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Review

Endoplasmic reticulum chaperones tweak the mitochondrial calcium rheostat to control metabolism and cell death

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ABSTRACT

The folding of secretory proteins is a well-understood mechanism, based on decades of research on endoplasmic reticulum (ER) chaperones. These chaperones interact with newly imported polypeptides close to the ER translocon. Classic examples for these proteins include the immunoglobulin binding protein (BiP/GRP78), and the lectins calnexin and calreticulin. Although not considered chaperones per se, the ER oxidoreductases of the protein disulfide isomerase (PDI) family complete the folding job by catalyzing the formation of disulfide bonds through cysteine oxidation. Research from the past decade has demonstrated that ER chaperones are multifunctional proteins. The regulation of ER-mitochondria Ca^{2+} crosstalk is one of their additional functions, as shown for calnexin, BiP/GRP78 or the oxidoreductases Ero1α and TMX1. This function depends on interactions of this group of proteins with the ER Ca^{2+} handling machinery. This novel function makes perfect sense for two reasons: *i.* It allows ER chaperones to control mitochondrial apoptosis instantly without a lengthy bypass involving the upregulation of pro-apoptotic transcription factors via the unfolded protein response (UPR); and *ii.* It allows the ER protein folding machinery to fine-tune ATP import via controlling the speed of mitochondrial oxidative phosphorylation. Therefore, the role of ER chaperones in regulating ER-mitochondria Ca^{2+} flux identifies the progression of secretory protein folding as a central regulator of cell survival and death, at least in cell types that secrete large amount of proteins. In other cell types, ER protein folding might serve as a sentinel mechanism that monitors cellular well-being to control cell metabolism and apoptosis. The selenoprotein SEPN1 is a classic example for such a role. Through the control of ER-mitochondria Ca^{2+}-flux, ER chaperones and folding assistants guide cellular apoptosis and mitochondrial metabolism.

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1. Introduction

The production of secretory proteins inside the endoplasmic reticulum (ER) requires the joint activity of the polypeptide import machinery, folding chaperones and oxidoreductases. The ensemble of these enzymes sequentially interacts with newly imported polypeptides that correspond to approximately one third of potential intracellular substrates [1]. Together, folding chaperones and oxidoreductive folding enzymes mediate the production of fully functional proteins and prepare them for an oxidizing extracellular environment that is very different from the reducing redox environment of the cytosol [2,3]. ER chaperones and folding assistants are typically very abundant in most cell types, reaching concentrations up to the millimolar range [4], due to the large load of polypeptides entering the ER to be subsequently exported [5]. However, most chaperones moonlight in other functions, some of which have been summarized in a recent review [6]. Most notably, ER protein folding has emerged as an important determinant of mitochondrial functions [7]. An important example of such proteins is calnexin, which determines the activity of ER Ca^{2+} import [8], but also the transfer of Ca^{2+} to mitochondria [9]. This novel role of ER chaperones and folding assistants depends on the interaction with Ca2+ handling proteins, a function that requires localization to the mitochondria-associated membrane (MAM), as shown in the calnexin paradigm [9]. Other ER chaperones and folding assistants perform similar, sometimes overlapping functions via the regulation of ER Ca^{2+} channels and pumps, as well as the storage of free Ca^{2+} within the ER lumen (Fig. 1) [7,10]. This review will focus on these secondary functions of ER chaperones and folding assistants in ER-mitochondria Ca^{2+} signaling to determine mitochondrial functions such as apoptosis and energy production.

2. ER-mitochondria contacts act as an intracellular Ca^{2+} signaling hub that determines mitochondria metabolism

MAMs are a subdomain of the ER that mediate the interaction of the ER with mitochondria and accommodate the exchange of lipids and Ca^{2+} ions between the two organelles [11,12]. These contacts had originally been discovered in pioneering studies by Bernhard, Fawcett, Hay and others in the 1950s [13–16]. For decades dismissed as contaminations, it became clear at the beginning of the 1990s that physical ER-mitochondria contacts are required for lipid synthesis in yeast and human cells by the laboratories of Jean Vance [17,18] and Günther Daum [19,20]. Further breakthrough research determined that MAMs allow for the transfer of Ca^{2+} ions from the ER to mitochondria, in particular during apoptosis [21–24]. A burgeoning body of research on MAMs has led to a detailed understanding of the build and function of this intracellular signaling hub. The latest insight on this has been recently published in a beautiful review [25]. ER-mitochondria contacts form when ER membrane domains approach mitochondrial domains to less than 80 nm of distance if studded with ribosomes, or less than 30 nm if lacking ribosomes [26]. Under conditions of ER stress, MAMs become tighter [27]. The distance between the two organelles decreases by approximately 25%, while the length of a contact site that is normally 220 nm increases by approximately 60% [28]. Most notably, this increased coverage of mitochondria with ER membranes during ER stress significantly increases the availability of Ca^{2+} within mitochondria. As a consequence, ER stress will improve the efficiency of mitochondrial dehydrogenases and, hence, ATP production [29]. Astonishingly, this function had been anticipated by Silvio and Anna Fiala in 1959, who observed that ER protein synthesis served as the switch that turns on mitochondrial activity in liver cells [30]. A question of ongoing research is how the MAM undergoes this plasticity and which proteins are connected to this function.

Another role of the MAM is the promotion of apoptosis progression, as occurs upon very high levels of Ca^{2+} flux from the ER to mitochondria [31]. Such Ca^{2+} flux results in microdomains that are necessary for mitochondrial Ca^{2+} import by uniporters [23] to result in quasi-synaptic Ca^{2+} signal transmission between the ER and mitochondria [32]. Ca^{2+} overload within mitochondria is antagonized by the mitochondrial Na^{+}/Ca^{2+} exchanger (NCLX), which extrudes excess Ca^{2+} from the mitochondrial matrix [33].

ER-mitochondria tethering is currently best understood in yeast, where the ER-mitochondria encounter structure (ERMES) links the two organelles [34]. However, of the members of this protein complex, only two ERMES-regulatory proteins (Gem1p and Lam6p) are conserved in mammalian cells [35,36]. In that latter system, phosphoacidic cluster sorting protein 2 (PACS-2, [37]) and mitofusin-2 [38] have been identified as tethering determinants. More recently, tethering complexes mediated by the outer mitochondrial membrane proteins PTPIP51 and SYNJ2BP have been described. These interact with the ER-localized vesicle-associated membrane protein- associated protein B (VAPB) [39] or ribosome binding protein 1 (RRBP1) [40], respectively. Another protein implicated in ER-mitochondria tethering is FATE1, a bridging factor that establishes longer distance ER-mitochondria contacts [41]. Moreover, protein kinase RNA-like endoplasmic reticulum kinase (PERK), a sensor protein of the unfolded protein response (UPR) also localizes to the MAM and boosts ER-mitochondria tethering [42], allowing for normal apoptosis progression [43] while associated with mitofusin-2 [44]. We have recently reviewed this topic in the context of cancer (Herrera-Cruz et al., in press). Upon interference with ER-mitochondria tethering, ER stress results, highlighting the intimate relationship between ER oxidative folding and the ER-mitochondria contacts [37,38].

3. ER oxidative protein folding 101

To understand their roles in MAM signaling, we will next discuss the roles of ER chaperones and folding assistants in their classic realm, ER oxidative protein folding. When performing their folding activities, ER folding assistants localize to the proximity of ribosomes, where secretory proteins enter the ER upon their recognition of a signal peptide by the signal recognition particle (SRP) and their subsequent import into the ER through the translocon pore [45]. This complex assembly of proteins comes together upon binding of the signal sequence to the SRP, which precedes the association of the ribosome with the translocon [46]. On the ER luminal side, chaperones immediately recognize the polypeptide that is about to be inserted into the ER lumen (Table 1).

The immunoglobulin binding protein (BiP/Grp78) is typically the first chaperone interacting with imported polypeptides [47]. As its name suggests, this chaperone had originally been identified as a major protein binding to nascent immunoglobulins [48]. When interacting with its client proteins, BiP/Grp78 interacts with disordered, hydrophobic patches [49]. Its chaperone activity

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