Mitochondria-associated membranes

Mitochondria-associated membranes (MAMs) were the first connection discovered between two intracellular organelles. Endoplasmic reticulum (ER) membranes have long been known to be located close enough to mitochondria to form lipid raft-like domains. MAMs are composed of membrane fragments from both the ER and the outer mitochondrial membrane. These membranes are involved in import of certain lipids from the ER to mitochondria and in regulation of calcium homeostasis, autophagy and apoptosis. They also play a role in development of neurodegenerative diseases and glucose homeostasis.

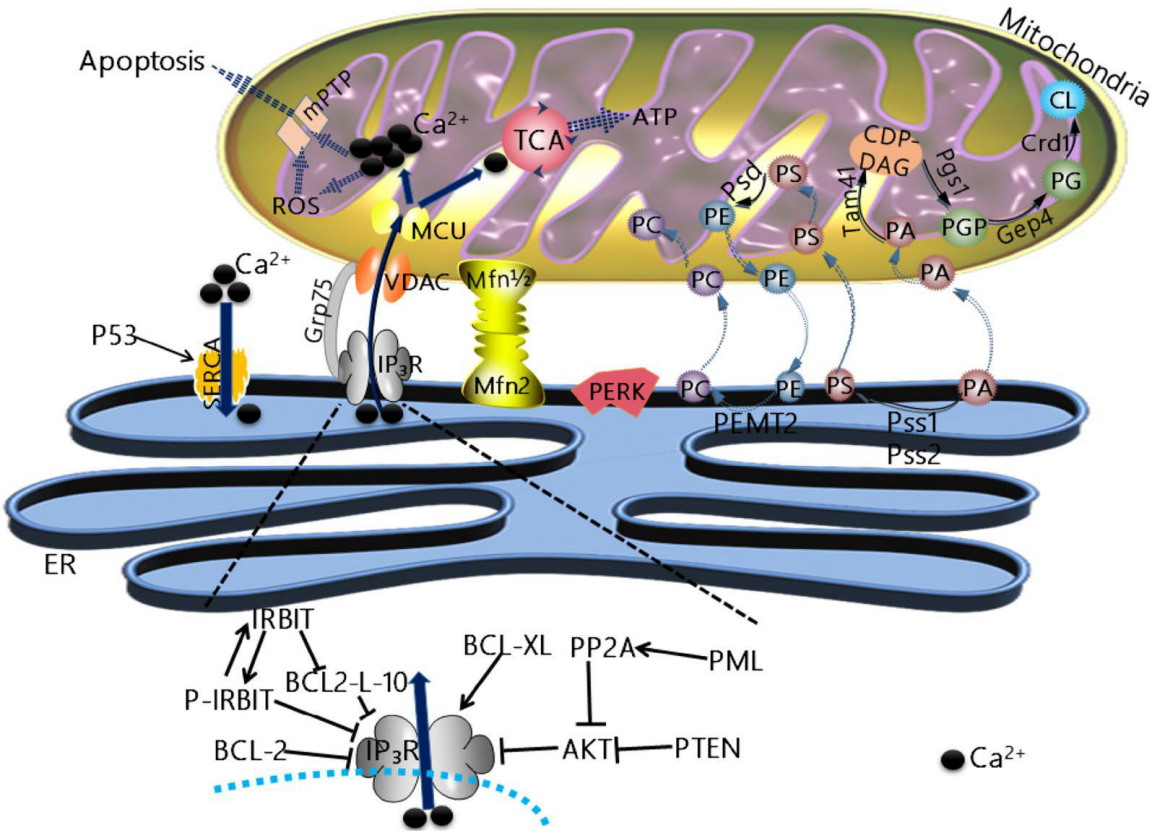
Calcium homeostasis

Intracellular calcium homeostasis is the basis of cell metabolism. Concentrations of calcium ions (Ca^{2+}) in mitochondria that are too low can cause cellular energy metabolism disorders, while a high concentration of Ca^{2+} can cause cell death. Normally, the ER releases Ca^{2+}, which is then transported to the mitochondrial matrix, where it activates the tricarboxylic acid (TCA) cycle to stimulate ATP synthesis.

After a cell is stimulated, the ER releases calcium ions through inositol 1,4,5 trisphosphate receptor (IP3R), which are the main Ca^{2+} channels of the ER. Because of the presence of MAMs, the ER and mitochondria have a spatial relationship with each other, thus allowing calcium ions to enter the mitochondria through voltage dependent anion channels (VDACs) on the outer mitochondrial membrane. Unlike the

passive movement of Ca^{2+} through the outer mitochondrial membrane, Ca^{2+} movement through the inner mitochondrial membrane is driven by an electrical gradient, and Ca^{2+} enters through the mitochondrial calcium uniporter (MCU). As a regulatory protein, Glucose-regulated protein 75 (Grp75) maintains the stability of the interaction between IP3R and VDAC, thus promoting the absorption of calcium ions by mitochondria.

High Ca^{2+} concentrations on the mitochondrial membrane activate MCU to mediate the entry of Ca^{2+} into the mitochondrial matrix. The transfer of excessive Ca^{2+} to the mitochondria caused opening of the mitochondrial permeability transition pore (PTP) leading to mitochondrial swelling and outer membrane of the mitochondria rupture. Moreover, the mitochondrial PTP opening induce releasing of caspase-activating factors and apoptosis. The transfer of excessive Ca^{2+} to the mitochondria induces the release of the cytochrome c through the Bax/Bak pore. This process further results in the activation of pro-apoptotic proteins and amplifies the apoptotic signal. Therefore, the MAMs act as the bridge between the ER and mitochondria, providing a buffer area for the transfer of calcium ions between the ER and mitochondria.



Phospholipid synthesis and transfer between mitochondria and ER

Phospholipids are a major component of all cell membranes, and the ER is the main site of phospholipid synthesis in cells. Phospholipids are normally transported in vesicles to their destination after synthesis in the ER. However, for transport into the mitochondria, phospholipids are directly imported through the membranes. A large number of lipid-metabolizing enzymes are abundant in MAMs, where lipid metabolism is also performed.

Phosphatidic acid (PA) is converted into phosphatidylserine (PS) in the ER, as the ER contains the relevant enzymes phosphatidylserine synthase 1 (PSS-1) and PSS-2. PS must be transferred to the OMM and further transferred to the IMM, where it is converted into phosphatidylethanolamine

PE due to the presence of PS decarboxylase (PSD), which converts PS into PE. Finally, PE returns to the ER, where phosphatidylethanolamine N-methyltransferase 2 (PEMT2) methylates PE to synthesize phosphatidylcholine (PC). However, as mitochondria also contain PC, PC is transferred from the ER into the mitochondria. Therefore, in order to achieve the final lipid composition of both organelles, a large amount of lipid exchange must be performed between these two organelles.

In addition, phosphatidic acid is an important source material for the synthesis of cardiolipin (CL). Phosphatidic acid is transferred from the ER to the OMM and then transferred to the IMM.