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Review

Calcium signaling at the endoplasmic reticulum: fine-tuning stress responses

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ABSTRACT

Endoplasmic reticulum (ER) calcium signaling is implicated in a myriad of coordinated cellular processes. The ER calcium content is tightly regulated as it allows a favorable environment for protein folding, in addition to operate as a major reservoir for fast and specific release of calcium. Altered ER homeostasis impacts protein folding, activating the unfolded protein response (UPR) as a rescue mechanism to restore proteostasis. ER calcium release impacts mitochondrial metabolism and also fine-tunes the threshold to undergo apoptosis under chronic stress. The global coordination between UPR signaling and energetic demands takes place at mitochondrial associated membranes (MAMs), specialized subdomains mediating interorganelle communication. Here we discuss current models explaining the functional relationship between ER homeostasis and various cellular responses to coordinate proteostasis and metabolic maintenance.

1. Introduction

Calcium is a highly versatile molecule, functioning as a key secondary messenger participating in the regulation of a wide variety of processes such as fertilization, metabolism, secretion, muscle contraction, neuronal activity and cell death, among many others [1]. Calcium signaling is fast and efficient due to the establishment of a steep calcium gradient concentration –as large as 10^5-fold –between the extracellular and intracellular spaces. Indeed, this gradient is also conserved between different intracellular organelles and the cytosol, facilitating a variety of specific calcium-driven signaling events. For instance, the endoplasmic reticulum (ER), the largest intracellular calcium store, has a free luminal concentration of about 100–800 μM. Calcium increases in the cytosol may result in the engagement of distinct cellular processes, such as the activation of the NFAT pathway in the cytosol, increase oxidative phosphorylation or even cell death through the canonical mitochondrial apoptosis pathway [1]. The maintenance of the calcium gradient has an energetic cost which is achieved through the activity of several pumps and transporters that use ATP to work against electrochemical gradients [2]. Importantly, disturbances on calcium gradients, and specifically on luminal calcium levels have been related to multiple diseases including diabetes, neurological and vascular disorders, viral infections and cancer [3].

The ER is responsible for the folding and maturation of around 30% of the total proteome, a process mediated by luminal resident chaperones and foldases. Many of these folding factors are characterized by a high capacity to bind calcium with low affinity, operating as a cofactor for their optimal chaperone activity. Various conditions can alter the protein folding process at the ER including ER calcium depletion, physiological demands such as high secretory activity, or the expression of mutant proteins of the secretory pathway, resulting in a condition termed ER stress [4,5]. ER stress engages the unfolded protein response (UPR), a signaling network that enforces adaptive programs to restore ER homeostasis. The UPR triggers an initial signaling phase that promotes cell survival through the activation of transcriptional responses aiming to alleviate the intracellular misfolded protein burden [6]. However, if ER homeostasis cannot be re-established, the UPR switches its signaling toward the activation of cell death by apoptosis [7,8].

As part of the adaptive phase of the UPR, crosstalk between the ER and the mitochondria has been reported to modulate energy consumption, boosting ATP production [9,10]. This increase in the generation of ATP is thought to be mediated by the release of calcium from the ER followed by its entry into the mitochondria through specialized structures named mitochondria associated membranes (MAMs). Importantly, MAMs have acquired great interest as they function as a signaling node, controlling different aspects of cellular biology, including lipid biosynthesis, ER-to-mitochondria calcium transfer, cell death and macroautophagy [11]. Importantly, many components of the

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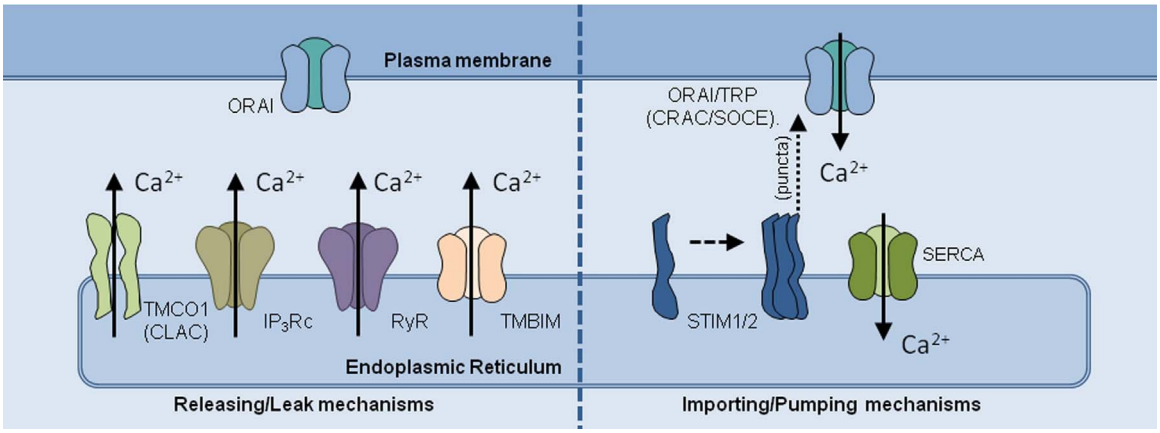

Fig. 1. Calcium homeostasis mechanisms in the ER. Left panel: Calcium leak mechanisms imply (among others) TMBIMs, which are speculated to pH-dependent calcium leak channels and TMCO1 that opens upon high ER calcium levels. In addition IP3Rc and RyRs are involved in calcium signaling in the cells and tightly controlled by different agonists form the plasma membrane to amplify calcium signaling. Right panel: calcium importing or pumping mechanisms are carried by a large family of proteins know as SERCA. SERCA pumps import calcium into the cell against the electrochemical gradient, thus expending ATP. SERCA activity is coupled to SOCE mechanisms that sense ER calcium depletion and communicate CRAC channels in the plasma membrane to open and induce a calcium entry to the cytosol in regions known as puncta, coupled to SERCA, to allow store refilling.

UPR pathway, as well as the calcium-handling machinery, are localized to the MAMs. In this review, we discuss the evidence supporting a functional relevance of ER calcium homeostasis in sustaining ER proteostasis, cellular bioenergetics and the threshold to undergo cell death.

2. Calcium handling mechanisms in the ER

Maintaining a high calcium concentration in the ER is essential to create a differential gradient with the cytosol, a phenomenon controlled by several mechanisms. Three main molecular systems generate and preserve this calcium gradient: i) molecular chaperones that bind and buffer calcium; ii) calcium importing mechanisms that increase ER calcium content; and iii) channels and pores that leak or release calcium from the ER to the cytosol. The crosstalk between these systems determines the maintenance of a steady-state calcium level within the ER [12].

The concentration of *free* luminal calcium in the ER is maintained at the micromolar level, but *total* calcium levels are in the order of 1–3 mM. Thus, the vast majority of the molecules of calcium within the ER are trapped in the surfaces of ER proteins [13]. As mentioned, many ER-localized chaperones can buffer many calcium molecules because either the number of binding sites are high, or the calcium association/dissociation ratio (Koff/Kon = Kd) is low. These chaperones include for example the lectin-like protein calnexin (CNX) and calreticulin (CRT), 78-kDa glucose-regulated protein/immunoglobulin heavy chain binding protein (GRP78/BiP), GRP94 and the protein disulfide isomerase PDI [14,15]. In addition to directly bind calcium and catalyze protein folding, some of these proteins physically associate with calcium pumps and channels, regulating their activities [16,17] (see below). Thus, ER chaperones and other ER-localized enzymes play a dual role, contributing to the maintenance of a high intraluminal free calcium environment in addition to assist protein folding and maturation.

ER calcium importing mechanisms are mainly driven by sarco/endoplasmic-reticulum Ca^{2+} ATPase (SERCA) proteins. SERCA proteins pump calcium to the luminal space of the ER against its electrochemical gradient, consuming ATP in the process (reviewed in Ref. [18]). SERCA pumps represent a large family of proteins whose expression and calcium affinities differ in a tissue and cell-specific manner [19]. Different mechanisms regulate SERCA activity, including posttranslational modifications by certain ER luminal chaperones (see above), membrane lipid composition, and the levels of co-factors (e.g. sarcolipin/phospholamban) [17,20–23]. Other mechanisms to refill intracellular stores are also relevant to sustain ER calcium homeostasis. For example, store operated calcium entry (SOCE) impacts ER calcium content through the activity of calcium-released activated channels (CRAC). CRAC channels are mainly composed by ORAI proteins, which are activated by the ER calcium sensors stromal interacting proteins or STIMs [24,25] (Fig. 1).

ER-calcium release is mediated by well-known channels and pores on its membrane including the ryanodine receptors (RyR) and inositol 1,4,5-triphosphate (IP_3)-receptors (IP_3R). Both families of proteins are composed by three members and form high-order homo- and hetero-tetramers. Like SERCA proteins, RyRs and IP_3Rs have different calcium affinities and are differentially expressed in distinct tissues. For instance RyR receptors are highly expressed in muscle and neurons and are activated by calcium to auto-amplify its signaling in the cytosol (reviewed in Ref. [26]). IP_3Rs are widely expressed in most cell types and their calcium conductance and affinity to agonists are regulated through their homo- and hetero-oligomerization, phosphorylation, chaperone binding, co-factors, and their suborganellar distribution within the ER (reviewed in Ref. [27]). RyRs and IP_3Rs are well-known to regulate a myriad of calcium-signaling related functions, reviewed elsewhere [1,28,29].

Calcium is also released from the ER in a passive manner. A constant leakage of calcium from the ER is normally observed, evidenced by the fact that the inhibition of the SERCA pump with thapsigargin results in the complete depletion of the ER calcium pool within minutes, triggering ER stress and cell death. The molecular identity of the calcium leak channel has remained elusive for many years and different proteins have been proposed to mediate this activity [27,30]. Some members of the Transmembrane BAX inhibitor motif-containing (TMBIM) family of proteins have been proposed as calcium leak channels. TMBIM proteins include six family members and are implicated in cell death control [31]. Structural and functional analysis of Bax inhibitor 1 (BI-1/TMBIM6) and its bacterial ortholog suggest that these proteins are pH-dependent calcium leak channels [32,33]. Some of these family members have been spotted in the ER where their expression reduce ER calcium levels [34]. Another well described leak channel is the translocon-ribosome complex where Sec61alpha plays a key role [35–37]. In addition, the anti-apoptotic protein BCL-2 also locates at the ER and has been suggested to have a calcium leakage function (reviewed in Ref. [38]) as well as other ER proteins including, presenilins [39], or a truncated version of SERCA pump named SERCA1T [27,40]. However, the role of some of these proteins as ER calcium leak channels is still debated [41]. Recently, an additional mechanism to prevent ER calcium overload has been proposed, mediated by the calcium load-activated calcium (CLAC) channel, involving the transmembrane and coiled-coil domains 1 (TMCO1)

protein [42]. Under high calcium concentration in the ER lumen, TMCO1 oligomerizes and forms a calcium-releasing pore [42].

In summary, ER calcium homeostasis is maintained by a complex network of interaction between various components that ensure precise calcium release and maintenance of steady-state ER luminal levels (Fig. 1). Alterations in this balance (*i.e.* reduced ER calcium levels or abnormal elevations in the cytosol) have the potential to perturb ER proteostasis, resulting in ER stress, and the induction of UPR and eventually apoptosis.

3. ER stress and the UPR

The UPR represents the major mechanism involved in maintaining protein folding at the ER when proteostasis is altered. The UPR is mediated by three main type-I ER transmembrane proteins: ATF6 (activating factor 6) alpha and beta, PERK (PKR-like endoplasmic reticulum kinase) and IRE1 (inositol-requiring enzyme 1) alpha and beta [43]. These stress sensors engage transcriptional programs to reduce the unfolded protein load and sustain cell survival. Under non-stress conditions the ER chaperone GRP78/BiP binds to the luminal domains of the three main UPR sensors, preventing their activation [44]. Under ER stress however, GRP78/BiP preferentially binds misfolded proteins, triggering its release from UPR stress sensors to assists protein folding [45,46], releasing its inhibitory effect on the UPR transducers (Fig. 2). ATF6 expression is constrained to the ER, however under ER stress it is exported to the Golgi apparatus where it is cleaved by site 1 and site 2 proteases (S1P and S2P) [6]. This cleavage results in the release of a cytosolic fragment (ATF6f), that shuttles to the nucleus to exert its function as a potent transcription factor, activating gene programs involved in restoring ER homeostasis [47]. PERK activation triggers its oligomerization and the activation of its kinase domain, phosphorylating the eukaryotic translation initiation factor eIF2α. This event induces a global inhibition of protein translation resulting in decreased ER protein load [6]. However, under these conditions, some mRNAs are selectively translated through upstream open reading frames (uORFs), escaping this global inhibition such as the mRNA of ATF4. ATF4 is a transcription factor that drives the upregulation of genes involved in protein folding, amino acid metabolism, autophagy and redox homeostasis [6]. PERK overactivation due to sustained or unresolved ER stress, shifts its pro-adaptive signaling toward a proapoptotic response, mediated in part by the upregulation of C/EBP homologous protein (CHOP), that in turn enhances oxidative stress and ATP depletion, leading to cell death. In addition, ATF4/CHOP induces the expression of several BCL-2 family proapoptotic proteins, resulting in apoptosis by engaging the canonical mitochondrial apoptosis pathway [5,48]. Many other pathways contribute to cell death under ER stress including miRNA regulation, caspase-2 activation, necroptosis and inflammosome activation, among other mechanisms [5].

Under ER stress, IRE1α activates diverse downstream signaling events impacting transcription, mRNA and microRNA stability, in addition to signaling crosstalk with other stress pathways [5]. Upon activation, IRE1α dimerizes and auto-transphosphorylates, activating its

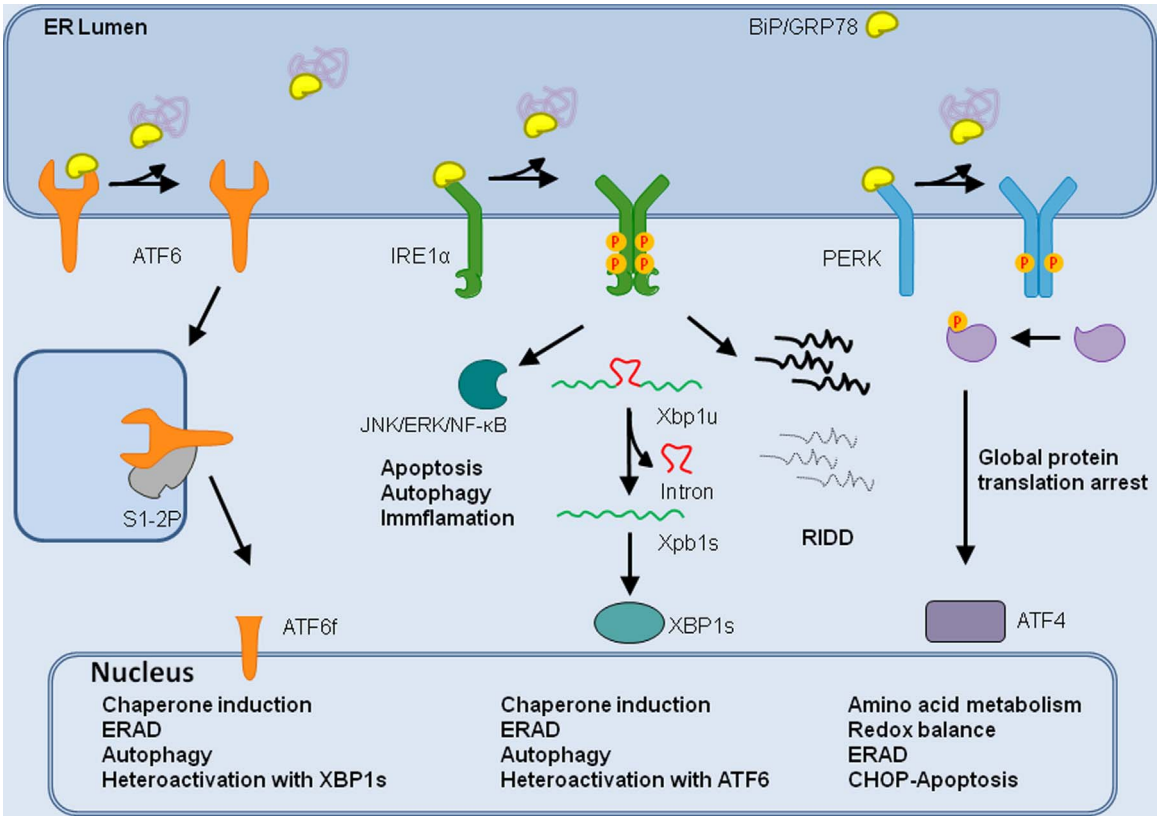

Fig. 2. ER stress and the UPR. ER proteostasis can be disrupted by different stimuli that result in protein misfolding. This condition is named ER stress and engages the UPR. ER stress promotes the dissociation of the ER luminal calcium-binding chaperone BiP/GRP78 from the luminal site of the three canonical UPR transducers activating their signaling. After BiP/GRP78 release ATF6 is exported to the Golgi apparatus where site1 and site 2 proteases (S1 and S2) cleave it, releasing a cytosolic fragment that activates gene transcription machinery related to degradation of misfolded proteins in the ER (ERAD) and folding. Upon activation, IRE1α undergoes auto-phosphorylation and forms dimmers/oligomers. Three main outputs are described for IRE1α, one is its kinase signaling *via* TRAF2 and JNK/ERK/NFKB, related to cell death, the other two involve its RNAse activity that on one hand induces a selective cleavage of mRNAs know as RNA-IRE1α dependent degradation (RIDD) and on the other promotes the splicing of XBP1 mRNA resulting in the expression of a stable transcription factor termed XBP1s. XBP1s induces different transcriptional programs involved in ERAD and chaperone induction, some of them in conjunction with ATF6. Finally, PERK also oligomerizes and phosphorylates eIF2α. This results in a global inhibition of protein translation and the specific translation of some mRNAs. Thus the PERK branch favors the selective expression of ATF4 protein, another transcription factor that is involved in the upregulation of genes related to ERAD, amino acid metabolism, redox signaling and CHOP, a factor tightly related to apoptosis.

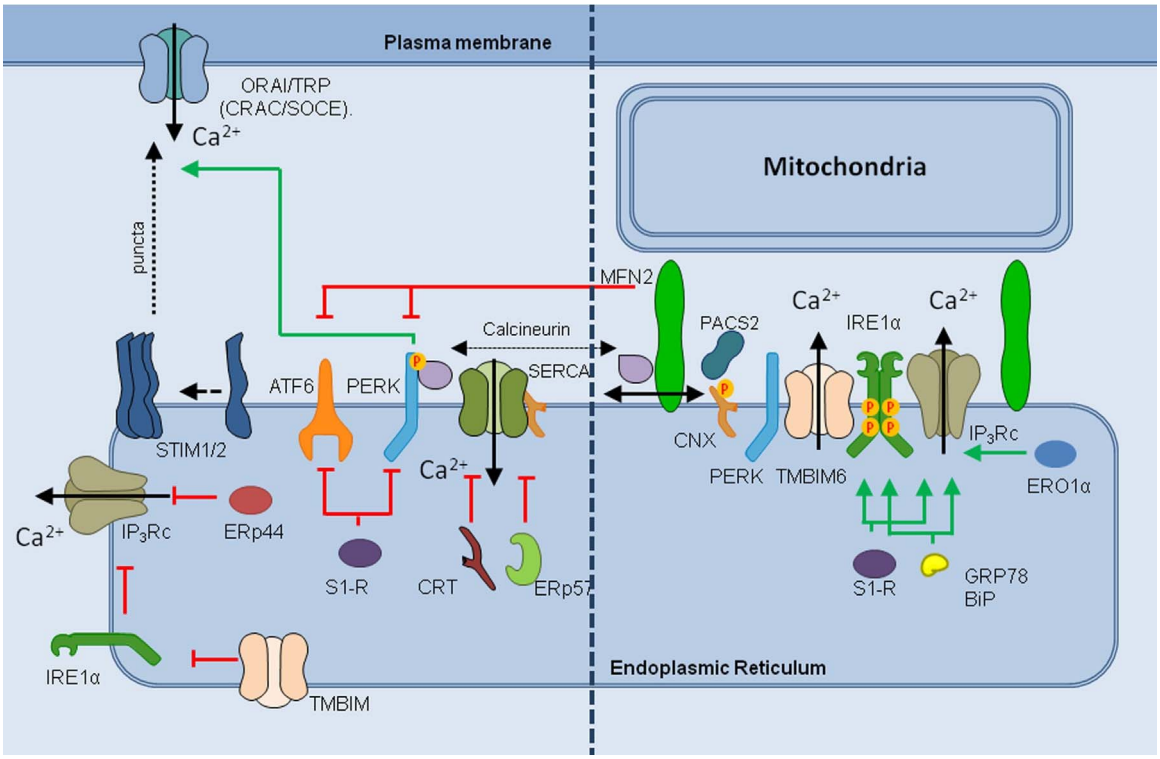

Fig. 3. Integration of the UPR and chaperones to control ER calcium. (A) Chaperones regulate ER calcium levels in different ways. In one hand chaperones buffer calcium and on the other modulate different channels and pumps. ERp44 reduces IP3Rc activity, and Sigma1R (S1-R) inhibits PERK and ATF signaling. Moreover, CRT, ERp57 and CNX reduce the activity of the SERCA pump. Moreover, IRE1α activity is reduced by TMBIM6 and in turn IRE1α can regulate IP_3R activity. Finally, PERK protein is involved on STIM1 translocation to plasma membrane to activate SOCE while in turn can bind calcineurin. (B) CNX role is intricate since its inhibition on SERCA is controlled depending on its location; it can be in the mitochondrial associated membranes in a PERK/Calcineurin phosphorylation dependent manner and also by associating with PACS2. The MAMs protein MFN2 has been described to block PERK and ATF6 signaling. Also, in this compartment BiP/GRP78 and S1-R stabilize the RNAse activity of IRE1α while in parallel can promote IP_3R opening, thus increasing calcium shuttle to mitochondria, altering bioenergetics and or cell death. This effect on IP_3R is also exerted by ERO1.

RNAse domain on its cytosolic region through a conformational change. Its RNAse domain catalyzes the unconventional splicing of the mRNA encoding X-box binding protein 1 (XBP1), resulting in the expression of XBP1s (for the spliced form), a potent transcription factor that –together with ATF6 –upregulates several genes involved in the adaptive phase of the UPR [49–52]. In addition to the splicing of XBP1 mRNA, a subgroup of mRNAs are degraded by IRE1α, a mechanism called regulated IRE1-dependent decay or RIDD [53,54]. Another output of IRE1α is mediated by the biding to adapter proteins, leading to the activation of alarm pathways including the c-JunN-terminal kinase (JNK) pathway, p38, ERK, and NF-κB [55–59]. All these XBP1-independent IRE1α outputs may modulate different cellular processes including apoptosis, autophagy and inflammation [4] (Fig. 2). Overall, UPR signaling engages different cellular responses to initially sustain cellular survival or trigger apoptosis of damaged cells. The control for the threshold of ER stress to induce the UPR, as well as the precise membrane subdomains involved in UPR signaling is acquiring more attention in recent years due to its relevance of the pathway to diverse human diseases.

4. UPR and calcium signaling

The role that ER calcium homeostasis plays during the ER stress response may be classified into three categories: (i) as a cofactor regulating the threshold for the induction of the UPR by adjusting the activity of several protein folding enzymes; (ii) as a modulator of bioenergetics during the early adaptive phase and (iii) as a factor that sensitizes cells to undergo apoptosis at the level of the mitochondria [48]. In this next section, we discuss the role of calcium in the modulation of UPR signaling and the role of MAMs as a site where this regulation occurs. For simplicity, we have split this section in molecular events that take place at the ER, and processes that have been spotted to the MAMs, thus having an impact in mitochondrial physiology.

4.1. Calcium handling mechanisms and the UPR

Alterations in the function of different chaperones and calcium channels can result in abnormal levels of ER stress. The interrelation between chaperones and the UPR is bidirectional: on one hand the activation of the UPR induces the expression of a variety of chaperones, foldases and cofactors, alleviating protein misfolding, while on the other hand, dysfunctional chaperones may lead to an increase in misfolded proteins and ER stress, engaging the UPR [6]. GRP78/BiP is probably the chaperone that exhibits a more profound effect on global proteostasis because it controls the activation of the UPR, in addition to account for approximately 25% of the calcium buffering capacity within the ER [60]. Other ER chaperones can also modulate the UPR either by acting directly on the sensors, or indirectly through the control of calcium channels and pumps [17,22]. For instance, the CNX and CRT cycle is essential to fold glycoproteins produced in the secretory pathway, representing a major protein quality control mechanism. These proteins are also involved in the formation of disulfide bonds assisted by a direct interaction with the disulfide isomerase ERp57 (also known as Grp58 or PDIA3) [61]. The malfunctioning of the CNX-CRT cycle results in the disposal of proteins to the ER-associated degradation (ERAD) machinery: a mechanism involving the retro-translocation of luminal proteins to the cytosol for proteasomal degradation [62]. Alterations to these protein quality control systems result on the accumulation of immature or misfolded proteins [63,64]. Interestingly, CRT is proposed to directly control ATF6 activation [65] while another chaperone known as PDIA6, has been also proposed to modulate the kinetics of activation of PERK and IRE1α [66,67]. Interestingly, despite

its implication in the CNX/CRT cycle, the disulfide isomerase ERp57 plays no evident role in the regulation of the UPR since mice deficient for ERp57 in the brain do not show any signs of spontaneous ER stress [68]. However, these chaperones might have effects on calcium homeostasis as the detrimental effects of ablating CRT expression are rescued by the expression of a constitutive active form of the calcium-dependent phosphatase calcineurin (CN), evidencing its role in calcium signaling [69]. This calcium signaling output is in agreement with different observations showing that these proteins alter the activity of the SERCA pump [22]. Specifically, the interaction of CNX, CRT and ERp57 with SERCA limits calcium waves *in Xenopus oocytes* [16,17,22]. Similar results were reported in mammals *in vitro*, where CRT inhibits the SERCA2a isoform under oxidative stress conditions [20].

Thus the CNX/CRT cycle and PDIs modulate the UPR either by directly acting on the transducers through protein-protein interactions or indirectly through the modulation of calcium steady-state levels (Fig. 3).

Other calcium mobilizers are also affected by chaperones and UPR transducers. For example, the activity of the IP_3R type 1 (IP_3R1) is reduced by the expression of GRP78/BiP and the oxidoreductase ERp44 under ER stress conditions [70]. These effects suggest a feedback loop where chaperones and oxidoreductases converge into the inhibition of calcium channels during ER stress, thus preserving a favorable protein-folding environment. Interestingly, it has been suggested that the activity of IRE1α can reduce the activity of IP_3R in neuronal cell lines [71]. In contrast, in a different study using embryonic fibroblasts where IRE1α was ablated, IP_3R-mediated calcium release was unaltered [72]. Finally, a recent study has unveiled another unexpected link between the UPR and the regulation of calcium homeostasis. PERK was shown to interact with the actin cytoskeleton regulator Filamin A modulating ER-plasma membrane contact sites, impacting calcium homeostasis at the level of STIM1 *puncta* formation [73]. Moreover, it has been proposed that PERK could modulate SERCA activity through an indirect control of CNX/calcineurin phosphorylation [74,75]. Overall, these observations point toward an intricate network of molecular players connecting ER proteostasis and calcium homeostasis on a bidirectional manner (Fig. 3).

4.2. MAMs: homeostatic interorganelle communication

The ER is the largest organelle in the cell and the contact sites between its membrane and other organelles have gained increased attention [11]. Plasma membrane-ER contact sites [24,25] or ER to lysosomal contact sites have been linked to the regulation of calcium homeostasis [76,77]. In this section, we discuss the role of MAMs as a site of control of the UPR and calcium signaling.

In the last decade, a great amount of literature has revealed the emerging functions of MAMs in cell physiology. In these membrane subdomains, a bidirectional communication between ER and mitochondria occurs governed by chaperones, ion channels and UPR transducers (Fig. 3). MAMs are membrane structures that operate as a hub for the control of autophagy, lipid synthesis, calcium transfer, mitochondria metabolism, apoptosis and the UPR [78]. The shuttle of calcium between the ER and the mitochondria relies on the coupling of ER-calcium release mechanisms with the inner membrane mitochondrial calcium uniporter (MCU) [79,80]. Due to its low calcium conductance and affinity, the MCU was initially thought to be physiologically irrelevant as a calcium importer during mitochondrial buffering of cytosolic calcium. This view changed with the discovery of MAMs and calcium microdomains, uncovering localized calcium microenvironments where MCU uptakes calcium directly coupled to IP_3Rs and RyR *via* voltage-dependent anion channels (VDAC) in the outer mitochondrial membrane (OMM) [81–83]. Calcium uptake by the mitochondria exhibits different functions depending on the intensity and pattern of the signaling [78,84]. A high frequency calcium oscillatory pattern results in increased mitochondrial respiration and ATP production due to the activation of calcium-dependent mitochondrial enzymes and metabolite carriers (reviewed in [85,86]). Basal IP_3R-mediated calcium transfer to mitochondria is necessary to avoid mitochondrial energetic failure [87] and to confer resistance to cytotoxic stimuli [70,88]. In contrast, sustained calcium uptake by the mitochondria sensitizes cells to cell death through the engagement of the mitochondrial transition permeability pore (mPTP) [89].

MAMs are dynamic structures, changing their composition depending on the stimuli and the cell type. For example, under ER stress there is an increase in the energetic demand that is coupled with a mitochondrial energy boost [90–92]. Interestingly, during the early phases of the UPR, mitochondria redistribute to the periphery of the ER and increase ATP production [9,91]. Importantly, this crosstalk may also have pathological relevance since many neurological diseases such as Alzheimer's, Parkinson's, amyothropic lateral sclerosis (ALS) and Charcot-Marie-Tooth's disease exhibit hallmarks of ER stress [93] together with biochemical and morphological alterations of the MAMs [94–96]. Along these lines, different chaperones, calcium channels as well as UPR sensors have been identified at MAMs, where they exert different functions.

Studies in PERK-deficient cells revealed that PERK expression influences MAMs biology. PERK KO cells showed lower content of MAMs, associated with altered ER-to-mitochondria calcium transfer and decreased sensitivity to ROS-induced cell death [72]. However, a different study has suggested that PERK plays a protective role at the MAMs during stress conditions [97]. In addition, Mitofusin 2 (MFN2) – a central structural component of the MAM – operates as an upstream regulator of PERK, preventing its activation through a physical interaction, impacting the induction of cell death and the overall mitochondrial morphology [97] (Fig. 3). Although it was suggested that PERK might influence MAMs abundance and function through the MFN2 axis, the role that MFN2 plays at this compartment is still debated since it may contribute to membrane tethering [98,99] or operate as a spacer [100,101]. MFN2 expression may have a direct implication to ER homeostasis since its deficiency results in spontaneous ER stress both *in vivo* and in cell culture models [97,102,103].

As mentioned before, PERK can control CNX phosphorylation through calcineurin. Interestingly, CNX is also located to MAMs at least due to two mechanisms. First, CNX phosphorylation status that limits its inhibitory effects on SERCA, altering SOCE [104]. Second, by interacting with phosphofurin acidic cluster sorting protein 2 (PACS-2) through a palmytoylation [105–107]. Overall, PERK favors ER to mitochondria communication impacting different processes, including ROS production, calcium homeostasis and cell death (Fig. 3B).

The role of IRE1α in the MAM is less explored. Mori *et al.* have directly spotted IRE1α in the MAMs, where its RNase activity is stabilized during ER stress by chaperone sigma 1 Receptor (S1-R) [108,109]. S1-R is a classical component of the MAMs that also blocks ATF6 and PERK activation and stabilizes type 3 IP_3R [110]. S1-R expression increases IP_3R activity during ER stress, contributing to cell death [111–113]. IP_3R is also modulated by the oxidoreductase ERO1α, which has been detected in this suborganellar region depending on oxidizing conditions [114]. Another protein that has been related to the UPR spotted at MAMs is BI-1 (also known as TMBIM6). BI-1 operates as an anti-apoptotic factor [31,34] (Fig. 3). In addition, BI-1 is known to regulate autophagy and the UPR through the inhibition of IRE1α, in addition to modulate IP_3R signaling and mitochondrial calcium uptake [115–117].

Overall, although many ER chaperones, cofactors and foldases, calcium mobilizing agents and ER stress transducers have been reported as MAM components, the specific functions these proteins play fine tuning ER stress responses, energetic stress, and/or pathological conditions is still poorly understood.

5. Perspective and concluding remarks

In this article we have reviewed the role of calcium in the regulation of ER proteostasis and the role of the UPR in the regulation of ER calcium-handing mechanisms. We have also discussed the role of MAMs as a specialized membrane subdomain that regulates calcium and UPR signaling. As mentioned above, the canonical UPR pathway (Fig. 2) can be triggered by ER stress mechanisms, however recent studies have unveiled non-conventional functions for the UPR transducers that involve calcium signaling.

IRE1α was claimed to modulate IP_3R independently of its RNase function, however this regulation appears to be cell type specific [71,72]. In contrast, PERK is better characterized regarding its non-canonical activation *via* calcineurin signaling, impacting SERCA2 function [74]. Indeed, in a recent study, Van vliet *et al.* described a novel function for PERK in actin cytoskeleton remodeling. This new function impacts STIM1 translocation to the plasma membrane, affecting calcium homeostasis independently of the ER protein folding status [73]. Interestingly, STIM1 proteins can also trigger SOCE independently of ER calcium depletion by temperature shifts and by oxidative stress [118,119], adding an additional layer of complexity to the ER stress/calcium handling system crosstalk.

ER-mediated calcium signaling has a pivotal role in many cellular processes. One of the most well characterized mechanism is SOCE in the context of the immune system's physiology [24], where CRAC-dependent refilling mechanisms drive T cell activation and prevent immunodeficiency [120]. Based on the evidence discussed here, the impact of MAMs in the regulation of the UPR and its connection to calcium homeostasis may have broad physiological relevance.

Cellular integration between ER homeostasis and mitochondrial function is highly complex and tightly regulated, allowing the cell to engage interorganelar responses to coordinate global cellular processes. MAMs may have bidirectional signaling responses to influence the energetic status of the cell and fine-tune proteostasis. The molecular mechanisms underlying this crosstalk and its relation to pathological conditions are starting to be understood [78,94,121]. A model is emerging where ER stress triggers signals to the mitochondria to coordinate a global cellular response, balancing metabolic demands, cell survival and apoptosis induction (Fig. 3). The interrelation between calcium and the UPR in the MAMs is complex and largely unknown. For example, the composition of the MAMs at the biochemical level might be indirectly modulated by the UPR since the trasncriptional reprogramming induced under ER stress upregulates the biosynthesis of a myriad of lipids [122]. Alteration in lipid composition at the MAMs may influence the threshold to undergo ER stress and therefore calcium homeostasis [123,124]. Interestingly, recent reports have revealed that in many neurological diseases, ER stress, calcium signalling and MAMs alterations occur at the same time, suggesting that under pathological conditions this axis might be of great relevance [94,125]. One of the most studied conditions where these three processes are altering is obesity, where activation of ER stress has an important role in insulin resistance and diabetes. Aberrant lipid metabolism during obesity may alter SERCA and IP_3R function, inducing ER stress and altered glucose homeostasis [123,126]. Altogether it can be inferred that the deregulation of interoganelle communication can result in adverse effects contributing to human pathology.

Some studies have suggested that under ER stress there is an altered mitochondrial function. However, little is known about whether alterations in mitochondrial function can promote ER disturbances, and even if those alterations occur in MAMs. Is this interrelation mediated by ROS, ATP, lipid composition or the presence of other factors at the MAMs? Further research is necessary to model the complex cellular network involving calcium signaling to bioenergetics and UPR signaling in MAMs. Importantly, UPR transducers are no longer viewed as protein misfolding sensors, but also as calcium handling regulators that have a direct implication on cell fate and bioenergetics.

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