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Research Highlight

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Mitochondria-associated endoplasmic reticulum membranes (MAMs) involve in the regulation of mitochondrial dysfunction and heart failure

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Both endoplasmic reticulum (ER) and mitochondria are fundamental organelles that coordinate high-order cell functions. ER is an extensive network of cisternae and microtubules, which stretches from the nuclear envelope to the cell surface in all eukaryotic cells. ER works as the site for protein synthesis and corrects post-translational 'folding' of proteins. ER also has the ability to transport proteins to their destination. Moreover, ER acts as a calcium ion (Ca^{2+}) reservoir which can be activated by both electrical and chemical stimulation.

Mitochondria contain two membranes that separate four distinct compartments, the outer mitochondrial membrane, the intermembrane space, the inner mitochondrial membrane, and the matrix. As a highly dynamic organelle, the steady-state of the entire mitochondrial network is maintained through constant fusion and fission, which is considered as mitochondrial dynamics. The dynamic balance of mitochondria between fusion and fission is the basis of the maintenance of many physiological activities in organisms, such as cell division, apoptosis, autophagy, and aging. At the same time, it also plays a major role in ATP production, Ca^{2+} buffering, free radical scavenging, and mitochondrial DNA genetic process [1]. The ER is responsible for folding, transport, and degradation of proteins, whereas mitochondria are the center of energy production [2].

Mitochondria and ER actively communicate with each other to promote a variety of cellular events, such as material transfer and signal transduction [3]. ER and mitochondria have several contact sites, which are named as mitochondria-associated endoplasmic reticulum membranes (MAMs). MAMs are involved in various biological functions, including lipid metabolism, Ca^{2+} signaling, inflammation, autophagy, and apoptosis [4].

Recent studies showed that the MAMs contain lipid and protein constituents. Proteins enriched at the MAMs can be classified as follows: (1) the signaling molecules of regulating Ca^{2+}: inositol 1,4,5-trisphosphate (IP_3) receptors, which act as Ca^{2+} channels [5], are highly expressed at the MAMs. Bcl-2 regulates IP_3 receptors and ER Ca^{2+} storage [6]; (2) molecular chaperones, such as BiP and HSP70 [7]; (3) lipid enzymes, such as Akt (PKB), which belongs to serine/threonine kinase and is involved in glucose metabolism, cell proliferation, and apoptosis [8]; (4) membrane tethering or sorting proteins, such as phosphoacidic cluster sorting protein 2 (PACS-2), which regulates the lipid-synthesizing enzyme, and tethers MAMs to mitochondria [9]; (5) apoptosis-related proteins; (6) proteins involved in protein degradation, such as dynamin-related protein 1 (DRP1), which is the classic example to regulate mitochondrial fission [10] (**Fig. 1**).

MAMs are closely related to neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease (AD). Area-Gomez *et al.* [11] demonstrated the enrichment of γ-secretase in MAMs, which mediates the amyloid precursor protein to generate Aβ and results in human familial AD. AD is a disorder of ER-mitochondrial hyperconnectivity. Parkinson's makes a positive effect on the ER-mitochondria interaction, which results in enhancement of physical coupling between ER and mitochondria and favor of calcium transfer from the ER to the mitochondria following IP_3 generating agonist [12] (**Fig. 1**).

Furthermore, MAMs are associated with insulin resistance and β-cell dysfunction in type 2 diabetes mellitus (T2DM). MAMs could be an important hub for hormonal and nutrient signaling in the liver. ER-mitochondria miscommunication could participate in hepatic insulin resistance. Targeting MAM structure and function might be a novel strategy for the treatment of T2DM [13] (**Fig. 1**).

MAMs also contribute to the development of cancers. In MAMs, IP_3 is responsible for the Ca^{2+} release in ER. Ca^{2+} is a ubiquitous intracellular second messenger required for functional mitochondrial metabolism during uncontrolled proliferation of cancer cells. More and more proteins are proved to finely regulate Ca^{2+} transfer from ER to mitochondria in cancers, including triple-negative breast cancer [14], colorectal cancer [15], cervical cancer [16], and liver cancer [13] (**Fig. 1**).

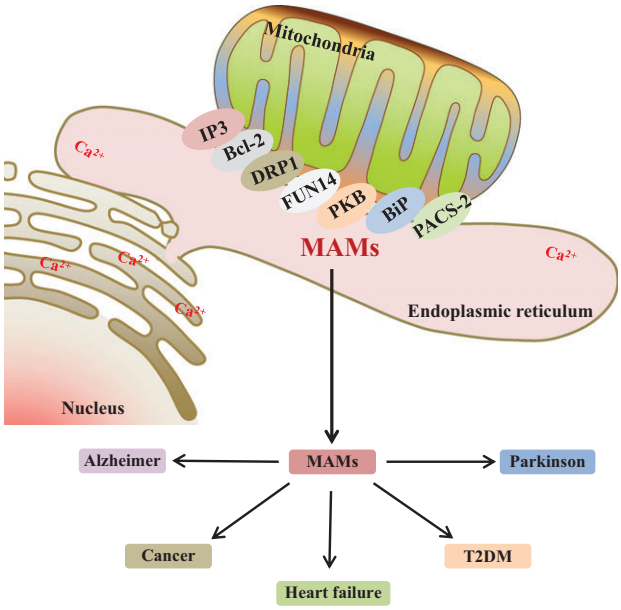

Figure 1. MAMs consist of several structural link proteins, such as Bcl-2, IP3, BiP, proteinkinase B (PKB), phosphoacidic cluster sorting protein 2 (PACS-2), dynamin-related protein 1 (DRP1) and FUNDC1 MAMs play important roles in multiple diseases, including Parkinson's disease, Alzheimer's disease, type 2 diabetes mellitus (T2DM), cancers, and heart failure.

Recently, Wu *et al.* [17] verified that MAMs are involved in the regulation of mitochondrial dysfunction. FUN14 domain containing 1 (FUNDC1) is a mitochondrial protein which binds to inositol 1,4,5-trisphosphate receptor type 2 (IP_3R2) resided in ER to mediate Ca^{2+} release from ER into both mitochondria and cytosol in cardiomyocytes. Cardiomyocyte with specific FUNDC1 deletion inhibits the integrity of MAMs, which leads to the decrease of $[Ca^{2+}]_m$ and $[Ca^{2+}]_i$, the inhibition of CREB/Fis1 pathway, and the impaired mitochondrial function caused by extended mitochondria. Eventually, these alterations result in cardiac dysfunction and heart failure. They also found that heart attack exacerbates the heart failure phenotype in Fundc1-ablated mice, which is likely to be via its suppression of MAM formation, and downregulation of FUNDC1/MAM/CREB/Fis1 signaling. Taken together, they revealed that MAMs are essential to maintain functional mitochondria and normal cardiac function (**Fig. 1**).

They first revealed that reducing FUNDC1 is related to cardiac dysfunction and ischemic insults' remodeling heart. The binding of FUNDC1 to IP_3R2 promotes Ca^{2+} release from ER into mitochondria and cytosol. Lacking of FUNDC1 reduces the levels of IP_3R2 and Ca^{2+} in both mitochondria and cytosol, which reduces mitochondrial fusion, mitochondrial dysfunction, cardiac dysfunction, and heart failure by suppressing Ca^{2+}-sensitive CREB-mediated Fis1 expression. It also helps to elucidate the suppressed function of FUNDC1 in heart failure as well as the participation of MAMs in such pathological process.

As we mentioned above, MAMs play a corroborative role in the calcium signaling. FUNDC1 binds to IP_3R2 to modulate ER Ca^{2+} release into mitochondria and cytosol, and a disruption of the interaction between FUNDC1 and IP_3R2 lowers the levels of Ca^{2+} in mitochondria and cytosol, both of which lead to aberrant mitochondrial fusion, mitochondrial dysfunction, cardiac dysfunction, and heart failure. All these results suggest that intact MAMs may serve as a bodyguard of the cardiovascular system. Future researches should focus particularly on exploring the detailed biological functions of proteins located in MAMs and comparing the unique signaling properties of MAMs, which will help understand the mechanism of proteins associated with MAMs in cardiovascular diseases.

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