER stress

The ER is the major storage location for intracellular Ca^{2+} in its free or conjugated form. The maintenance of Ca^{2+} homeostasis in the ER mainly depends on the endoplasmic reticulum Ca^{2+} ATPase, SERCA, and Ca^{2+} release channels [Ryanodine receptor (RyR) and inositol 1,4,5-triphate receptor (IP3R)] [19]. Ca^{2+} homeostasis becomes unbalanced under ER stress. Thapsigargin, an ER stress inducer, can inhibit SERCA activity, leading to perturbed ER Ca^{2+} homeostasis and induction of ER stress [20]. Protein disulfide isomerase (PDI) is an ER oxidoreductase that can reversibly catalyze the formation of disulfide bonds of oxidized proteins and generate reactive oxygen species (ROS) in the ER. Under normal conditions, the ROS produced by this process can be eliminated by the homeostasis mechanism of cells. When the ER protein folding function is damaged, disulfide bonds alternate between formation and release, resulting in a significant increase in ROS production [21]. ROS can impair SERCA activity and activate IP3R and RyR, resulting in a large amount of Ca^{2+} release [22,23]. After release from the ER, Ca^{2+} flows into the cytoplasm or transfers into mitochondria through Ca^{2+} channels between the ER and mitochondria. Mitochondria have Ca^{2+} buffering capacity, which is vital for Ca^{2+} homeostasis in the cell. Disruption of mitochondrial Ca^{2+} buffering capacity may be involved in diseases such as amyotrophic lateral sclerosis (ALS) [24]. Bip may also be involved in the regulation of ER Ca^{2+} homeostasis. Overexpression of Bip can reduce Ca^{2+} transfer from the ER to the cytoplasm, while mitochondria in astrocytes have a protective effect under ER stress, which indicates that Bip may inhibit IP3R and RyR [25]. Ca^{2+}, as a critical intracellular signaling molecule, can enter mitochondria through Ca^{2+} channels in MAMs after release under ER stress, thus transporting stress signals to mitochondria and affecting mitochondrial function. We will focus on this in later chapters.

3. Three levels of MQC

Mitochondria are double membranes organelle, which composed of inner and outer mitochondrial membranes, the inner mitochondrial membrane space and the mitochondrial matrix. Mitochondria are important for energy generation, cell differentiation, cell signaling and apoptosis [2–4]. Mitochondrial function properly depending on the integrity of mitochondrial structure and function. MQC is an important mechanism to maintain the numbers of mitochondria and ensure the structure and function integrity of mitochondria. It contains three levels: molecular level, organellar level and cellular level.

3.1. MQC at the molecular level

Mitochondria can maintain MQC at the molecular level by reducing protein import, improving protein folding ability and clearing damaged and non-functional proteins. Most mitochondrial proteins are encoded by nuclear DNA and synthesized in the cytoplasm. They are then imported into mitochondria by the mitochondrial protein import mechanism and function after correct folding [26]. When cells are under stress, the proteins imported into mitochondria cannot be properly folded, resulting in the accumulation of unfolded/misfolded proteins in mitochondria, which activates the mitochondrial UPR (UPR^{mt}) [27]. During mitochondria dysfunction, GCN2, an EIF2α kinase, is activated, resulting in a global decrease of translation. This inhibits the expression of TiM17A, the main subunit of mitochondrial inner membrane

channel, TIM23, reducing protein import and protein load in mitochondria. [28,29]. In *C. elegans*, ATFS-1, a key molecule of UPR^{mt}, contains a nuclear localization sequence (NLS) and a mitochondrial targeting sequence (MTS). Under normal conditions, ATFS-1 can be transported into the mitochondrial matrix and be degraded by a protease [30]. When the efficiency of mitochondrial protein import declines, ATFS-1 can translocate into the nucleus and up-regulate the expression of mitochondrial chaperones and proteases, such as HSP60/10 and the caseinolytic protease subunit P (ClpP). Hsp60/10 is mitochondrial matrix chaperones that can help the folding of newly imported mitochondrial proteins [31]. ClpP is a mitochondrial matrix protease mainly responsible for degradation of unfolded, misfolded and damaged proteins to maintain mitochondrial protein homeostasis [32]. In mammals, ATF5, a functional ortholog of ATFS-1, may play the same role as ATFS-1. It can restore UPR^{mt} activation in *C. elegans* lacking ATFS-1 [33]. In addition, multi-omics analysis showed that ATF4 is also involved in UPR^{mt} regulation [34]. The relationship between ATF4 and ATF5 remains unclear in mitochondrial stress. However, it is certain that both are important for restoring mitochondrial protein homeostasis and for ensuring MQC at the molecular level.

3.2. MQC at the organellar level

Mitochondrial dynamics is an important mechanism to ensure mitochondrial quality and includes mitochondrial fusion, fission, mitophagy and mitochondrial motility [35,36]. Mitochondria are in a dynamic state, changing between fusion and fission. When mitochondria are subjected to mild stress, mitochondria are more likely to undergo fusion. With the help of mitochondrial fusion proteins, including mitofusin 1/2 (MFN1/2) and optic atrophy 1 (OPA1), partially impaired mitochondria can fuse to form a functional one [37]. MFN1/2 is located in the outer mitochondrial membrane (OMM) and is mainly responsible for fusion of the OMM [38]. OPA1 is located in the IMS and is responsible for fusion of the inner mitochondrial membrane [39]. Mitochondrial division can increase the number of mitochondria under normal conditions to meet the energy needs of cells. In severe stress, phosphorylated Drp1 can be recruited to the outer membrane of damaged mitochondria, which then divide and are removed by mitophagy [40]. In addition, when the environment surrounding mitochondria is abnormal, the mitochondria can move to a suitable environment to ensure normal mitochondrial function. This involves the OMM receptor, Miro, which is a Rho-GTPase that facilitates mitochondrial transport with its two Ca^{2+}-binding EF-hand motifs and two GTPase domains [41].

3.3. MQC at the cellular level

When stress is too severe to be accommodated by molecular and organellar level MQC, mitochondria will initiate the mitochondrial apoptotic pathway to ensure MQC. Bax and Bak are pro-apoptotic proteins of the Bcl-2 family. They can oligomerize in the mitochondrial outer membrane and contribute to mitochondrial permeability transport pore (mPTP) opening when cells are under lethal stress [42]. The structural components of the mPTP are not completely determined; however, it is a multi-protein channel complex containing the voltage-dependent anion channel (VDAC), the adenine nucleotide translocator (ANT) and cyclophilin-D (Cyp-D) [43]. Pro-apoptotic factors, such as cytochrome C (Cyt C) and apoptosis-inducing factor (AIF) are released into the cytoplasm from mitochondria after the mPTP opens [44]. After release into the cytoplasm, Cyt C can form apoptosomes with Apaf-1, which can activate caspase 9 and downstream apoptotic factors, caspase 3/7, which mediate programmed cell death [45,46]. AIF can also translocate into nucleus leading to chromatin fragmentation and DNA degradation, resulting in cell death [47].

4. MAMs promote close physical and functional connection between the ER and mitochondria

4.1. Introduction to MAMs

MAMs are membrane structures that closely connect the ER and OMM. They were first proposed by Copeland and Dalton in 1959 [48], but were not confirmed until 1990 [49]. Electron microscopy revealed that the ER and OMM are not fully fused in MAMs, and there can be a distance of 10–25 nm between them [50]. Besides, the close apposition of mitochondrial surface to ER accounts for 5% to 20% of the mitochondrial network in different type cells [51]. MAMs do not simply structurally link ER and mitochondria; they also contain a variety of connected and functional proteins, such as the Ca^{2+} channel IP3R located in the ER, voltage dependent anion channel 1 (VDAC1) in the OMM, chaperones [e.g., calnexin, glucose-regulated protein 75 (Grp75)], mitochondrial dynamic-related proteins [e.g., mitochondrial fusion protein 1/2 (MFN1/2)], lipid synthesis-related enzymes and lipid transporters (e.g., cholesterol acyltransferase, oxysterol-binding protein-related protein), and enzymes involved in ER redox regulation [e.g., endoplasmic reticulum oxidoreductin 1α (Ero1α)] [8]. They connect the ER and mitochondria structurally and functionally and are important for the transport of materials and signaling molecules between the two.

4.2. MAMs tether the ER and mitochondria in close physically proximity

MAMs contain a variety of scaffold proteins that structurally link ER and mitochondria. The IP3R Ca^{2+} channel in the ER can be linked to VDAC1 in the OMM by Grp75 to form an ER:mitochondrial bridge and Ca^{2+} channel between the two organelles [52]. Vesicle-associated protein (VAPB) in the ER and tyrosine phosphatase-interacting protein 51 (PTPIP51) in the OMM are present in MAMs and regulate ER and mitochondrial connections [53]. MFN2 can link ER and mitochondria through homotypic or heterotypic (with MFN1) interaction [54]. MFN2 can also interact with the ER transmembrane protein, PERK, to link the ER and mitochondria, while PERK knockout can disrupt ER morphology and reduce ER-mitochondrial contact points [55]. In addition, B cell receptor associated protein 31 (Bap31) is linked to mitochondrial fission protein 1 (Fis1), which also acts as a tether for MAMs [56]. In conclusion, there is a variety of connective proteins in MAMs that physically connect the ER and mitochondria.

4.3. MAMs provide a close functional connection between the ER and mitochondria

MAMs functionally connect the ER and mitochondria. They play an important role in intracellular signal transmission and cell functions, such as Ca^{2+} signal transmission, mitochondrial energy synthesis, mitochondrial dynamics, lipid transport and apoptosis [57]. ER and mitochondrial Ca^{2+} signaling are the most prominent functions of MAMs. After release from the ER, Ca^{2+} can enter the IMS of mitochondria through the IP3R-Grp75-VDAC1 channel in MAMs. Ca^{2+} can then enter the mitochondrial matrix and transmit the stress signal to mitochondria through the mitochondria Ca^{2+} uniporter (MCU) in the inner mitochondrial membrane (IMM) [58]. Ca^{2+} has important effects on mitochondrial ATP production and cell fate after entering mitochondria. Normal mitochondrial Ca^{2+} uptake can increase TCA cycle and mitochondrial complex activity, increasing ATP production, but excess Ca^{2+} can lead to mPTP opening and induction of apoptosis [59,60]. MAMs are also involved in mitochondrial dynamics. The Miro GTPase 1/2 (miro1/2) is present in the OMM and contains a Ca^{2+} sensing domain, which can regulate mitochondrial movement according to the Ca^{2+} concentration in MAMs and maintain mitochondrial Ca^{2+} homeostasis [61]. It has been reported that the ER can loop around mitochondria at the first mitochondria fission, forming ring-shaped

MAMs and promoting OMM constriction. Only then can the OMM recruit phosphorylated DRP1 to complete mitochondrial fission [62,63]. MAMs are also important sites for lipid synthesis and shuttling. Phosphatidylserine (PS) synthase, a key enzyme in PS synthesis, is located in the ER and is enriched in MAMs. After synthesis, PS can enter the IMS though MAMs to generate phosphatidylethanolamine (PE) which can go back to the ER via MAMs or transfer to the Golgi, where it will be converted to phosphatidylcholine (PC) by PE methyltransferase 1/2 [64]. In addition, cholesterol acyltransferase (ACAT) is enriched in MAMs and can catalyze cholesteryl ester formation [65]. In summary, MAMs functionally connect the ER and mitochondria and play an important role in signal transmission and material transportation.

5. The role of MAMs in the regulation of MQC under ER stress

5.1. ER stress and MAMs

As part of the ER, MAMs are closely related to ER stress. In the early stage of ER stress, the number of MAMs increase, promoting the transport of Ca^{2+} between the ER and mitochondria, which increases mitochondrial energy synthesis and provides energy for adaptive responses [66]. IRE1 can be enriched in MAMs under ER stress and can promote cell survival by inhibiting IP3R, which stabilizes mitochondrial Ca^{2+} concentration [67]. ER stress can affect stress signaling by regulating MAM number and ER-mitochondrial Ca^{2+} channels. PERK is enriched in MAMs and linked to MFN2 on the OMM to form the scaffold of MAMs. MFN2 elimination can lead to ER stress, while silencing PERK can reduce ROS production, stabilize mitochondrial Ca^{2+} concentration, and improve mitochondrial morphology, indicating that MFN2 in MAMs has an inhibitory effect on PERK activation [68].

MAMs are rich in chaperones, such as sigma 1 receptor (S1R), calnexin (CNX) and calreticulin (CRT), which have important effects on ER stress signaling [69,70]. The transcription of S1R can be increased by the PERK/EIF2α/ATF4 pathway, and S1R can inhibit Caspase-4 activation and play a protective role under ER stress [69]. In addition, S1R can also stabilize IP3R and reduce ER Ca^{2+} release to stabilize the concentration of Ca^{2+} in MAMs [71]. CNX and CRT have high Ca^{2+} affinity, and they can buffer Ca^{2+} concentration in MAMs and stabilize the mitochondrial Ca^{2+} balance under ER stress. CNX can also directly interact with SERCA and regulate its activity [72].

In summary, ER stress is closely related to MAMs. ER stress can influence the content of MAMs, Ca^{2+} channel opening and chaperone expression in MAMs. In turn, changes to MAMs can affect the transmission of ER stress to mitochondria. We have already discussed the importance of MQC; therefore, the role of MAMs in mitochondrial function during ER stress is worthy of further consideration.

5.1.1. The role of MAMs in molecular level MQC under ER stress

ER stress can regulate mitochondrial protein homeostasis by decreasing the import of protein into mitochondria and by increasing the expression and activity of mitochondrial chaperones and proteases. As discussed above, PERK can inhibit global translation by phosphorylating elf2α and reducing Tim23-dependent protein import, which can reduce mitochondrial protein load and maintain mitochondrial protein homeostasis. PERK can also increase the expression of LON, which can strictly regulate mitochondrial protein homeostasis and degrade stress-damaged mitochondrial proteins [73]. PERK can also up-regulate the expression of Grp75 through ATF4 [74]. In addition to its role in linking MAMs, Grp75 can also help protein folding in the mitochondrial matrix [75]. In addition, Hsp60 increases in the cells treated with thapsigargin [76]. These chaperones and proteases require energy from ATP to function properly [77,78]. In the early stage of ER stress, MAMs increase and promote the transport of Ca^{2+} between the ER and mitochondria. Moderately increased Ca^{2+} in mitochondria enhances mitochondrial metabolism by modulating Ca^{2+}-dependent dehydrogenase activity in the Krebs cycle and promoting respiratory chain complex activity, increasing ATP synthesis [66,79]. Increased ATP levels provides energy for ATP-dependent chaperone and protease functions in mitochondria, thereby reducing misfolded or unfolded protein accumulation and maintaining mitochondrial protein homeostasis. Therefore, moderately increased numbers of MAMs can promote ATP production through Ca^{2+} signaling to maintain mitochondrial chaperone and protease function ensuring MQC at the molecular level.

5.1.2. The role of MAMs in organellar level MQC under ER stress

In organellar level MQC, ER stress maintains mitochondrial functional integrity through mitochondrial fusion and removal of damaged mitochondria by mitochondrial division and mitophagy. Mouse fibroblast mitochondria become highly fused when treated with an ER stress inducer for a short time [80]. A cell-free mitochondrial fusion assay revealed that Ca^{2+} is a vital regulator of mitofusin-dependent mitochondrial fusion [81]. Short-term starvation can induce mitochondrial elongation. Starvation can also increase contact sites between ER and mitochondria because it is also an ER stress inducer [82,83]. Therefore, increased MAM content and moderate increases of Ca^{2+} concentration in the mitochondrial matrix may be important factors for mitochondrial fusion in the early adaptive stage of ER stress. However, cytosolic Ca^{2+} overload can up-regulate cytosolic xanthine oxidase XO activity, leading to ROS production, and ROS can phosphorylate serine 616 of Drp1, which leads to the accumulation of Drp1 on the OMM and promotes OMM division [84]. In addition, IMM division depends on an increase in mitochondrial matrix Ca^{2+}, but not on Drp1 [84]. Therefore, ER stress-induced mitochondrial Ca^{2+} overload also plays an important role in both OMM and IMM division. The damaged parts of mitochondria that are cleaved away by the mitochondrial division mechanism can be eliminated by mitophagy. When the mitochondrial membrane potential decreases, PINK1 can locate to the OMM and then recruit Parkin to initiate mitophagy. PINK1 can be relocated to MAMs when mitophagy occurs to promote ER binding to mitochondria and autophagosome formation [85]. In conclusion, MAM-mediated Ca^{2+} signaling has an important effect on mitochondrial fusion and division under ER stress, and the relocation of PINK1 to MAMs also contributes to mitochondrial autophagy. MAMs, therefore, play an important role in regulating mitochondrial organellar quality under ER stress.

5.1.3. The role of MAMs in cellular level MQC under ER stress

When ER stress is too severe, MAMs can transmit stress signals to mitochondria and initiate apoptosis programs, exerting MQC at the cellular level. Severe or persistent ER stress leads to massive Ca^{2+} release from the ER. The released Ca^{2+} causes mitochondrial Ca^{2+} overload through the IP3R-VDAC1 channel, which leads to mitochondrial depolarization, Bax and Bak oligomerizing on the OMM, mPTP opening, the release of pro-apoptotic factors and activation of the mitochondrial apoptotic pathway [86]. ER stress can regulate the levels of multiple proteins on MAMs and aggravate the Ca^{2+} pro-apoptotic signal. The anti-apoptotic Bcl-2 family proteins, Bcl-2 and Bcl-xL, can locate to MAMs and promote cell survival by interacting with IP3R and inhibiting its activity, while the pro-apoptotic Bcl-2 family proteins, Bax and Bak, do the opposite [87,88]. Furthermore, the BH4 area of Bcl-xL, targeting VDAC1, reduces mitochondrial Ca^{2+} influx mediated by VDAC1 to inhibit apoptosis [89]. Bax can interact with VDAC to increase mPTP opening, promoting apoptosis [90]. When ER stress is lethal, the increased level of CHOP can inhibit expression of anti-apoptotic Bcl-2 family proteins and increase the expression of pro-apoptotic Bcl-2 family proteins, resulting in exacerbation of ER Ca^{2+} release and cell death [91]. In addition, truncated SERCA1 (S1T) is localized on MAMs and induced by the PERK-EIF2α-ATF4 axis of the UPR during ER stress. Increasing expression of S1T can also amplify the Ca^{2+} apoptosis signal during ER stress [92]. We conclude that MAMs can transfer death signals to mitochondria to mediate MQC at the cellular level under severe ER stress.

6. Concluding remarks and future perspectives

In summary, MAMs play important roles in MQC under ER stress. MAMs promote mitochondrial protein homeostasis and regulate mitochondrial dynamics to enhance mitochondrial function and promote cell survival under mild ER stress. However, MAMs can also amplify stress signals to induces apoptosis under severe ER stress. However, the mechanism of ER-mitochondrial signal transmission is not fully elucidated and requires further investigation. A variety of diseases are known to be associated with ER stress and mitochondrial dysfunction, including type 2 diabetes [93] and Alzheimer's disease [94]. Most tumor cells are under mild ER stress under basal conditions and can survive chemotherapy through adaptive ER stress responses. In this review, we have highlighted the important roles of MAMs in MQC under ER stress. Therefore, further study of the mechanisms regulating MAMs in MQC under ER stress can provide new targets and therapeutic strategies for tumor chemotherapy and for the treatment of ER stress-related diseases.

Authors contribution

Beiwu Lan: Writing - original draft
Yichun HE: Graphics
Hongyu Sun: Writing - review & editing
Xinzi Zheng: Writing - review & editing
Yufei Gao: Conceptualization, Project administration, Funding acquisition
Na Li: Visualization, Funding acquisition

Declaration of Competing Interest

The authors declare no conflict of interest.

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