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Research Advances in Endoplasmic Reticulum-Mitochondria Interactions in Disease

Yirui Wang[1], Yujinpeng Hao[2], Jun Shao[2] and Mianli Bian[1]*

[1]*School of Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China*

[2]*The First Clinical College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China*

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***Corresponding author:** Mianli Bian, School of Medicine, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China

Abstract

Mitochondria-Associated Endoplasmic Reticulum Membranes (MAMs) are important structural and functional coupling platforms between endoplasmic reticulum and mitochondria. They are mainly composed of two adjacent membrane regions of organelles and are rich in a variety of resident proteins. They play a key role in calcium homeostasis, lipid transport and metabolism, energy metabolism regulation and cellular stress response. In recent years, a number of studies have shown that the structural and functional abnormalities of MAMs can participate in the occurrence and development of various diseases by disrupting calcium signal transduction, inducing oxidative stress, affecting mitophagy and lipid metabolism reprogramming. This article systematically reviews the structural composition, physiological functions, and mechanism of action of MAMs in diseases, focusing on the regulatory effects of key resident proteins and potential therapeutic targets, and discusses the current research bottlenecks and future development directions, in order to provide a reference for the mechanism research and targeted intervention of related diseases.

Keywords: Mitochondria-endoplasmic reticulum related membranes; Mitochondria-endoplasmic reticulum related membrane resident proteins; Ischemic stroke; Nonalcoholic fatty liver disease; Cancer

Introduction

In recent years, the physical and functional interaction between endoplasmic reticulum and mitochondria has become a hot spot in organelle biology research. Among them, MAMs, an important contact site between endoplasmic reticulum and mitochondria first proposed in the 1950 s, are composed of adjacent membrane structures and their enriched resident proteins, and play an important role in calcium homeostasis, lipid transport and metabolism, energy homeostasis maintenance, redox balance, organelle stress response and cell fate regulation. More and more studies have shown that the structural and functional abnormalities can be involved in the occurrence and development of diseases by disrupting Ca^{2+} signaling, inducing oxidative stress, damaging mitochondrial quality control, promoting lipid metabolism disorders, and affecting cell death procedures [1].

Based on this, this paper focuses on the concept, structural basis and physiological functions of MAMs, systematically reviews its mechanism of action in related diseases, focuses on the regulatory networks of related resident proteins and key molecular pathways, and further discusses its research progress as potential therapeutic targets, in order to provide reference for the mechanism research and targeted intervention of related diseases.

Definition of MAMs

The membrane contact area between Endoplasmic Reticulum (ER) and mitochondria is called Mitochondria-Associated Endoplasmic Reticulum Membranes (MAMs), which is a dynamic subcellular domain formed by the two closely adjacent to each other and plays an important role in the maintenance of cell homeostasis. As an important hub of organelle interaction, MAMs are rich in a variety of proteins and lipids, which can participate in a variety of physiological and pathological processes by regulating calcium homeostasis, lipid metabolism, redox balance and apoptosis [2]. Studies have shown that MAMs dysfunction

is closely related to cancer, cardiovascular and cerebrovascular diseases and metabolic diseases. For example, Jia et al. [3] proposed that ER stress and mitophagy are important regulatory factors for Ischemic Stroke (IS). In the study of tumor drug resistance, the latest research found that the integrity of MAMs is related to cisplatin resistance in ovarian cancer patients [4]. In the study of the pathogenesis of NAFLD, proteins involved in Ca^{2+} signal transduction in MAMs are associated with a variety of liver diseases, including Non-Alcoholic Fatty Liver Disease (NAFLD) [5]. Therefore, in-depth study of MAMs not only helps to elucidate the mechanism of the occurrence and development of cardiovascular and cerebrovascular diseases, cancer and metabolic diseases, but also provides a theoretical basis for the optimization of treatment strategies for related diseases.

The main functions of MAMs

MAMs are involved in calcium signal transduction, mitophagy, oxidative stress and lipid metabolism in cells. These functions are mainly achieved by related proteins enriched in MAMs and their mediated molecular pathways. For example, the IP3R-GRP75-VDAC1 complex mediates Ca^{2+} transport from ER to mitochondria to maintain cellular energy metabolism and signal transduction [6]; ULK-1 is activated and further triggers FUNDC1 to initiate mitophagy, thereby removing damaged organelles [7]; PERK / ATF4 pathway mediates oxidative stress [8]; Mitofusion1 (MFN1) and Mitofusion2 (MFN2) interact to promote mitochondrial fusion and further regulate mitochondrial ROS production [9]. In general, MAMs play a key role in the maintenance of cell homeostasis by integrating multiple biological processes such as calcium homeostasis maintenance, mitochondrial quality control and oxidative stress regulation, and their dysfunction may be involved in the occurrence and development of various diseases.

Ca^{2+} signal transduction

As an important second messenger in cells, Ca^{2+} is widely involved in many physiological processes such as muscle contraction, gene transcription, exocytosis and metabolic regulation. ER is the main calcium store in cells, and its intracellular Ca^{2+} concentration can be as high as millimolar, which is significantly higher than the resting calcium level in the cytoplasm [10]. When cell membrane receptors are stimulated, G Protein-Coupled Receptors (GRCPs) bind to ligands and activate Phospholipase C (PLC), thereby promoting Phosphatidylinositol4,5-bisphosphate (PIP2) is hydrolyzed into Inositol triphosphate (IP3) and Diacyl glycerol (DAG). IP3 binds to the corresponding receptor IP3 R on the ER membrane and induces Ca^{2+} release to the cytoplasm; subsequently, Ca^{2+} can be reuptake by SERCA, thereby maintaining cell calcium homeostasis. In the MAMs region, locally formed high-concentration calcium microdomains can enter the mitochondria through Voltage-Dependent Anion Channel 1 (VDAC1) and further enter the matrix through mitochondrial calcium uniporters (Figure 1). In addition, regulatory proteins such as MFN1 and MFN2 in the MAMs region help maintain the sensitive response of mitochondria to calcium signals and reduce the risk of calcium overload-induced Mitochondrial Permeability Transition Pore (MPTP) opening and cell death [11]. In the past five years, several studies have shown that abnormal Ca^{2+} signal transduction mediated by IP3R-GRP75-VDAC1 complex can lead to ER and mitochondrial Ca^{2+} overload, which can induce stress response, and is closely related to neuronal damage in IS, tumor cell survival and aggravation of hepatic steatosis in NAFLD [12]. The imbalance of calcium homeostasis may be an important mechanism basis for the occurrence and development of many diseases.

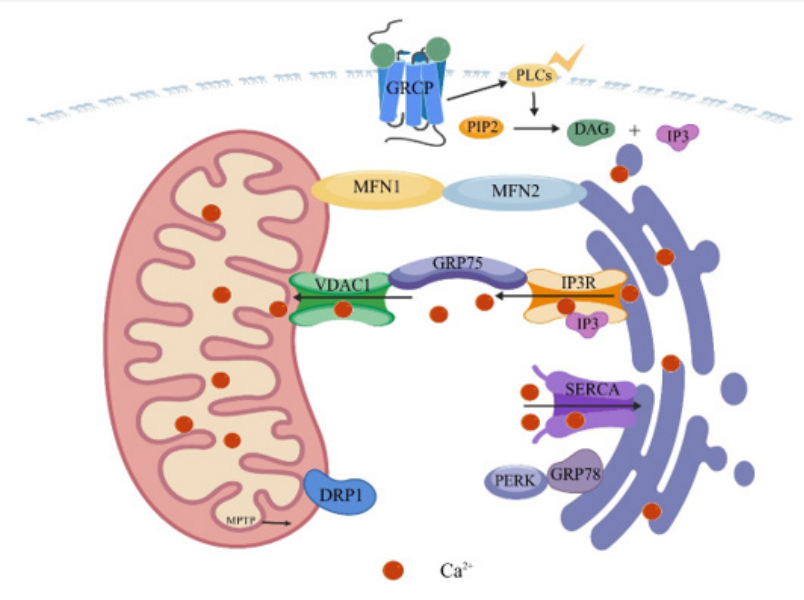

Figure 1: MAMs composition and Ca2+ signal transduction. This figure shows the Ca2+ signal transduction process between ER and mitochondria mediated by various MAMs resident proteins and IP3R-GRP75-VDAC1 complex.

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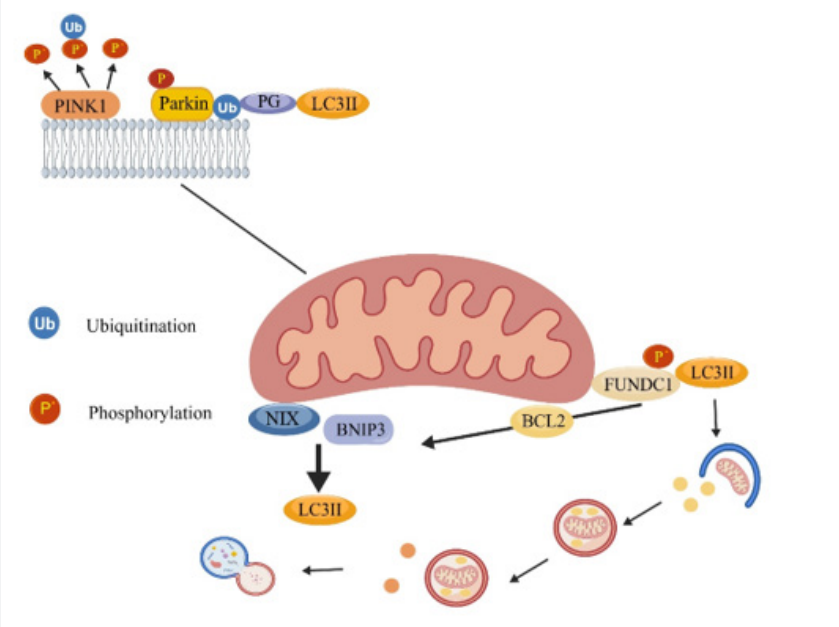

Figure 2: Mitochondrial autophagy. This figure shows the three main pathways of mitophagy: PINK / Parkin pathway, BNIP3 / NIX pathway and FUNDC1 pathway phagocytosis, digestion and degradation of damaged mitochondria.

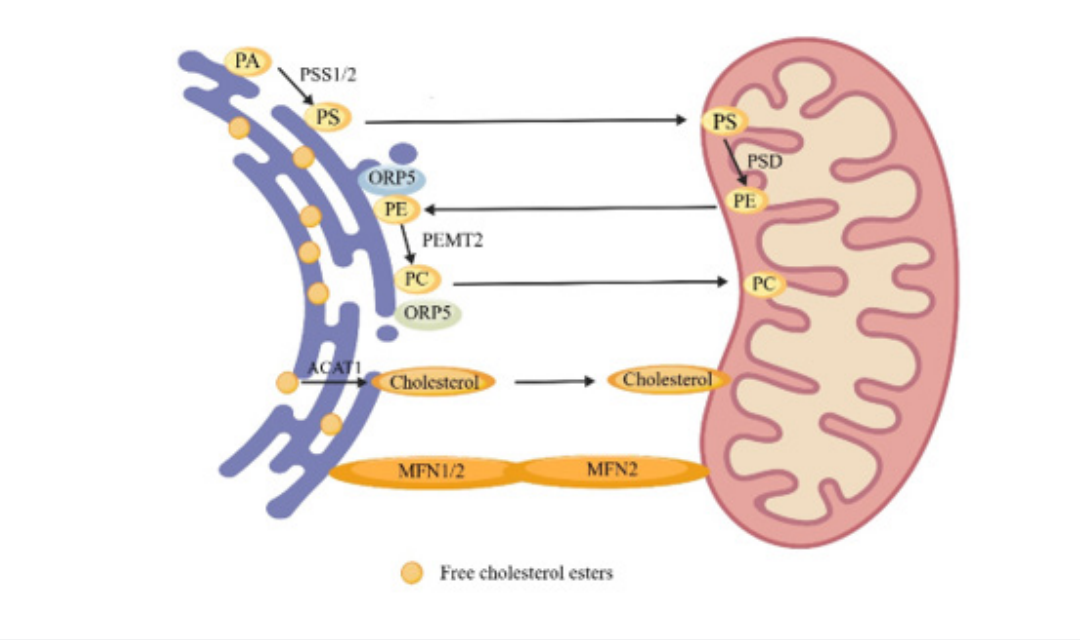

Figure 3: Lipid metabolism. This figure shows the synthesis and circulation of phospholipids such as PA, PS, PE and PC between ER and mitochondria, as well as the process of free cholesterol esterification to form membrane-bound cholesterol.

Mitochondrial autophagy

Mitophagy is a selective autophagy process regulated by Mitochondrial Quality Control (MQC). It mainly maintains mitochondrial network homeostasis by removing damaged or dysfunctional mitochondria and cooperating with mitochondrial biogenesis. As an important protective mechanism for cells to cope with acute stress, mitophagy helps to maintain the stability of the intracellular environment. The main pathways reported so far include: PTEN induced putative kinase1 (PINK1) / Parkin

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pathway, Bcl2-adenovirus E1B 19kDa interacting protein 3 (BNIP3) / NIP3-like protein X (NIX) pathway, FUN14 domain containing 1 (FUNDC1) pathway and cardiolipin pathway [13,14]. In the process of mitophagy, related receptors or adapter proteins can interact with Microtubule-Associated Protein Light Chain 3 II (LC3II), promote the damaged mitochondria to be wrapped to form autophagosomes, and finally degraded by lysosomes to achieve mitochondrial component recovery and cell homeostasis recovery (Figure 2). Mitochondrial autophagy disorders are closely related to cardiovascular and cerebrovascular diseases, cancer and chronic metabolic diseases. Therefore, in-depth research on the above pathways is of great significance for the interpretation of related disease mechanisms and the development of innovative treatment strategies.

Lipid metabolism

MAMs are an important structural platform for the directional transport of lipids between ER and mitochondria, which depends on the close contact between the two organelle membranes and the synergistic effect of related proteins. In the process of phospholipid synthesis, Phosphatidylserine synthase 1,2 (PSS1, PSS2) in the ER catalyzes the synthesis of Phosphatidylserine (PS) from Phosphatidic acid (PA), which is then transferred to mitochondria by specific lipoproteins at MAMs. At present, studies have shown that ORP5 and ORP8 enriched in MAMs are closely related to the transport process and the maintenance of mitochondrial morphology and function [15]. After entering the mitochondria, PS is decarboxylated by Phosphatidylserine decarboxylase (PISD) to form Phosphatidylethanolamine (PE) in the mitochondrial inner membrane. Part of PE returned to ER and converted to Phosphatidylcholine (PC) under the action of Phosphatidylethanolamine N-methyltransferase 2 (PEMT2) and returned to mitochondria, thus maintaining the dynamic balance of membrane phospholipid composition. In the process of cholesterol metabolism, intracellular free cholesterol can be esterified into cholesterol esters under the Action of acetyl-CoA acetyltransferase 1 (ACAT1) to maintain the dynamic balance of bound cholesterol and free cholesterol in the resting state (Figure 3). In addition, silencing MFN2 and GRP75 in NAFLD model can reduce the integrity of MAMs, promote triglyceride synthesis and aggravate lipid deposition. Overexpression of related proteins can improve the structure of MAMs and enhance intracellular cholesterol esterification and storage capacity [16]. The results imply that proteins related to MAMs, such as ORP5, ORP8, MFN2 a

nd GRP75, may serve as potential therapeutic targets for NAFLD.

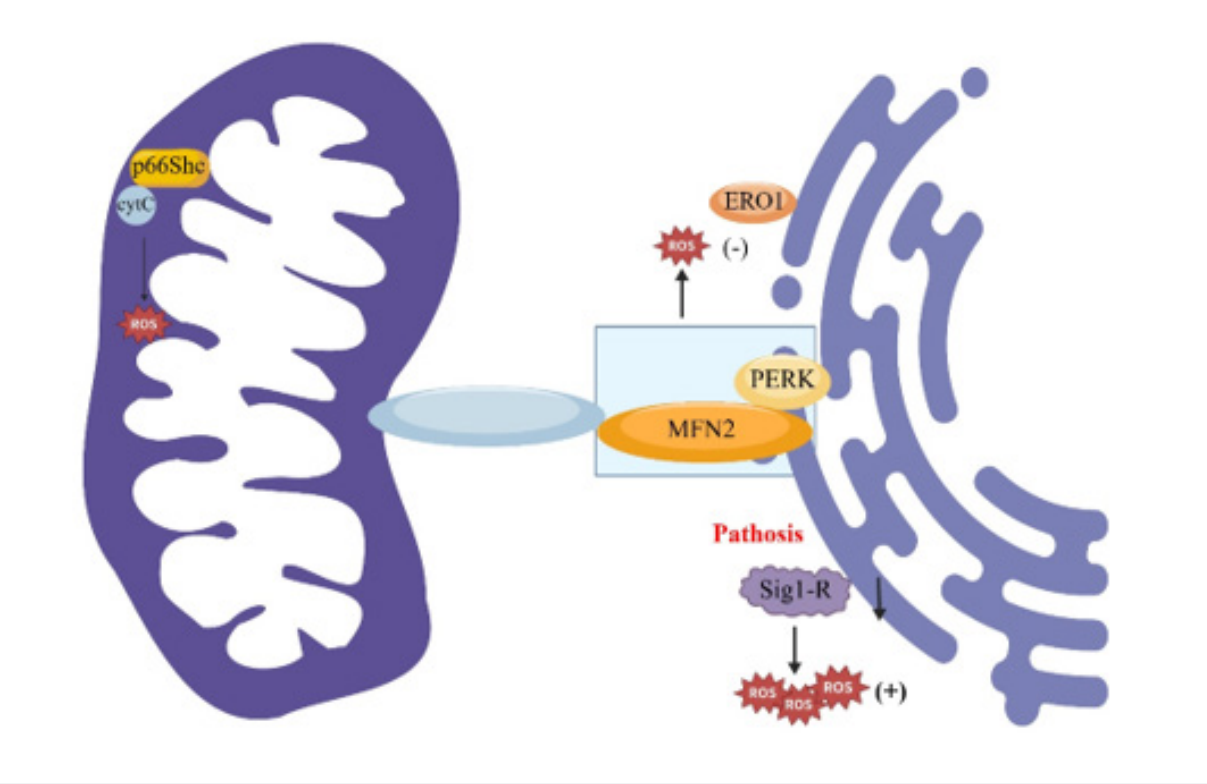

Figure 4: Oxidative stress, which shows the interaction between p66Shc and cytochrome c, the process of ROS accumulation induced by knockdown of Sig-1R in pathological state, and the process of MFN2 activating PERK to inhibit ROS accumulation.

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Oxidative stress

Oxidative stress refers to the pathological state caused by the imbalance between the production and clearance of Reactive Oxygen Species (ROS) in cells, which can cause ER and mitochondrial dysfunction and destroy cell homeostasis. The continuous increase of ROS not only damages the structure and function of cells but also is closely related to the occurrence and development of many diseases such as cancer, cardiovascular and cerebrovascular diseases. During the interaction between ER and mitochondria, a variety of membrane-related proteins are involved in the regulation of oxidative stress, including Endoplasmic Reticulum Oxidoreductase 1 (ERO1), Sigma-1 Receptor (Sig-1R), p66 Shc and MFN2. Under oxidative stress conditions, phosphorylation of some residues of p66Shc can reduce ubiquitination degradation and translocation to mitochondria, interact with cytochrome c to promote ROS production, and then induce apoptosis. Knockdown of p66Shc can reduce ROS levels, further supporting its pro-oxidative effect [17]. The specific mechanism by which Sig-1R is involved in the regulation of oxidative stress has not been fully elucidated. However, studies have shown that knockdown of Sig-1R in pathological conditions can lead to ROS accumulation, and some Sig-1R agonists have antioxidant effects [18]. Studies have found that MFN2 can directly activate the Pancreatic Endoplasmic Reticulum Kinase (PERK) pathway in cardiac fibroblasts, thereby inhibiting ER stress pathway and ROS formation, thereby protecting normal physiological activities of cells [19]. In inflammatory macrophages, MFN2 promotes ROS production to enhance oxidative stress (Figure 4) [20]. Therefore, the different functions of MFN2 in different cells and under different stress conditions still need to be further studied to gain a more comprehensive understanding of its role.

The above processes of calcium homeostasis, mitophagy, lipid metabolism and oxidative stress are precisely regulated by specific resident proteins in MAMs. With the development of super-resolution microscopy and adjacent marker proteomics, emerging resident proteins such as GPAT4, Mtus1, FMO2, and PDZD8-FKBP8 have been identified, and the molecular mechanisms in diseases such as cancer and NAFLD have gradually become clear. Relevant literature has confirmed that MAMs can be remodeled and expanded when ferroptosis occurs in cells, thereby promoting membrane phospholipid peroxidation and enhancing the transmission of oxidative stress signals to mitochondria, thereby aggravating the ferroptosis process. Among them, triple-negative breast cancer LAR subtype tumor cells highly express MAMs-related proteins and are more sensitive to ferroptosis [21]. Therefore, in-depth research on emerging resident proteins will help to further elucidate the regulatory mechanism of MAMs structure and function and provide new theoretical basis and potential targets for related disease intervention.

MAMs Resident Proteins and their Functions

MAMs resident proteins are an important part of MAMs. The molecular network composed of related resident proteins and their complexes can finely regulate MAMs-mediated physiological processes such as calcium homeostasis, lipid metabolism, oxidative stress and mitophagy, thereby maintaining the stability of organelle interaction. The in-depth study of the structure and function of related resident proteins not only helps to clarify the basic physiological regulation mechanism of MAMs but also provides potential targets for the screening of early cancer markers, tumor progression intervention, and the regulation of pathological processes related to chronic metabolic disorders and cardiovascular and cerebrovascular diseases.

GPAT4

Glycerol-3-Phosphate Acyltransferase 4 (GPAT4) is an anchor protein located in the ER membrane, which can maintain its morphological integrity and functional stability by maintaining ER lipid homeostasis. Related research. Using transmission electron microscopy, GPAT4 deficiency in related animal models can lead to obvious swelling and expansion of ER. Molecular biology studies have found that GPAT4 deficiency can promote the phosphorylation of elF2α by PERK kinase, and then activate PERK-eIF2α-ATF4-CHOP, ATF6, IRE1-XBP1 three Unfolded Protein Response (UPR) , triggering ER stress and destroying cell homeostasis ; in addition, UPR can lead to a significant increase in the contact sites of MAMs, and the expression levels of IP3 R, GRP75 and VDAC1 are significantly increased, which in turn induces a large number of Ca^{2+} transport to mitochondria, induces mitochondrial calcium overload, mitochondrial DNA release, and aggravates mitochondrial stress and dysfunction. GPAT4 overexpression can improve ER morphology and enhance cell tolerance to oxidative stress and calcium overload [22]. Based on the above research, targeted regulation of GPAT4 to alleviate ER stress caused by Ca^{2+} imbalance may provide new potential targets for the intervention of diseases such as IS and NAFLD.

Mtus1

Mitochondrial tumor suppressor gene 1 (Mtus1) is a MAMs-related regulatory molecule with both tumor suppressor and scaffold protein functions and is involved in a variety of cancer-related signaling pathways. Its subtype Mtus1A can regulate mitochondrial calcium signaling and energy metabolism by maintaining the stability of ER-mitochondrial IP3R1-Grp75-VDAC1 complex. Experimental studies reveal that Mtus1A significantly regulates myocardial ischemic damage, and its deletion can aggravate myocardial ischemic injury, expand myocardial infarction area, and lead to decreased cardiac function [23]. In addition, the expression level of Mtus1 is closely related to the clinical outcomes of various tumors. Logistic regression analysis showed that the expression of Mtus1 was related to N stage, TNM stage and tumor type. Compared with normal tissues, Mtus1A expression is downregulated in Colorectal Cancer (CRC) samples, and the Overall Survival (OS) of patients with low expression was poor. Multivariate analysis further showed that down-regulation of Mtus1 was an independent predictor of poor OS [24]. Similar results were also found in Lung Adenocarcinoma

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(LUAD) [25]. Therefore, Mtus1 is expected to be a potential biomarker for colorectal cancer and lung adenocarcinoma screening and will also become an important target for inhibiting tumor growth and metastasis to improve OS of cancer patients, which is of great significance for promoting cancer immune screening and treatment.

FMO2

Flavin Containing Monooxygenase 2 (FMO2) is an ER membrane resident protein closely related to calcium homeostasis and lipid metabolism in MAMs. Related literature shows that FMO2 can participate in the formation and stability of the IP3R2-Grp75-VDAC1 complex, thereby maintaining ER-mitochondrial contact and regulating Ca^{2+} signaling between the two organelles [26]. In terms of lipid metabolism, the role of FMO2 in chronic liver disease has gradually attracted attention. Related studies have found that FMO2 expression is significantly down-regulated in NAFLD and Nonalcoholic steatohepatitis (NASH) patients and mouse models. Further experiments showed that up-regulation of FMO2 could bind to Sterol Regulatory Element Binding Protein 1 (SREBP1) and competitively interact with SREBP cleavage activating protein (SCAP) at amino acids 217-296, thereby activating SREBP1 and inhibiting its transport to Golgi apparatus. Thus, reducing De novo lipogenesis (DNL) and improving NAFL / NASH [27]. Therefore, up-regulation of FMO2 to activate SREBP1 may be a potential target for interfering with NAFL and NASH-related lipid metabolism disorders.

PDZD8-FKBP8

PDZ domain-containing protein 8 (PDZD8) and FK506 binding protein 8 (FKBP8) are located in ER and mitochondrial outer membrane, respectively, which can maintain the structural integrity of MAMs through stable chain. Functional studies have shown that PDZD8 can enhance mitochondrial network complexity by inhibiting FKBP8 [28]. Recent studies have suggested that PDZD8-FKBP8 axis abnormalities are closely related to the progression of malignant tumors. Wang et al. [29] reported that the expression of PDZD8 was significantly up-regulated in CRC tissues. Knockdown of PDZD8 by Short Hairpin RNA (shRNA) can inhibit CRC proliferation and induce apoptosis. Further exploration of its carcinogenic mechanism found that miR-1283 can negatively regulate the expression of PDZD8, and PDZD8 overexpression can partially antagonize the anti-tumor effect of miR-1283. In LUAD, PDZD8 is also highly expressed and promotes cell proliferation and migration. Unlike CRC, circ-0020123 acts as a competing endogenous RNA (ceRNA) sponge to adsorb miR-1283 and remove its inhibition of PDZD8, thereby up-regulating PDZD8 expression [30]. The above studies suggest that PDZD8 is not only a potential biomarker for prognosis evaluation of CRC and LUAD, but also a candidate target for targeted intervention of MAMs structure to inhibit tumor metastasis.

The pathogenic mechanism of MAMs in different diseases

As a key structural platform connecting ER and mitochondria, MAMs are involved in maintaining organelle synergy and cell fate homeostasis by coordinating calcium homeostasis, lipid metabolism, redox balance, autophagy and inflammatory signal transduction. Recent advances in super-resolution microscopy and proteomics have shown that MAMs can undergo dynamic remodeling under the stimulation of ischemia, metabolic disorders and tumor microenvironment. Abnormalities in contact distance, protein composition, and molecular interactions often lead to ER stress, mitochondrial dysfunction, and ROS accumulation, and further amplify cell damage or abnormal proliferation responses. Therefore, MAMs dysfunction has become an important pathological link involved in diseases such as IS, NAFLD and cancer, and is also a key bridge connecting organelle imbalance and disease phenotype transformation. Research on the structural homeostasis, dysfunction and regulatory networks of MAMs not only helps to reveal the common mechanisms of different diseases but also offers a novel theoretical foundation of precise intervention.

MAMs and IS

Studies have shown that MAMs play an important role in the occurrence and development of IS, in which mitophagy and ER stress are the key links involved in neuronal damage and repair. Mitophagy has a two-way regulatory effect in IS: moderate activation helps to remove damaged mitochondria, reduce ROS accumulation and exert neuronal protection, while excessive activation may promote neuronal death, and its specific effects depend on autophagy intensity, timing of occurrence and related protein expression levels. In IS, activation of the classic ubiquitin-dependent pathway PINK1-Parkin clears damaged mitochondria and the large amount of ROS they produce, thereby reducing oxidative stress and exerting neuroprotective effects [31]; the non-ubiquitin-dependent pathway relies on the accumulation of FUNDC1 under hypoxic conditions. It initiates mitophagy by dephosphorylation and binding to LC3 and interacts with OPA1 and Drp1 to regulate mitochondrial fission and fusion, and interacts with IP3R2 to participate in calcium signaling, thereby reducing IS damage. In addition, Beclin1 also showed obvious temporal and spatial dependence: in the early stage of ischemia, Parkin recruited and formed Beclin1-Vps34 complex, which promoted the formation of autophagosomes and played a neuroprotective role; however, in the late stage of reperfusion or when calpain is overexpressed, it may induce excessive mitophagy and aggravate ischemic injury (Figure 5A) [32]. Similar to mitophagy, ER stress-related UPR pathway also has a two-way regulatory effect. During the initial phase of IS, Glucose-regulated protein 78 (GRP78) separates from PERK, Inositol-requiring enzyme 1 (IRE1) and Activating Transcription Factor 6 (ATF6), and binds to misfolded

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proteins to correct them to initiate a protective response [33]. However, as the stress continues, the PERK-Activating Transcription Factor 4 (ATF4) pathway continues to be activated, and IRE1 can promote neuronal apoptosis and inflammatory response through the RIDD process (Regulated IRE1-dependent decay) (Figure 5B) [34].

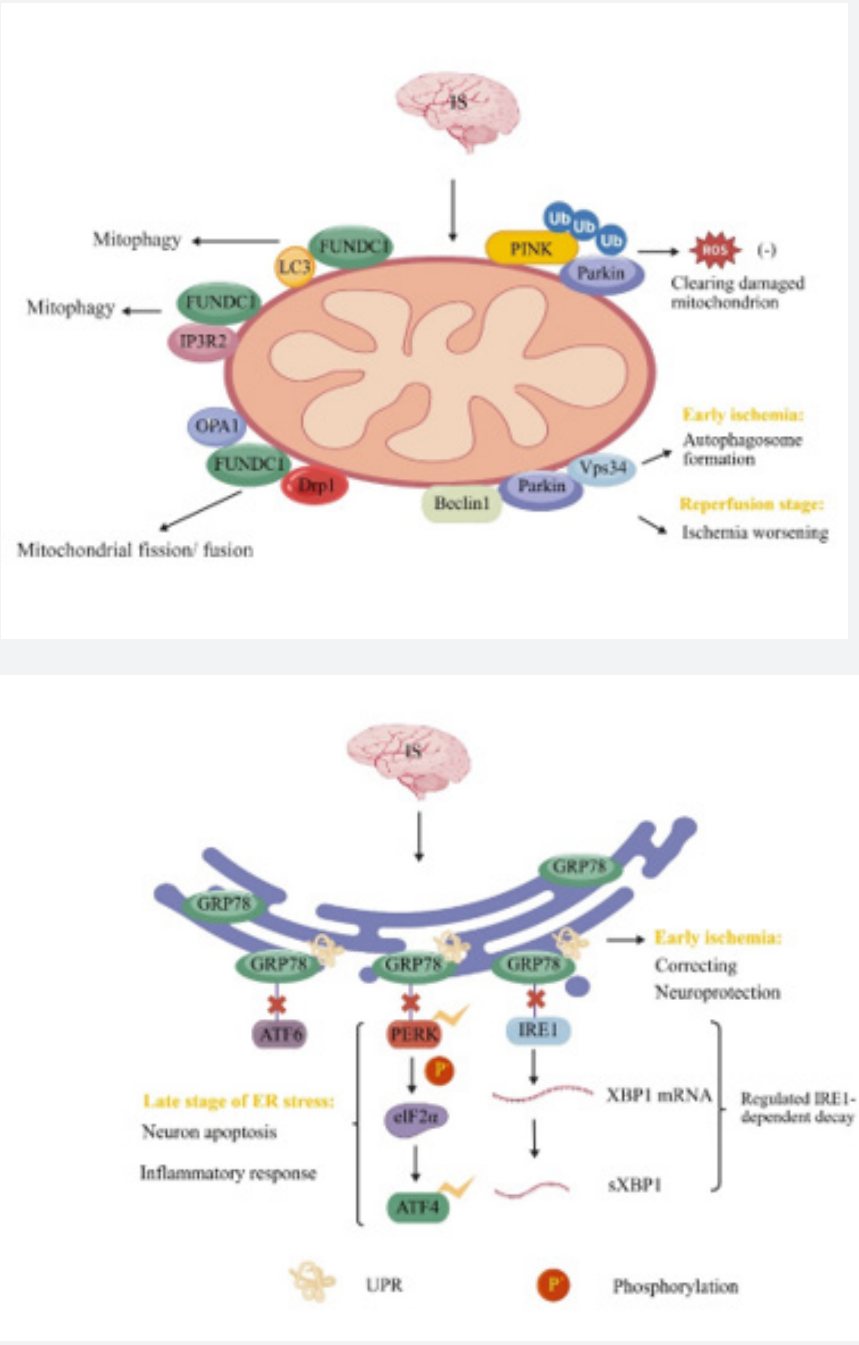

Figure 5: MAMs and IS, Figure A shows the different effects of PINK-Parkin pathway, FUNDC1-OPA1-Drp1 pathway, FUNDC1-IP3R2 pathway and Parkin-Beclin1-Vps34 pathway in the early stage of ischemia and the late stage of reperfusion. Figure B shows the dissociation of three pathways in the ER in the early stage of IS to correct the protective neurons of UPR, and the continuous activation of PERK, ATF4 and IRE1 in the late stage of IS to aggravate the ER stress through RIDD process.

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MAMs and NAFLD

NAFLD is a chronic metabolic disease with complex pathological mechanism. With the deepening of the research on the interaction of organelles, more and more evidence show that the structural integrity of MAMs is essential for maintaining the normal operation of calcium homeostasis and lipid metabolism in hepatocytes. Its structural damage can lead to abnormal Ca^{2+} signal transduction and lipid metabolism disorders, thus promoting the development and deterioration of NAFLD. In NAFLD tissues, the abnormal Ca^{2+} signal transduction mediated by IP3R-GRP75-VDAC1 leads to the continuous transfer of Ca^{2+} in ER lumen to mitochondria, which in turn causes Ca^{2+} depletion in ER lumen, affects protein folding and induces ER stress. At the same time, excessive mitochondrial Ca^{2+} uptake enhances ROS generation and worsens oxidative stress. The above processes are mutually amplified and eventually lead to liver cell damage [35]; in addition, the imbalance of PC / PE ratio in NAFLD tissue can destroy the stability of ER membrane, further induce ER stress and promote lipid synthesis. In addition, the structural integrity of MAMs is of great significance for insulin signal transduction. When the structure of MAMs is damaged, ER stress can activate the stress-activated protein kinase pathway (c-Jun N-terminal kinase pathway), thereby promote insulin receptor substrate-1 (Insulin Receptor Substrate-1, IRS-1) serine phosphorylation, and ultimately cause insulin resistance [36]. Insulin resistance further weakens the lipid metabolism ability of hepatocytes, which eventually leads to liver lipid deposition and aggravates the progression of NAFLD (Figure 6).

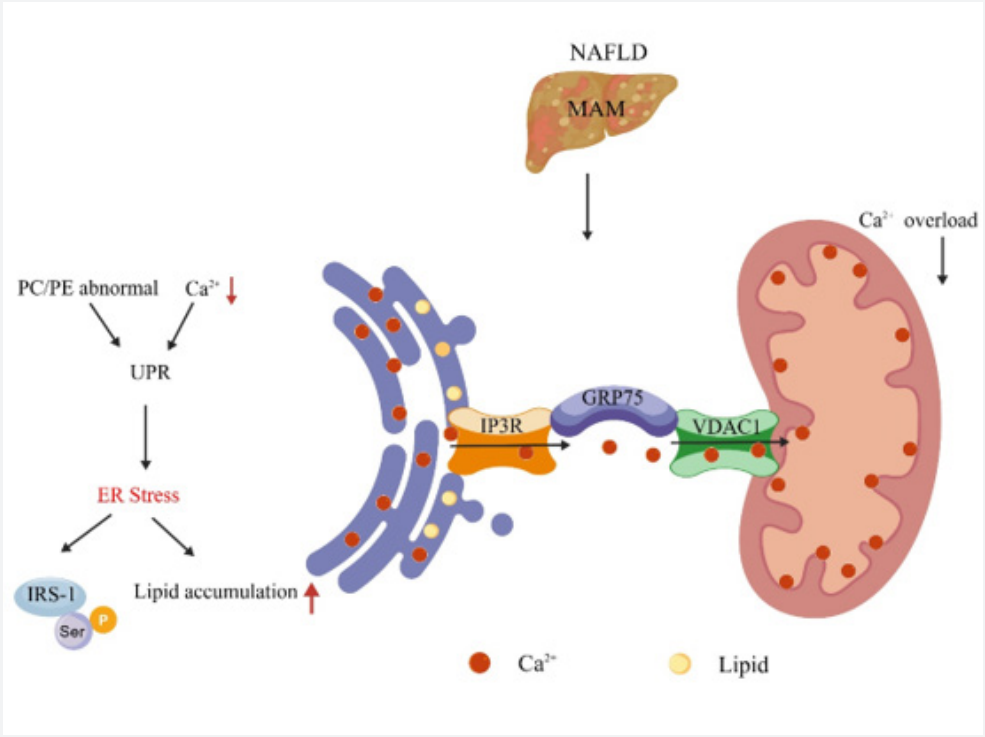

Figure 6: MAMs and NAFLD. This figure show the process of ER stress caused by UPR caused by ER calcium depletion and PC / PE imbalance in NAFLD, which leads to insulin resistance and impaired lipid metabolism, and mitochondrial calcium overload leads to ROS accumulation to accelerate the development of NAFLD.

MAMs and cancer

MAMs maintain cell homeostasis through Ca^{2+} signal transduction, lipid metabolism, mitophagy and oxidative stress, and their functional imbalance is closely related to the occurrence and development of tumors. In cancer tissues, abnormal Ca^{2+} signal transduction plays an important role in anti-apoptosis of cancer cells. As an anti-apoptotic protein, BCL2 can promote the survival of cancer cells by acting on the IP3R-GRP75-VDAC1 complex. Specifically, overexpression of BCL2 in cancer cells can interact with IP3R and VDAC1, inhibit the transport of Ca^{2+} to mitochondria, and interfere with the release of cytochrome C from mitochondria, thereby promoting the anti-apoptosis of cancer cells. Related studies have shown that overexpression of BCL2 can also weaken Ca^{2+} signal transduction through this mechanism, reduce the cytotoxicity of chemotherapy drugs, and improve the drug resistance of cancer cells [37]. In addition, the coordination imbalance between the mitogenic protein DRP1

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and the fusion protein MFN1 / 2 in MAMs can lead to abnormal mitochondrial network structure and promote tumorigenesis [38]. PINK1 / Parkin-mediated mitophagy abnormalities help cancer cells to remove dysfunctional mitochondria and enhance their survival advantages. On the other hand, overexpression of MAMs-related proteins ERO1α and p66Shc can lead to excessive production of ROS, triggering oxidative damage and activating pro-survival or pro-tumor signals. At the same time, the abnormal interaction between PERK and Mfn2 expands the range of tumor-promoting signals and allows more tumor cells to survive (Figure 7). In general, MAMs promote the occurrence and development of malignant tumors through abnormal expression of various proteins, interaction and imbalance of related signaling pathways.

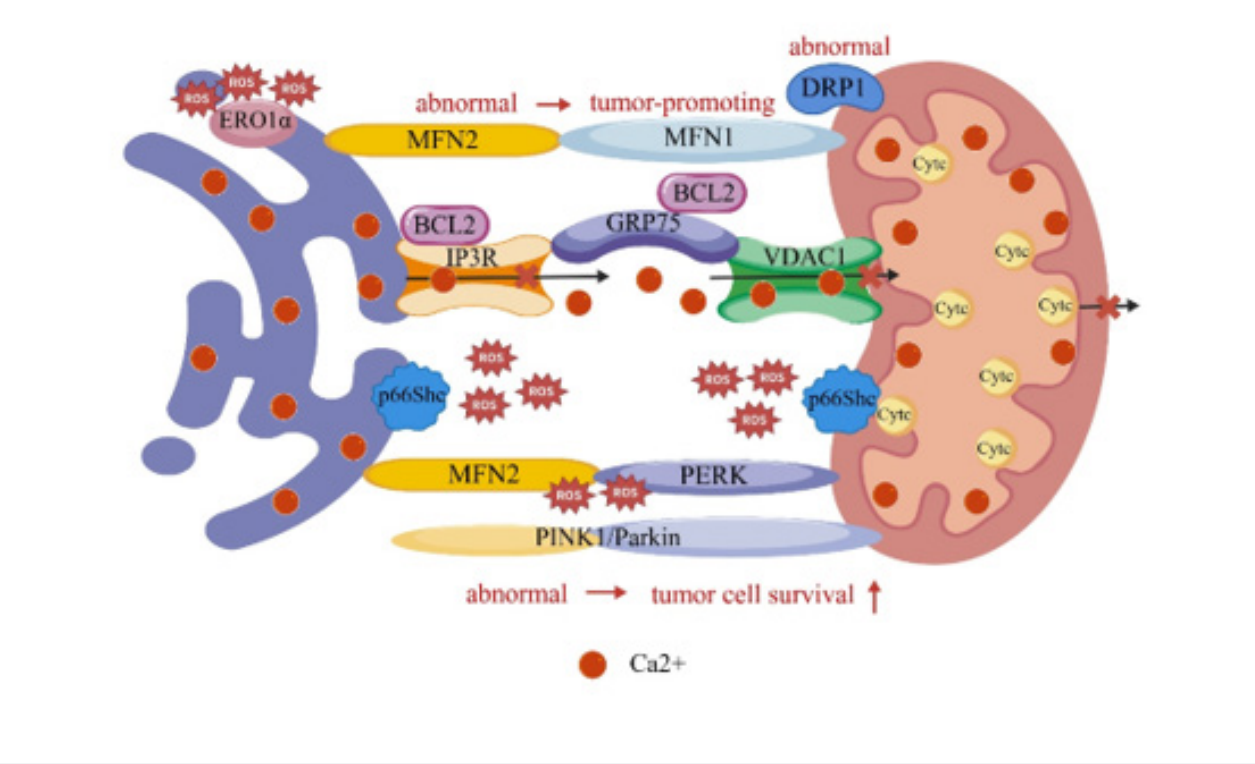

Figure 7: MAMs and cancer. The interaction between BCL2 and IP3 R, VDAC1, the coordination imbalance between DRP1 and MFN1 / 2, PINK / Parkin pathway, ERO1α, p66 Shc overexpression and the abnormal interaction between PERK and MFN2 promote the survival and proliferation of tumor cells.

The mechanism of ncRNA regulating MAMs structure in different diseases

Recently, researches have increasingly focused on the pathophysiology and pathogenesis of IS, cancer and nonalcoholic fatty liver disease from the perspective of molecular biology and structural biology, and to use ncRNA for targeted diagnosis and treatment. The above review has revealed that miR-1283 affects CRC progression by regulating PDZD8 expression, and that circ-0020123 competitive sponge adsorbs miR-1283 to up-regulate PDZD8 to promote LUAD progression. On this basis, the latest studies have further found that MAMs are not only the subcellular localization sites of miRNAs, but also the key hub for miRNA transport between mitochondria and ER. The redistribution of inflammatory reactive miRNAs between two organelles is closely related to the stress state of organelles and the occurrence and development of diseases. Relevant animal experiments have confirmed that miR-146a is a key miRNA that regulates the production of inflammation-related cytokines and participates in innate immunity and inflammatory response. Its deficiency is closely related to excessive inflammatory response, continuous activation of NF-κB pathway and tumorigenesis during aging [39]. In addition, the redistribution of this miRNA is considered to be an important signal for acute and chronic neurological diseases (such as IS) caused by mitochondrial dysfunction, and is expected to be a potential accurate marker for the diagnosis and treatment of IS. In terms of metabolic disorders, Arun et al. [40] found that the expression of lncRNA H19 in the liver of diabetic mice decreased, while the expression of MAMs protein VDAC1 increased, which caused mitochondrial calcium overload and ROS accumulation. This lncRNA H19-VDAC1 axis abnormality is closely related to gluconeogenesis and impaired insulin signaling. Based on this, the researchers speculate that targeting lncRNA H19 to reduce

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VDAC1, enhance insulin sensitivity and reshape the balance of glucose and lipid metabolism is expected to be a candidate target to alleviate the progression of NAFLD.

The commonness and individuality of MAMs dysfunction in different diseases

In IS, cancer and NAFLD, MAMs-mediated interactions have both common pathological mechanisms and disease-specific functional differentiation. In terms of Ca^{2+} signaling, IP3R-GRP75-VDAC-mediated Ca^{2+} transport from ER to mitochondria is a common upstream event in the three diseases. In IS and NAFLD, abnormal activation of this complex leads to ER cavity Ca^{2+} depletion and mitochondrial matrix Ca^{2+} overload, which consequently causes the mitochondrial permeability transition pore to open and induces ER stress, accelerating neuronal and hepatocyte damage. However, in cancer, restoration of IP3R-GRP75-VDAC-mediated Ca^{2+} signal transduction can instead promote Ca^{2+} overload-induced apoptosis of tumor cells, becoming a potential anti-cancer strategy. In terms of mitophagy, the PINK1 / Parkin pathway is the core regulatory mechanism of MQC in three diseases, and its role is obviously stage-dependent and scenario-dependent. In IS, moderate mitophagy can remove damaged mitochondria after ischemia-reperfusion injury and play a neuroprotective role; however, excessive activation may aggravate cell damage. In cancer, this pathway is dysfunctional. On the one hand, it can maintain mitochondrial homeostasis to support tumor cell survival. On the other hand, it can lead to the accumulation of damaged mitochondria. ROS signal activation promotes genomic instability and tumor progression. In terms of oxidative stress, although the upstream signals that trigger mitochondrial ROS accumulation in the three diseases are different-IS is mainly due to reperfusion-induced electron transport chain dysfunction, NAFLD is closely related to lipid metabolism overload, and cancer is involved in metabolic reprogramming-mitochondrial oxidative damage caused by excessive ROS accumulation is a common driver of disease progression. In terms of lipid metabolism, MAMs are a key platform for lipid transport, and their dysfunction has a particularly prominent impact on NAFLD. Liver is the core organ of lipid metabolism. MAMs-mediated transport disorder of lipids such as PC between two organelles can directly lead to liver lipid accumulation, which is a characteristic pathological link of NAFLD different from the other two diseases. In summary, abnormal Ca^{2+} signal transduction and abnormal mitophagy are the common molecular basis of the three diseases, and the specific microenvironment and metabolic background of each disease determine the different or even opposite pathological outcomes of the same pathway.

Targeted Therapies

As an important structural platform connecting ER and mitochondria, the imbalance of MAMs homeostasis is closely related to the occurrence and development of various diseases such as cancer, NAFLD and IS. With the deepening of related research, MAMs have become an important entry point for the above-mentioned disease intervention research. Based on the key proteins related to MAMs and their functional abnormalities, existing studies have proposed a variety of targeted regulation strategies from different levels. The following will summarize the MAMs-related targeting methods in combination with the research progress of the above diseases.

IS targeted therapies

IS is an acute neurological deficit disease caused by the interruption of local cerebral blood perfusion. It has high mortality and high disability rate, and its reperfusion time window is limited. Therefore, effective targeted intervention strategies are urgently needed. MAMs-mediated abnormal mitophagy, calcium homeostasis imbalance and ER stress play an important role in the occurrence and development of IS and provide multiple potential targets for its treatment. The PINK1 / Parkin pathway can remove damaged and aging mitochondria. Studies have found that docosahexaenoic acid and remote ischemic treatment can up-regulate PINK1 / Parkin levels to improve ischemic injury. FUNDC1 is an important molecule that mediates mitophagy and alleviates reperfusion injury under hypoxia. Tissue plasminogen activator and Unc-51-like autophagic activating kinase can up-regulate FUNDC1 level to improve reperfusion injury and hypoxia-induced neuronal death, respectively. Inhibition of calcium overload mediated by glucose-regulated protein75 (GRP75) also has potential therapeutic value. Salidroside, a natural drug, can alleviate calcium overload and improve IS symptoms by inhibiting GRP75 activity and reducing the formation of ER-mitochondrial contact sites [41]. In addition, Sig-1R is an important target for regulating Ca^{2+} homeostasis. Its agonists, such as fluvoxamine and dexmedetomidine, can stabilize intracellular calcium homeostasis by activating Sig-1R and reduce ER stress and cell death caused by ER calcium depletion. In the regulation of organelle stress, acupuncture at Zusanli and Baihui can significantly up-regulate the ER chaperone protein GRP78, promote the correct folding of UPR, alleviate the ER stress response caused by UPR accumulation, and then protect the function of neurons [42]. In the early stage of ischemia, resveratrol can induce the phosphorylation of Beclin1-VPS34 by regulating the upstream signaling pathway of Beclin1, promote the formation of autophagosomes, reduce the area of cerebral infarction and improve neurological function (Table 1) [43]. In addition, the use of PERK inhibitors GSK2606414 and GSK2656157 in the middle and late stages of ischemia can reduce the ER stress response caused by excessive activation of PERK and improve the prognosis of IS, but it still has the off-target risk of acting on RIPK1 and KIT. Therefore, the precise effect exerted by PERK has not been conclusively established and requires more investigation [44].

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Table 1: IS targeted therapy methods, targets and specific effects.

Methods to treat	Targets	Effects
Docosahexaenoic acid and remote ischemic treatment	PINK1/ Parkin	Increase the level of PINK1 / Parkin and improve the ischemic condition.
Tissue-type plasminogen activator	FUNDC1	Up-regulate the level of FUNDC1 and improve reperfusion injury
Unc-51-like autophagic activating kinase		Up-regulation of FUNDC1 level improves neuronal death caused by hypoxia.
Rhodioloside	GRP75	Inhibition of GRP75 activity reduces MAMs sites, improves calcium overload and alleviates IS symptoms.
Fluvoxamine and dexmedetomidine	Sig-1R	Stabilize intracellular calcium homeostasis and reduce ER stress and cell death caused by ER calcium depletion.
Acupuncture Zusanli, Baihui point	GRP78	Increase the level of GRP78 and improve ER stress
Resveratrol	Beclin1	Regulate the upstream pathway of Beclin1, induce Beclin1-VPS-34 phosphorylation, and promote the formation of early autophagosomes.
GSK2606414 and GSK2656157	PERK	Inhibition of PERK overactivation alleviates ER stress, protects neurons, and improves IS outcomes.

Cancer targeted therapy drugs

MAMs-related calcium homeostasis imbalance, stress response and lipid metabolism disorders can significantly affect the anti-apoptotic ability and drug sensitivity of tumor cells and provide potential targets for anti-tumor therapy. In the aspect of calcium homeostasis, cisplatin can promote the transport of Ca^{2+} from ER to mitochondria and induce ER stress, thereby mediating apoptosis; however, long-term application can lead to drug resistance of tumor cells. On this basis, ABT737, which inhibits the interaction between BCL2 and IP3R / VDAC1, can restore calcium signal transduction and reverse drug resistance of ovarian cancer cells [45]. In addition to calcium homeostasis, lipid metabolism regulation is also an important intervention direction. ACAT-1 is highly expressed in a variety of tumors, which can promote the accumulation of cholesterol esters and support tumor growth [46]. Mitotane promotes the apoptosis of adrenocortical carcinoma cells by targeting ACAT-1, inducing free cholesterol accumulation and triggering ER stress. In addition, the use of cell stress response to induce tumor cell death also provides new ideas for cancer treatment. Studies have found that 20 (S) -protopanaxadiol can enhance the overall activity of UPR in liver cancer cells, aggravate ER stress by phosphorylating PERK, and then inhibit the survival of tumor cells (Table 2) [20]. In the future, it is still necessary to further clarify the specific expression and functional differences of MAMs-related proteins in different tumor types, so as to promote their transformation to high-specific biomarkers and precise therapeutic targets.

Table 2: Cancer targeted therapy methods, targets and specific effects.

Drugs	Targets	Effects
Cisplatin	Ca^{2+} homeostasis	It promotes the transfer of Ca^{2+} from ER to mitochondria, induces ER stress and mediates apoptosis.
ABT737	BCL2 and IP3R / VDAC	Restoring calcium signaling and reversing drug resistance in ovarian cancer cells
Mitotane	ACAT-1	Targeted inhibition of ACAT-1 causes accumulation of free cholesterol and ER stress, thereby inducing apoptosis of adrenocortical carcinoma cells.
20(S)-protopanaxadiol	PERK, UPR	Phosphorylation of PERK aggravates ER stress, thereby inhibiting tumor survival.

NAFLD targeted therapy drugs

At present, the global prevalence of NAFLD is as high as 38 %. As a ' silent organ ', the liver 's pathological process is often difficult to be detected early, and traditional treatment strategies focus more on metabolic abnormalities themselves. With the deepening of microscopic imaging and molecular biology research, the intervention perspective of metabolic diseases has gradually shifted from simple metabolic regulation to organelle interaction and precise regulation of key molecular targets. MAMs have become a new focus of NAFLD intervention research. Since the structural and functional integrity of MAMs is closely related to insulin signal transduction in hepatocytes, targeted regulation of insulin signal transduction and reduction of insulin resistance are expected to become an important target for improving NAFLD.

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At present, drugs such as rosiglitazone and metformin have been shown to have related effects: rosiglitazone can up-regulate the expression of MAMs-related proteins such as CypD, VDAC1 and PACS2, and promote the normal conduction of insulin signaling pathway. Metformin alleviated insulin resistance in hepatocytes by improving the interaction between ER and mitochondria [47]. In addition, targeting CHOP and GRP78 can also alleviate abnormal lipid synthesis. Studies have found that sulforaphane can increase the content of MAMs protein and the expression of CHOP and GRP78, thereby improving lipid metabolism disorders [48]. Targeting SERCA to maintain calcium homeostasis in hepatocytes is also an important intervention direction for NAFLD. Liver stimulating substance (HSS) can maintain the calcium homeostasis of MAMs by enhancing SERCA activity, thereby delaying the progression of NAFLD (Table 3) [49]. In general, the multi-target and multi-pathway comprehensive intervention strategy around MAMs is expected to provide new ideas for the precise treatment of NAFLD.

Table 3: NAFLD targeted therapy methods, targets and specific effects.

Drugs	Targets	Effects
Rosiglitazone	CypD, VDAC1 and PACS2, etc.	Up-regulate the target protein to promote the normal conduction of insulin signaling pathway
Metformin	MAMs binding sites	Improve the interaction between ER and mitochondria, alleviate the insulin resistance of liver cells.
Sulforaphane	CHOP and GRP78	Improve abnormal lipid synthesis
HSS	SERCA	Enhance SERCA activity, maintain calcium homeostasis of MAMs, and alleviate disease progression.

Research bottleneck of MAMs

Although some progress has been made in the research on the structural characteristics, functional regulation and related targets of MAMs in recent years, the microenvironment and regulatory network of MAMs are highly complex due to their involvement in various physiological and pathological processes such as calcium homeostasis regulation, lipid metabolism, mitochondrial dynamics and cell stress response. Therefore, the relevant intervention strategies still face many unsolved technical bottlenecks. As far as the current drug research on the relative targets of MAMs is concerned, some traditional drugs, such as cisplatin, can affect the Ca^{2+} signaling pathway to induce endoplasmic reticulum stress in tumor cells to a certain extent, but its strong drug resistance and strong cytotoxicity limit its application prospect as a candidate drug for precise treatment. Natural drugs such as resveratrol have problems such as low bioavailability, poor pharmacokinetics, and potential nephrotoxicity. Therefore, the determination of safe and effective doses and the avoidance of toxicity risks remain to be further studied [50]. In addition, although GSK2606414 and GSK2656157, two PERK inhibitors, have certain research value, they may also act on other targets such as RIPK1 and KIT, suggesting that they have a non-negligible off-target effect. In conclusion, the subsequent development of MAMs targeted intervention drugs not only needs to further improve the target selectivity but also should achieve a more reasonable balance between efficacy, safety and *in vivo* stability.

Summary and Prospect

This paper systematically reviews the physiological functions of MAMs and the regulatory effects of related resident proteins under the endoplasmic reticulum-mitochondrial interaction mechanism, and links them with the pathological mechanisms of IS, cancer and NAFLD. Based on the theory of multi-target, multi-pathway and integrated traditional Chinese and Western medicine, the targeted treatment strategies and research targets of different diseases are summarized, and the limitations of the current interaction mechanism and the future clinical value are analyzed.

Although the structural biology research of some targets has made progress, the precise function, dynamic regulation mechanism and action mode of most key proteins under different pathological conditions are still fully elucidated, which limits the precise design and transformation application of targeted drugs to a certain extent. In addition, the existing intervention strategies generally have problems such as insufficient selectivity and off-target effects; For natural drugs, it faces challenges such as difficult extraction of active ingredients, poor pharmacokinetics, and strong potential toxic and side effects. How to improve the specificity and safety of targeted drugs is still an urgent problem to be solved in MAMs related research.

In general, further analysis of the complex roles of MAMs and surface resident proteins in the maintenance of organelle homeostasis and disease progression not only helps to deepen the understanding of the pathophysiological mechanisms of IS, cancer and NAFLD, but also is expected to provide a new theoretical basis for the development of more targeted treatment strategies and the promotion of clinical transformation.

Author Contributions

Yirui Wang wrote the manuscript and produced the figures. Yujinpeng Hao, Jun Shao and Mianli Bian reviewed the manuscript

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and contributed to the revision. Mianli Bian coordinated the work and led the revision of the manuscript. All authors contributed to the manuscript and approved the version submitted.

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