Acta Biochim Biophys Sin 2022, 54(3): 412–414
https://doi.org/10.3724/abbs.2021020
Advance Access Publication Date: 23 December 2021
Research Highlight

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FAM134B-mediated ER-phagy regulates ER-mitochondria interaction through MAMs

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Endoplasmic reticulum (ER) is the largest organelle in eukaryotic cells, which can participate in the maintenance of calcium (Ca^{2+}) homeostasis, protein synthesis and organelle communication [1]. Endoplasmic reticulum autophagy (ER-phagy) is a cellular quality control pathway mediated by autophagy receptors. ER-phagy involves the engulfing of excess or misfolded proteins and superfluous ER membrane to form autophagosomes which are degraded by lysosome [1]. ER-phagy occurs under normal conditions and is enhanced during starvation. At present, the receptors of ER-phagy in mammalian cells include family sequence similarity 134 [1], membrane B (FAM134B), SEC62, reticulin 3 (RTN3), cell cycle progression 1 (CCPG1), atlastin GTPase 3 (ATL3), testis expressed gene 264 (TEX264), tripartite motif containing 13 (TRIM13, also known as RFP2), and coiled-coil domain protein 1 (CALCOCO1) [2]. FAM134B is recognized as the most characteristic receptor for ER-phagy in mammalian cells [1]. FAM134B consists of a reticulon-homology domain (RHD), a C-terminal cytoplasmic domain and an N-terminal cytoplasmic domain [1]. The RHD region of FAM134B senses and induces ER membrane curvature for ER-phagy. The LC3-interacting region (LIR), located in the C-terminal cytoplasmic domain of FAM134B, is responsible for recruiting and binding the autophagy modifiers LC3 and GABARAP, which involves the engulfing of degradable cargo to phagophore membranes for ER-phagy [1,3]. FAM134B plays a critical role in ER function and quality control through mediating ER-phagy. Inhibition of FAM134B expression leads to ER expansion. Contrarily, up-regulation of FAM134B level results in ER fragmentation [1].

ER does not exist in isolation in the cytoplasm. The dynamic structure of ER determines that it can form contact sites with many organelles, including mitochondria, Golgi apparatus, peroxisomes, lysosomes, lipid droplets, as well as plasma membrane [4]. Particularly, the distance between ER and outer mitochondrial membrane is only 10–25 nm. This short distance enables ER proteins to interact directly with proteins and lipids of the outer mitochondria membrane, which forms a dynamic signal communication platform known as the mitochondrial-associated ER membranes (MAMs) [5]. MAM maintains a stable distance between ER and mitochondria to prevent membrane fusion [6]. MAM involves in various cellular functions, such as Ca^{2+} homeostasis, autophagy, lipid metabolism, and cell apoptosis. These functions are carried out by proteins in the MAMs [7]. One of the key group of proteins involved in MAM formation is the inositol 1,4,5-trisphosphate receptor (IP3R)-glucose-regulated protein 75 (Grp75)-voltage-dependent anion channel (VDAC) complex. The IP3R-Grp75-VDAC complex is responsible for Ca^{2+} exchange between ER and mitochondria. IP3R located on ER contacts with GRP75, transporting Ca^{2+} from ER to the VDAC on the outer mitochondrial membrane. Subsequently, Ca^{2+} enters the mitochondrion through VDAC [8]. Under normal conditions, Ca^{2+} of ER is transferred to mitochondria through MAMs to participate in the regulation of metabolism, energy production, and cell apoptosis [9,10]. However, mitochondrial Ca^{2+} upload can lead to the abnormal oxidative phosphorylation and the opening of the mitochondrial permeability transition pore (mPTP), which leads to mitochondrial dysfunction. Furthermore, excessive cytochrome C (CytC) can also be released from mitochondria into the cytoplasm through the opening of mPTP. Excessive CytC is released from mitochondria into cytoplasm, which can activate the downstream caspase-3 protein expression, and ultimately acts as a pro-apoptotic factor to induce cell apoptosis [8]. Therefore, to maintain the normal physiological function and metabolism homeostasis of cells, Ca^{2+} exchange between ER and mitochondria must be strictly controlled.

Recently, Wang *et al.* [10] reported that FAM134B-mediated ER-phagy can regulate the ER-mitochondria interaction through MAMs, which reduces mitochondrial Ca^{2+} level to prevent the mitochondrial dysfunction and cell death. To explore the mechanism by which FAM134B-mediated ER-phagy regulates ER-mitochondria interaction through MAMs, they used lentivirus to interfere with the expression of FAM134B in hippocampal neuronal culture (HNC) model of acquired epilepsy (AE). First, they demonstrated that the overexpression of FAM134B alleviates AE-induced hippocampal neuronal apoptosis, while downregulation of FAM134B aggravates

hippocampal neuronal apoptosis. These results suggest that FAM134B overexpression can decrease the AE-induced hippocampal neuronal apoptosis. Increased IP3R expression can result in excess ER Ca^{2+} released and transfer to mitochondria, increasing mitochondrial Ca^{2+} overload and activating the mitochondrial apoptotic pathway [8–11]. They further identified that FAM134B overexpression obviously elevated the level of ER-phagy and decreased the level of IP3R. In contrast, downregulation of FAM134B presents the opposite result. IP3R is a Ca^{2+} release channel expressed in the MAMs, which mediates Ca^{2+} exchange between the ER and mitochondria. Moreover, FAM134B overexpression reverses the AE-induced Ca^{2+} transfer from ER to mitochondria. These results proved that FAM134B-mediated ER-phagy reduces the expression of IP3R in MAMs to inhibit the exchange of Ca^{2+} between ER and mitochondria, which ultimately inhibits AE-induced hippocampal neuronal apoptosis. Additionally, the authors also verified that overexpression of FAM134B can inhibit AE-indued mitochondrial membrane potential (mMP), CytC release and caspase-3 activation, which prevents mitochondrial structure damage. Altogether, FAM134B-mediated ER-phagy prevents Ca^{2+} exchange between ER and mitochondria through modulating IP3R expression in MAMs, inhibiting the decrease of mMP, the release of CytC, mitochondrial damage and caspase-3 activation, which prevents AE-induced neuronal apoptosis (Figure 1).

This work provides a novel insight into FAM134B-mediated ER-phagy and shows its ability to modulate ER-mitochondria interaction through MAMs. Mechanistically, FAM134B-mediated ER-phagy can attenuate the Ca^{2+} transfer between ER and mitochondria by decreasing the expression of IP3R in MAMs. The inhibition of Ca^{2+} transfer between ER and mitochondria can prevent mMP reduction, CytC release, mitochondrial damage, and caspase-3 activation, which reduces the epileptic hippocampal neurons cell death. However, despite its fascinating findings, this work has some limitations. For example: how does FAM134B-mediated ER-phagy reduce the expression of IP3R? Is IP3R inhibition caused by ER-phagy degradation or by interaction with FAM134B? Further studies are needed to address these issues.

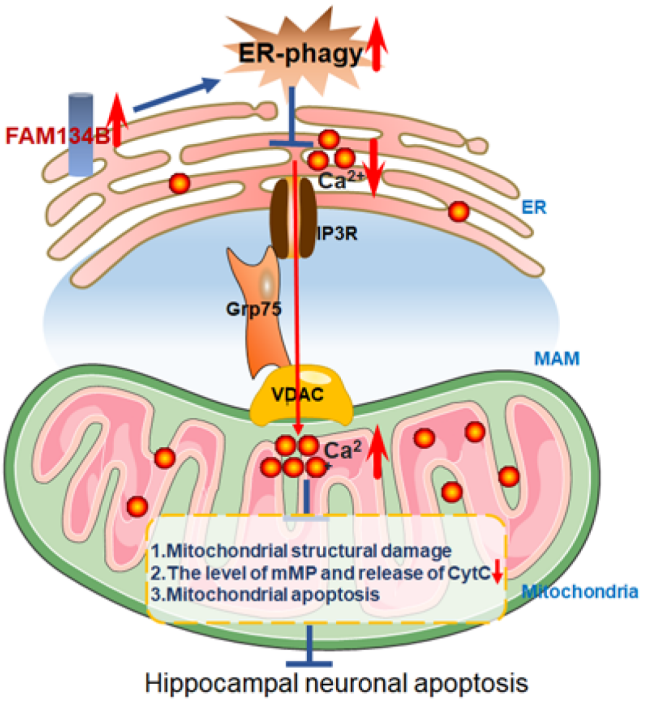

Figure 1. FAM134B-mediated ER-phagy regulates ER and mitochondria interaction through MAMs The IP3R-GRP75-VDAC complex in MAM mediates Ca^{2+} transfer from ER to mitochondria. FAM134-mediated ER-phagy decreases excessive Ca^{2+} transport from ER to mitochondria by inhibiting IP3R, which inhibits the decrease of mMP, the release of CytC, mitochondrial damage, and caspase-3 activation to prevent AE-induced neuronal apoptosis.

In fact, FAM134 can also interact with autocrine motility factor receptor (AMFR) and inner mitochondrial membrane protein optic atrophy 1 (OPA1) to mediate "reticulo-mito-phagy": a dual organelle interaction mechanism. In addition to mitochondria, ER can also interact with Golgi apparatus and peroxisomes to mediate the transport of lipids and proteins, as well as interact with lipid droplet in the cytoplasm to facilitate the transport of lipids [12–14]. Currently, an increasing number of organelle interactions are being discovered. Organelles are no longer isolated functional structures separated by biological membranes. Many cellular physiological activities, such as the transport of proteins and lipids, the fusion and scission of organelles, and the regulation of calcium signaling, need to be coordinately carried out among different organelles, and these processes rely on the precise regulation of organelle interactions. Therefore, Further studies are needed to reveal whether FAM134B-mediated ER-phagy can regulate the interaction of ER and other organelles or not. In addition, the reduction of MAMs can affect ER-mitochondria tethering, Ca^{2+} signaling transduction, mitochondrial dynamics, biogenesis, and protein import, as well as induce stress response. These functional changes are closely related to the pathogenesis of epilepsy, Alzheimer's disease, inflammation, and amyotrophic lateral sclerosis. Further elucidation of the precise molecular mechanism of FAM134B-mediated ER-phagy in regulating MAMs may help to develop novel therapeutic strategies for the treatment of MAMs-related diseases.

Funding

This work was supported by the grants from the National Natural Science Foundation of China (No. 81970431) and the Hunan Provincial Natural Science Foundation of China (No. 2020JJ4079).

Conflict of Interest

The authors declare that they have no conflict of interest.

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