Review

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Stress-responsive regulation of mitochondria through the ER unfolded protein response

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The endoplasmic reticulum (ER) and mitochondria form physical interactions involved in the regulation of biologic functions including mitochondrial bioenergetics and apoptotic signaling. To coordinate these functions during stress, cells must coregulate ER and mitochondria through stress-responsive signaling pathways such as the ER unfolded protein response (UPR). Although the UPR is traditionally viewed as a signaling pathway responsible for regulating ER proteostasis, it is becoming increasingly clear that the protein kinase RNA (PKR)-like endoplasmic reticulum kinase (PERK) signaling pathway within the UPR can also regulate mitochondria proteostasis and function in response to pathologic insults that induce ER stress. Here, we discuss the contributions of PERK in coordinating ER–mitochondrial activities and describe the mechanisms by which PERK adapts mitochondrial proteostasis and function in response to ER stress.

ER stress impacts mitochondrial function through interorganellar signaling

The traditional view of ER and mitochondria as discreet intracellular organelles has been profoundly altered in recent years. Unlike the well-defined organelles described in cell biology textbooks, the ER and mitochondria are highly dynamic and undergo continuous structural and spatial reorganization in response to specific cellular signals. An interesting aspect of these organelles is that they form physical ER–mitochondrial contacts (reviewed in [1–3]). These contacts facilitate the transfer of metabolites, including lipids and Ca^{2+}, between the ER and mitochondria that are involved in the regulation of biologic functions including lipid homeostasis, mitochondrial metabolism, and the regulation of apoptotic signaling (Box 1). Thus, ER–mitochondrial contacts serve as a platform for interorganellar communication, essential for the coordination of cellular function.

A consequence of the physical and functional interaction between ER and mitochondria is that mitochondria function is sensitive to pathologic insults that induce ER stress (defined by the increased accumulation of misfolded proteins within the ER lumen). ER stress can be transmitted to mitochondria by alterations in the transfer of metabolites such as Ca^{2+} or by stress-responsive signaling pathways, directly influencing mitochondrial functions. Depending on the extent of cellular stress, the stress signaling from the ER to mitochondria can result in prosurvival or proapoptotic adaptations in mitochondrial function.

During the early adaptive phase of ER stress, ER–mitochondrial contacts increase, promoting Ca^{2+} transfer between these organelles [4]. This increase in Ca^{2+} flux into mitochondria stimulates mitochondrial metabolism through the activity of Ca^{2+}-regulated dehydrogenases involved in the tricarboxylic acid (TCA) cycle. The increased activity of these dehydrogenases promotes mitochondrial respiratory chain activity, resulting in a transient increase in mitochondrial ATP synthesis during the initial phase of ER stress. This surge in bioenergetic capacity increases the available energetic resources to mount an adaptive response and alleviate ER stress. Alternatively, chronic exposure to ER stress negatively impacts cellular metabolism by reducing mitochondrial respiration and decreasing cellular ATP levels [4,5]. This has been shown to lead to depletion of Ca^{2+} stores in the ER and increased Ca^{2+} within mitochondria ([6,7] and discussed below). Ultimately, this signaling results in mitochondrial fragmentation and the opening of the mitochondrial permeability transition pore (MPTP), which initiates intrinsic apoptotic signaling and programmed cell death. Varying levels of ER stress in multiple cell types have also been reported to impact other mitochondrial functions including mitochondrial DNA (mtDNA) biogenesis [8], the transcription of respiratory chain subunits [5], and increases in mitochondrial-derived reactive oxygen species (ROS) [5,9,10], further reflecting the capacity for ER stress to influence mitochondrial function.

Many metabolic diseases including nonalcoholic fatty liver disease, type 2 diabetes (T2D), and obesity are associated with unresolved ER stress, suggesting that mitochondrial dysfunction in these diseases may be dysregulated through mechanisms involving ER stress-dependent alterations in ER–mitochondria communication [11,12]. For example, stress-dependent alterations

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Box 1. Metabolite transfer through ER–mitochondrial contacts

ER and mitochondria form tight physical junctions stabilized by tethering complexes anchored in the ER and mitochondrial outer membrane (reviewed in [1–3]). In higher eukaryotes, these tethers are mediated by interactions between ER-localized MFN2 with MFN2 and MFN1 in the mitochondrial outer membrane. These tight interactions facilitate the transfer of metabolites between the two organelles (Figure I).

Transfer of Ca^{2+} between the ER and mitochondria is a major function for ER–mitochondrial contacts and is carried out through the IP_3R and VDAC transporters localized to the ER and mitochondria outer membranes, respectively (see [1–3]). These channels form a tight interaction stabilized by the cytosolic isoform of the mitochondrial HSP70 chaperone HSPA9/GRP75/mortalin. Ca^{2+} is imported into the mitochondrial matrix through the high-capacity, low-affinity mitochondrial Ca^{2+} uniporter (MCU). The close physical proximity between these various Ca^{2+} transporters at ER–mitochondrial contacts increases local Ca^{2+} concentration to levels sufficient to drive import through MCU into the mitochondrial matrix.

Flux of Ca^{2+} through the ER–mitochondrial contacts is highly regulated by accessory proteins both at the ER and mitochondria membranes [1–3,6]. ER-localized phosphofurin acidic cluster sorting protein 2 (PACS2) recruits the chaperone calnexin to the ER luminal face of MAMs to mediate their formation and stability. The ER Sigma-1 receptor stabilizes IP_3R and promotes protective ER to mitochondria Ca^{2+} exchange in response to ER Ca^{2+} depletion. Alternatively, MCU regulators including MICU1 and MCUR1 have also been identified to influence ER–mitochondria Ca^{2+} transfer and Ca^{2+}-regulated mitochondrial activities [1–3,6]. ER–mitochondrial Ca^{2+} transfer is also influenced by a truncated isoform of SERCA (S1T) localized to MAMs that can promote ER Ca^{2+} leakage and mitochondria Ca^{2+} overload associated with cellular death [1–3]. These regulators provide a significant level of control over ER–mitochondrial Ca^{2+} transfer, reflecting the importance of this process in cellular physiology.

Apart from Ca^{2+}, other metabolites including lipids are also transferred between the ER and mitochondria through ER–mitochondrial contacts [1–3]. Lipid biosynthesis enzymes involved in the synthesis of phospholipids, cholesterol metabolites, and sphingolipids localize to the ER and mitochondrial membranes. Lipid transfer between the ER and mitochondria is required for the biosynthesis of these critical metabolites, including cardiolipin (CL). CL has been shown to have a variety of essential functions in the mitochondria including maintaining membrane curvature at cristae tips and providing structural integrity to both electron transport chain and mitochondrial import complex components [93–96]. The synthesis of CL involves the transfer of ER-derived phosphatidic acid to the mitochondrial inner membrane followed by the action of a cascade of mitochondrial enzymes including cardiolipin synthase (CLS). Thus, maintaining ER–mitochondrial contacts is critical for the proper synthesis of essential lipids, such as CL, and for maintaining normal mitochondrial function and cellular physiology.

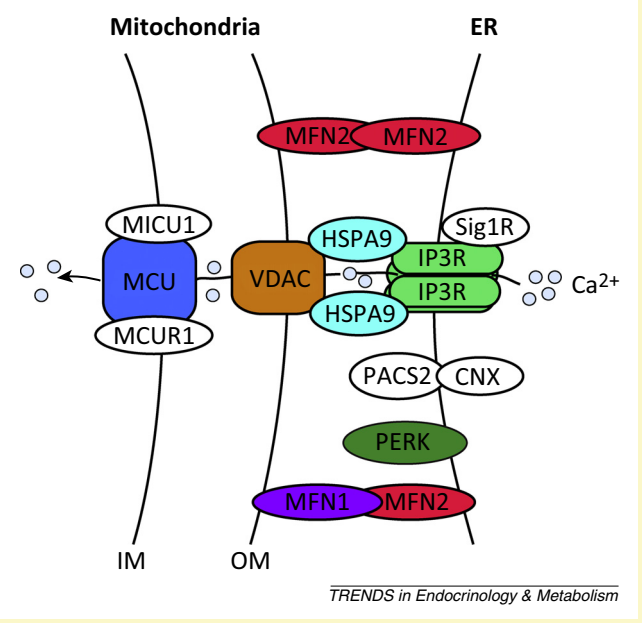

Figure I. Illustration of the components and interactions of proteins localized to ER–mitochondrial contacts. The colored proteins represent core components of ER–mitochondrial contacts required for organelle tethering (MFN2 and MFN1) or Ca^{2+} transfer between these organelles (IP_3R, VDAC, MCU, and HSPA9). The white proteins are regulatory factors that influence the Ca^{2+} signaling through ER–mitochondrial contacts. Abbreviations: ER, endoplasmic reticulum; MFN, Mitofusin; IP_3R, inositol trisphosphate receptor; VDAC, voltage-dependent anion-selective channel; MCU, mitochondrial Ca^{2+} uniporter.

in ER–mitochondrial Ca^{2+} transfer has been proposed to contribute to the pathophysiology of T2D where increased cytosolic calcium leads to aberrant insulin signaling in the pancreas and disrupted routine metabolic functions (e.g., gluconeogenesis) in the liver [13]. Increased activation of TOR signaling has also been linked to the development of metabolic disease [14]. Interestingly, in addition to promoting a diabetic phenotype, ablation of tuberous sclerosis complex (TSC), a suppressor of TOR activity, also induces chronic ER stress. Alleviation of this ER stress reestablishes insulin sensitivity even in the background of sustained TOR activation suggesting that chronic UPR activation has detrimental metabolic consequences [15].

ER stress and mitochondrial dysfunction are also intricately linked in the pathology of other diseases including α1-antitrypsin deficiency [16,17], cardiovascular disorders [18,19], and neurodegenerative diseases such as Alzheimer's disease [20,21], Parkinson's disease [22,23], and amyotrophic lateral sclerosis [24,25]. Despite the pathologic relationship between ER stress and mitochondrial dysfunction in these diseases, the specific contributions of altered ER–mitochondrial communication in disease pathogenesis are only beginning to come to light. For example, familial Alzheimer's disease is associated with mutations in presenilins 1 and 2 (PS1 and PS2), which are involved in the generation of the toxic Amyloid β (Aβ) peptide [20,21]. PS1 and PS2 are enriched in a subcompartment of the ER physically associated with mitochondria called mitochondrial-associated ER membranes (MAMs) and appears to be involved in coordinating ER–mitochondrial Ca^{2+} and lipid transfer, suggesting that these mutations could directly contribute to disease pathogenesis through alterations in ER–mitochondrial signaling [20,21,26–29]. These data suggest that dysregulation of ER–mitochondrial signaling could broadly contribute to the pathogenesis of human diseases with diverse etiologies. Therefore, the possibility of intervening in the transfer of chronic ER stress to mitochondria could be a promising avenue for therapeutic development for many of the debilitating diseases mentioned above.

The PERK signaling pathway of the UPR regulates mitochondrial function during ER stress

The predominant stress-responsive signaling pathway that regulates cellular physiology during ER stress is the UPR (reviewed in [30–32]). The UPR consists of three