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Potential Role of Mitochondria-Associated Endoplasmic Reticulum Membranes in Heart Failure

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Abstract: The endoplasmic reticulum (ER) and mitochondria are physically connected to form dedicated structural domains known as mitochondria-associated ER membranes (MAMs), MAMs is involved in Ca^{2+} transfer, Lipid synthesis and transfer, mitochondrial dynamics, ER stress, mitophagy, inflammation and apoptosis. Many studies have proved MAMs is related to the occurrence of cardiovascular diseases, Parkinson's disease, Alzheimer's disease, diabetes and metabolic diseases. Here, we review the knowledge regarding the components of MAMs according to their different functions and the specific roles of MAMs in heart failure.

1. Introduction

Cardiovascular disease is still a main reason for death across the world[1],heart failure(HF),in particular, is the the leading cause of death worldwide, seriously affects people's health. Given that HF is a major global epidemic associated with high morbidity, mortality,and elevated healthcare costs in the population, the pursuit of possible new interventions targets would be of paramount importance[2]. At present, the mechanism of HF is not clear. The following mechanisms may be involved: endoplasmic reticulum (ER) stress, mitophagy, abnormal calcium signal conduction, apoptosis, inflammatory reaction, lipid metabolism disorder and so on.

Mitochondria and endoplasmic reticula are crucial organelles that play important roles in cellular energy and protein production, respectively[3]. Mitochondria and other subcellular organelles, which are not existing alone in the cytoplasm, usually couple to the membranes of other organelles. It has been reported that mitochondria can be coupled to Golgi apparatus, ER, lipid droplets, and peroxisome. Among them, mitochondria are contacted with the ER to form mitochondria-associated endoplasmic reticulum membranes (MAMs)[4]. ER is a Ca^{2+} pool in cells, which plays an important role in maintaining Ca^{2+} balance and stability in cells. Mitochondria is the main site of ATP production, accompanied by the production of reactive oxygen species (ROS)[5]. The function of mitochondria also includes maintaining Ca^{2+} stability, participating in lipid oxidation and hormone metabolism. MAMs are biochemical and physical contact sites, which play important roles in Ca^{2+} transfer, Lipid synthesis and transfer, mitochondrial dynamics, ER stress, mitophagy, inflammation and apoptosis. Here, we review the knowledge regarding the components of MAMs according to

their different functions and the specific roles of MAMs in HF.

2. Structure of MAMs

The structure of MAMs is not constant[6]. It was found that many kinds of protein aggregated between mitochondrial outer membrane and ER membrane, which maintained the structural stability of MAMs. The proteomics analysis show that there are 991 different proteins in MAMs. These MAM proteins can be mainly divided into three categories: the first category is specifically located in MAMs, the second category is not only presented on MAMs but also on other organelles, and the third category is referred to those MAM protein located in MAMs under special circumstances, which include Dynamic-related protein 1 (Drp1),DJ-1,PTEN-induced putative kinase 1 (PINK), α-synuclein (α-syn),Sigma-1 receptor (S1R), Mitofusin 2 (Mfn2),Presenilin-1 (PS1), Protein kinase R (PKR)-like ER kinase (PERK), Parkin, Cyclophilin D (CypD), Glucose-regulated protein 75 (Grp75), FUN14 domain containing 1 (Fundc1),Vesicle-associated membrane-protein- associated protein B (VAPB), Phosphofurin acidic cluster sorting protein 2 (PACS-2), ER oxidoreductin 1α (Ero1α),Receptor expression-enhancing protein 1 (REEP1)[7].

3. Function of MAMs

3. 1 Calcium transport

Ca^{2+} is the second messenger in cells, which affects many functions of cells, such as gene expression, protein synthesis, protein folding and modification, and cell energy and substance metabolism. The energy released by electron transport from the mitochondrial oxidative respiratory chain is used to form a proton gradient across the inner membrane of mitochondria, which drives ATP synthesis and also creates a driving force for Ca^{2+} absorption. However, the entry of Ca^{2+} into mitochondrial matrix is a process that exhausts mitochondrial potential and competes with ATP generation, thus requires precise regulation[8]. Importantly, mitochondria must be exposed to high concentration of Ca^{2+} in order to take up Ca^{2+} due to the limitation of MCU on IMM. Thus, mitochondrial Ca^{2+} uptake is most likely to occur near the Ca^{2+} releasing stores, such as ER[8]. Through MAMs, Ca^{2+} is transferred directly from the ER to mitochondria and controls key mitochondrial functions, such as apoptosis and energy generation[8]. This local and rapid uptake of mitochondrial Ca^{2+} can prevent excessive increase of cytosolic Ca^{2+} and control the Ca^{2+} signals to occur locally[9].

3. 2 Lipid synthesis and transfer

ER-mitochondria contact sites are enriched with phospholipid-, cholesterol-, and triacylglycerol-related synthetases. Currently, it is widely accepted that phospholipid transport between mitochondria and ER does not depend on vesicle transport but rather occurs in a MAM-dependent manner[10]. The enrichment of synthetic enzymes at MAM promote the local generation of main structural component of biological membranes, phosphatidylcholine, PE, and phosphatidylserine. Phosphatidylserine synthesized in ER requires mitochondrial specific phospholipase to produce PE, which is then converted to phosphatidylcholine in the ER. This transferring process is carried out by ORP5 and ORP8, two proteins known to be involved in the phosphatidylserine transfer from the ER to plasma membrane or MAM. In addition, phospholipid acids are synthesized in ER and must be transferred to mitochondria for modification to produce mitochondrial cardiolipin that exerts cardioprotective function. Cardiolipin interacts strongly with, and is required for the stability and activity of many integral membrane proteins of the

IMM[11],including the mitochondrial Ca^{2+} uniporter (MCU) that mediates Ca^{2+} uptake in mitochondrial matrix [12]. Levels of individual species of cholesterol esters, PEs, and triacylglycerols are associated with cardiovascular diseases.

3. 3 Mitochondrial dynamics

Mitochondria are dynamic organelles continuously undergoing fusion and fission. A proper balance between these two opposing processes is essential for cell survival and for maintaining the shape, the size and the number of mitochondria. The main mitochondrial dynamic protein accounting for fission is DRP1[12]. The dynamic changes of mitochondria are also influenced by the concentration of Ca^{2+} in cytoplasm, and MAMs is an important channel for Ca^{2+} to transfer from endoplasmic reticulum to mitochondria, so MAMs can also regulate the dynamic changes of mitochondria by regulating Ca^{2+} transfer.

3. 4 ER stress

The unfolded protein response (UPR) is initiated to relieve ER stress by inhibiting protein translation and promoting protein folding, as well as the onset of ER-associated degradation [13]. Under various pathological conditions, endoplasmic reticulum proteins cannot be folded correctly and modified after translation, and the ability to secrete and produce transmembrane proteins decreases, which leads to the accumulation of misfolded proteins in endoplasmic reticulum, excessive and unresolved UPR elicits uncontrolled cell death. When the formation of MAMs increases, it not only leads to mitochondrial dysfunction, but also leads to the activation of endoplasmic reticulum stress pathway. This is because the increase of MAMs formation leads to enhanced Ca^{2+} transport and overload of Ca^{2+} in mitochondria, which in turn leads to protein kinase R(PKR)-like endoplasmic reticulum kinase, PERK), phosphorylated eukaryotic initiation factor 2 (P-EIF2 α), activating transcription factor 4 (ATF4) and Grp78 are highly expressed,which promotes the occurrence of endoplasmic reticulum stress.

3. 5 Mitophagy, inflammation and apoptosis

In addition to regulating the morphology and function of mitochondria, MAMs are also involved in many important cellular behaviors, such as Mitophagy, inflammation and apoptosis. MAMs not only provide an appropriate space for the occurrence of cell pathways, but also recruit some key regulatory factors responsible for these behaviors.

Autophagy is an evolutionarily conserved self-digestion process of intracellular material turnover in eukaryotes, which involves the formation of double-membrane vesicles called autophagosomes. The formation of autophagosome is initiated by the recruitment of pre-autophagosome marker ATG14L at the MAMs. At rest, syntaxin-17 binds to DRP1, but in the absence of nutrients, DRP1 is replaced by ATG14L, which promotes the enrichment of different proteins involved in autophagy in MAMs. mTORC2, a key inducer of autophagy, is located in MAMs and regulates its integrity. It is also required for normal cardiac physiology and ensures cardiomyocyte survival in response to pressure overload [11].

A class of nucleotide oligomerization domain-like receptors (NLRs) sense abnormal cytosolic changes, such as microbial invasion, tissue damage and cell stress, and form multiprotein complexes called “inflammasome,” which are linked to the pathogenesis of several cardiovascular diseases[14]. The NLRP3 inflammasome initiates proteolysis of pro-inflammatory cytokine interleukin 1β (IL-1β). In resting state, NLRP3 localizes in cytoplasm and ER. Upon stimulation, NLRP3 inflammasome could be recruited to the MAM sites accompanied with its adaptor ASC,

suggesting that NLRP3 strategically accumulates at mitochondria to sense mitochondrial damage. Thus, MAMs play a critical role in initiating inflammation by acting as an inflammatory platform[11].

Ca^{2+} transfer from ER to mitochondria is a key factor in a series of events leading to apoptosis, and there are many proteins that control death and survival in MAMs. For example, BCL-2 protein family includes anti apoptotic and pro-apoptotic members, which control the sensitivity of cells to apoptosis signals. BCL-XL (also known as Bcl-2-like protein 1), a member ofthe anti-apoptotic family, partially localizes to MAM, increases Ca^{2+} transfer from ER to mitochondria as an adaptive response to increase mitochondrial bioenergetics and prevent intracellular Ca^{2+} overload after thapsigargin stimulation[15].

4. The potential role of MAMs in the development of heart failure

Coronary artery disease, as well as other cardiovascular diseases, initially leads to compensatory myocardial hypertrophy, which, if worsened, can lead to HF. HF, primarily characterized by reduced cardiac output, is the end stage of many forms of heart diseases. However, most treatment options do not fully reverse the progression of cardiac dysfunction, making heart failure a menacing threat worldwide. Although the pathogenesis of heart failure is still not well-understood, the significance of Ca^{2+} homeostasis and mitochondrial function on the progression of chronic remolding and heart failure is widely acknowledged. Specifically, a disordered calcium cycling is accompanied by reduced Ca^{2+} amplitude and prolonged calcium reuptake duration. During heart failure, defects in function and content of the sarcoplasmic reticulum (SR) results in elevated cytosolic calcium overload and oxidative stress, both implicated in mPTP opening, thereby affecting mitochondrial energy production and triggering cell death pathways. On the one hand, mitochondrial calcium overload renders myocardial oxidative injury, fibrosis, and remodeling. While on the other hand, reduced mitochondrial Ca^{2+} hinders the Krebs cycle, thereby impairing ATP production and pyruvate dehydrogenase activity. Similar to ischemia and reperfusion, hypertrophy and heart failure are accompanied by mitochondria-ER coupling disorders, which result in Ca^{2+} oscillation[10].

5. Conclusions

As a bridge between endoplasmic reticulum and mitochondria, MAMs plays an important role. There are many proteins involved in the formation of MAMs, and the structure of MAMs is also complex. MAMs is involved in Ca^{2+} transfer, Lipid synthesis and transfer, mitochondrial dynamics, ER stress, mitophagy, inflammation and apoptosis. MAMs is closely related to cardiovascular diseases, neurodegenerative diseases and metabolic diseases. However, the research on the structure and function of MAMs is still very limited, and more research is needed to explore the relationship between MAMs and various diseases.

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