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The Relationship between Mitochondria Ca^{2+} Intake Mediated by Mitochondria-associated Endoplasmic Reticulum Membranes and Tumor Genesis

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Abstract

Mitochondria-associated endoplasmic reticulum membranes (MAMs) are regions of the endoplasmic reticulum (ER) tethered to mitochondria, which play a key role in mediating material transfer and signal transduction between the two organelles. The findings from recent studies on MAMs contributed to deeper understanding of the complexities associated with the structure, the important proteins involved and the intricacies in the related biological pathways. A large number of Ca^{2+} transporter proteins and their regulatory proteins are located on MAMs, which finely regulate a series of important cellular activities such as mitochondrial Ca^{2+} homeostasis, ATP production and cell apoptosis. MAMs are also enriched with many oncogenic proteins and tumor suppressor proteins, which are closely related to the regulation of Ca^{2+} transport. Therefore, the role of MAMs in tumorigenesis has received extensive attention. In this review, we focused on the regulatory mechanisms of Ca^{2+} transport mediated by MAMs and their role in tumorigenesis, aiming to acquire the new insight to further understanding the pathogenesis of tumors.

Keywords: Mitochondria; Mitochondria-associated endoplasmic reticulum membranes; Ca^{2+} signal; Tumor

Introduction

Mitochondria and the endoplasmic reticulum (ER) regulate numerous cellular processes, and are critical contributors to cellular and whole-body homoeostasis. Interestingly, about 5-20% of the mitochondrial membranes are directly in contact with ER [1]. Therefore, the mitochondria and ER cannot be considered as static structures, they intimately communicate, forming very dynamic platforms termed Mitochondria-associated endoplasmic reticulum membranes (MAMs). With the development of super-resolution fluorescence imaging, electron tomography and proteomics, MAMs have been found in various eukaryotes [2,3]. In particular, the MAMs accommodate flux of Ca^{2+} from the ER to mitochondria, which decode them into specific inputs to regulate essential functions, including metabolism, energy production and apoptosis [4-6]. Furthermore, previous studies have suggested that many human diseases are closely linked to the mitochondria abnormal Ca^{2+} intake mediated by MAMs, such as tumor genesis [7] and neurodegeneration[8]. Hence, MAMs are not simply be considered as a static bridge between the ER and mitochondria, but also as dynamic organelles that play a variety of roles both in physiological and pathological processes that are crucial in maintaining the health or establishing a disease due to functional disturbances. Recently, there is an increased focus on MAMs because numerous oncogenic proteins and tumor suppressors were found on the MAMs, which exert an important influence on cell fate and the emerging picture of MAMs seems to indicate that deregulated MAMs-mediated mitochondrial Ca^{2+} intake play an important role in tumor genesis. This review has focused on the findings from publications from the past ten years.

Structure Basis of MAMs

The association between the ER and mitochondria was first visualized in the 1970s with electron microscopy by Morre et al. [9]. It was not until 1990s, however, the Vance group made great progress in the MAMs field by presenting a detailed protocol describing the isolation of pure MAMs fractions by differential ultracentrifugation [1]. In recent years, multiple methods have been developed to dissect MAMs' specific properties and the protein composition, either using biochemical or fluorescent microscopy-based strategies. We have enormously extended our comprehension on MAMs that MAMs contain several crucial proteins involved in many biological pathways. In addition, some researches show that MAMs are closely related to cellular lipid metabolism [1] and energy metabolism [10].

Molecular Components of the MAMs in Ca^{2+} Transfer

It has recently become clear that MAMs are crucial for highly efficient transmission of Ca^{2+} from the ER to mitochondria, thus controlling fundamental processes involved in energy production and also determining the cell fate by triggering or preventing apoptosis.

Therefore, many Ca^{2+} transporter proteins, such as Inositol 1,4,5-trisphosphate receptors (IP3Rs), voltage-dependent anion channel (VDAC)[11], mitochondrial calcium uniporter (MCU) and their regulatory proteins were identified on MAMs [12](Figure 1).

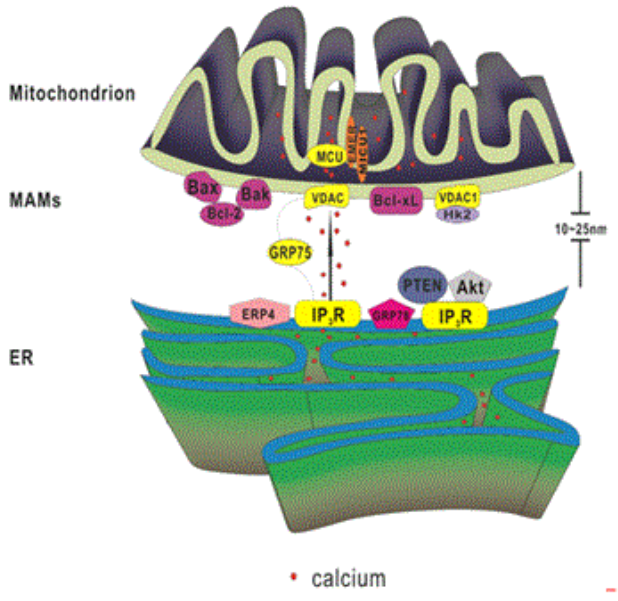

Figure 1: Schematic representation of the mitochondria-associated endoplasmic reticulum membranes (MAMs) [16].

IP3Rs

A key role in the control of Ca^{2+} signals is attributed to the inositol 1,4,5-trisphosphate (IP3) receptors (IP3Rs), the main Ca^{2+}-release channels in the ER. As expected, all three IP3R isoforms (IP3R1, IP3R2 and IP3R3) are also enriched in MAMs and precisely control Ca2+ transfer into mitochondria [13]. When the G protein-coupled receptors are activated, intracellular IP3 binding with IP3Rs can lead to the release of Ca^{2+}. This creates a micro-domain in which the Ca^{2+} concentrations are manifold higher than in the cytosol, allowing for rapid mitochondrial Ca^{2+} uptake [14]. In addition, some metabolites can also affect Ca^{2+} transfer efficient in MAMs by regulating the activity of IP3Rs. For example, glucose-regulated protein 78 (GRP78) promotes the activity of IP3Rs and increases the Ca^{2+} intake of mitochondria [15]. A fraction of endoplasmic reticulum protein 44 (ERp44) also localizes to the MAM, where it interacts with IP3R1 and competes with BiP/Grp78 for the same binding site on the IP3R1. Cells over-expressing ERp44 show reduced IP3R1 Ca^{2+}-release [16,17]. In addition, ATP can promote the release of Ca^{2+} mediated by IP3R, but heparin is the specific inhibitor [13].

VDAC

VDAC is a large, high-conductance, weakly anion-selective channel that represents the primary permeability pathway through which solutes enter the mitochondria. VDAC is associated with MAMs and controls metabolic cross-talk between mitochondria and the rest of the cell by allowing the influx and efflux of metabolites, ions, nucleotides, Ca^{2+} and more [18]. Human cells have three distinct VDAC genes (VDAC1, VDAC2 and VDAC3), with VDAC1 representing the best characterized one [19]. For example, VDAC1 selectively interacts with IP3R3, thereby potentiating the transfer of low-amplitude apoptotic Ca^{2+} signals to mitochondria. Therefore, VDAC1 mediates Ca^{2+} released by ER transmits into the mitochondrial intermembrane space [19]. Arbel N found that the over expression of VDAC1 led mitochondrial Ca^{2+} increase in skeletal muscle cells and Hela cells [20]. Consistently, VDAC1 knockdown decreased mitochondrial Ca^{2+} [21]. In addition, it has been reported that, glucose-regulated protein 75 (GRP75) promoted the connection between VDAC1 and IP3Rs with the subsequent mitochondrial Ca^{2+} intake [22].

MCU

The mitochondrial Ca^{2+} uniporter is a complex of proteins including the Ca^{2+} selective pore-forming subunit MCU and accessory proteins including MICU1, MICU2, MCUR1 and EMRE located in the mitochondrial inner membrane (IMM) and also enriched in MAMs [23-25]. Ca^{2+} crosses the IMM through the MCU depending on the considerable driving force represented by the negative Trans membrane potential. Several lines of evidence indicate that MICU1 and MICU2 operate together with MCU [24]. MICU1 acts as a gatekeeper of the uniporter complex, preventing Ca^{2+} entry under resting conditions and activating the channel at high cytosolic Ca^{2+} concentrations [26]. While, MICU2, a paralog of MICU1, can inhibit MICU1-mediated Ca^{2+} uptake [27]. Moreover, EMRE was required for the interaction of MCU with MICU1 and MICU2. Thus, EMRE bridges the calcium-sensing role of MICU1 and MICU2 with the calcium-conducting role of MCU [28]. In addition, the expression of MCU appears to be controlled by microRNA-25, which can efficiently reduce MCU levels and subsequent mitochondrial Ca^{2+} transfer [29]. Therefore, Ca^{2+} transferred by MAMs is an intricate and tightly regulated process.

Influence of Ca^{2+} Intake on Mitochondrial Function

The main physiological role of mitochondrial Ca^{2+} uptake was assessed to be the control of metabolic activity of the mitochondria. It has been reported that various enzymes directly involving in the Krebs cycle are modulated by mitochondrial matrix Ca^{2+} [30]. For example, pyruvate dehydrogenase (PDH), which converts pyruvate into acetyl-CoA, is phosphorylated and activated when the level of mitochondrial Ca^{2+} is elevated [30,31]. While mitochondrial Ca^{2+} was also demonstrated to increase the affinity of dehydrogenase (ICDH) or oxoglutarate dehydrogenase (OGDH) with their substrates [31]. In addition, mitochondrial Ca^{2+} also directly activates the electron transport chain and the activity of F0F1ATP synthase [32,33]. On the contrary, the mitochondrial Ca^{2+} overload results in dramatic alterations in mitochondrial functions, including increased reactive oxygen species (ROS) production and "mitochondrial permeability transition pore"(mPTP) activity[34]. The mPTP opening can induce mitochondrial swelling, and these large-scale alterations of organelle morphology allow the release of caspase cofactors into the cytosol, which can lead to cell death finally [35]. Therefore, Mitochondria are not only the energy powerhouse of the cell but also a major hub for cellular Ca^{2+} signaling crucial for cell life and death.

Impact of Ca^{2+} Transfer Regulated by MAMs on Tumor Genesis

Recently, increasing evidence is beginning to reveal that the abnormal remodeling of mitochondrial Ca^{2+} homeostasis has

important roles in tumor initiation and progression [36]. For example, decrease of Ca^{2+} in mitochondria was reported to shift the cancer cells toward glycolysis, providing chemo resistance but leading to a poor overall survival [37]. Notably, a wide range of tumor suppressors and oncogenic proteins were identified to be located on MAMs and play important roles in mitochondrial Ca^{2+} transfer [37]. Generally, tumor suppressors were believed to promote the mitochondrial Ca^{2+} uptake, while oncogenic proteins exert opposite roles [38]. Therefore, enhancing the mitochondrial Ca^{2+} uptake through MAMs might be a potential strategy for cancer treatment.

Oncogenic proteins on MAMs

There are some oncogenic proteins on MAMs (Table 1), they can interact with different molecules and inhibit the apoptosis of tumor cells. Among oncogenic proteins, Akt is an important sensor of the bioenergetics of the cell and therefore it is linked to the function of the mitochondria. Recently, several studies have proved that Akt could phosphorylate all IP3R isoforms, thus inhibits Ca^{2+} release from ER and protects cells from apoptosis. Moreover, Akt also was demonstrated to promote the interaction between VDAC1 and hexokinase 2 (HK2) on MAMs through phosphorylation events. Therefore, this association inhibits apoptosis mediated by mitochondrial Ca^{2+}. In addition, it has been also found that PTEN could dephosphorylate PIP3 and reverse PI3K/Akt signaling, which further promotes the apoptosis of tumor cell. Bcl-2 protein family also contains numerous anti-apoptotic and pro-apoptotic members. Therefore, Bcl-2 protein family plays an important role in mitochondria dependent apoptosis [39]. Recently, researches have demonstrated that Bcl-2 protein family members interact with different functional domains of IP3Rs and promote or inhibit Ca^{2+} signals and the apoptosis of tumor cells [39, 40]. For example, Williams A. et al. have found that numerous Bcl-2 are rich on MAMs. Moreover, Bcl-2 interacts directly with IP3Rs to inhibit channel opening and ER Ca^{2+}-release, thus inhibit tumor cells apoptosis [41]. Monaco G has proved that anti-apoptotic protein Bcl-XL, which is deregulated in several cancer types, exerts its anti-apoptotic functions by inhibiting the activity of Ca^{2+} channels, including IP3Rs and VDAC isoforms [42, 43]. In addition, Bcl-XL also blocks the apoptosis pathway by neutralizing pro-apoptotic Bcl-2 members, such as Bak, Bax, Bid and Bim [44]. Sig1-R is a Ca^{2+}-sensitive and ligand-operated receptor chaperone and localizes at MAMs, stabilizes the conformation of IP3R3 and the ER stress sensor IRE1. Normally, Sig1-R forms a complex at MAMs with the chaperone BiP/GRP78 to regulate Ca^{2+} homeostasis between the ER and the mitochondria, but upon Ca^{2+} depletion or via ligand stimulation, Sig1-R dissociates from BiP leading to a prolonged Ca^{2+} signaling into mitochondria via IP3R3. [4-14]

Protein	Impact on ER-mitochondrial Ca2+ transfer	References
AKT	Inhibition of Ca2+ release from ER	[4-43]
Bcl-2	Induction of Ca^{2+} leakage from ER	[4-42],[4-43]
Bcl-XL	Induction of Ca^{2+} leakage from ER	[4-44]
Sig-1R	Regulation of Ca^{2+} homeostasis on MAMs	[4-14]

Table 1: Summary of the ant apoptotic proteins on MAMs.

Tumor suppressors on MAMs

Many tumor suppressors are located on MAMs and here we list several most important tumor suppressors on MAMs (Table 2). The tumor suppressor PTEN is among the most commonly lost or mutated tumor suppressors implicated in human cancers, and it is a key regulator of a wide range of biological functions other than tumor suppression. Recent findings have shown that it localizes at MAMs where it interacts with the IP3R3 and regulates Ca2+ release from the ER in a protein phosphatase-dependent manner that counteracts AKT activation; thus, it can inhibit AKT-mediated phosphorylation of IP3R3, which protects from Ca2+-mediated apoptosis [4]. In addition, the tumor suppressor PML also localizes at the MAMs where it modulates IP3R3 activity and the ER-mitochondria Ca2+ fluxes by promoting the formation of a multi protein complex containing IP3R3, AKT and the protein phosphatase 2A (PP2a) [4-49]. The tumor suppressor p53 regulates tumor genesis also in a Ca2+ dependent pathway. P53 physically interacts with SERCA and this increases the efficiency of the transfer of Ca2+ ions between the ER and mitochondria, augmenting the propensity of (pre)malignant cells exposed to oncogenic or chemotherapeutic stress to succumb to apoptosis. The interplay between p53 and Ca2+ signaling is not limited to chemotherapy but is also relevant for cellular response following the photodynamic therapy (PDT) [4-49].

Protein	Impact on ER-mitochondrial Ca2+ transfer	References
PTEN	Regulation of Ca^{2+} release via IP3R3	[4-7]
PML	Modulation of the ER-mitochondria Ca^{2+} flux	[4-48], [4-49]
P53	Modulation of Ca^{2+} transfer from ER to mitochondria interacting with Serca	[4-49]

Table 2: Summary of the tumor suppressors on MAMs.

Conclusion

We presented clear evidence to indicate that loss of Calcium homeostasis in the mitochondria due to defective transfer between the ER and mitochondria mediated by MAMs has been shown to contribute to tumor genesis. And above all, we can conclude that there are two main ways that proteins on MAMs affect tumor cells fate, one is to interact with Ca^{2+} tunnels, such as IP3R and VDAC, and another way is the mutual effect between oncogenic proteins and tumor suppressors. As a consequence, MAMs dysfunctions have been linked to many types of human cancer. However, several outstanding questions still need to be answered before reaching a complete mechanistic and functional understanding of the MAMs-mediated mitochondrial Ca^{2+} uptake. For example, how does cancer cell regulate the dynamics of the structure of MAMs and the protein located in MAMs? Which proteins located in MAMs is crucial for cancer cell survival, inflammation, and therapy responses? Additionally, it is still not clear how MAMs modulate the mitochondrial unfolded protein response (UPR) and ER stress in cancer cells. All these are outstanding questions that await future studies.

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