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Commentary

Avoiding raising the ire of IRE1α

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ABSTRACT

IRE1α is well known as a regulator of one branch of the UPR pathway that is activated during ER stress that operates to regain ER proteostasis. In a recent paper, Carreras-Sureda et al. show that IRE1α is also a structural component of MAMs and facilitates the uptake of Ca^{2+} by mitochondria.

Inositol-requiring enzyme (IRE1α) is an endoplasmic reticulum (ER) transmembrane protein encoded by the *ERN1* gene. It was originally cloned by complementation of a yeast mutant auxotrophic for inositol and subsequently characterized as a serine/threonine protein kinase required for myo-inositol synthesis [1]. Since then, IRE1α has been identified as a component of the unfolded protein response (UPR) signaling pathway important for sensing and responding to ER stress in a variety of eukaryotic organisms [2]. IRE1α also functions as an endoribonuclease, and it is this enzymatic activity that has come to be associated with its canonical role in metazoan cells for facilitating the condition-dependent nonconventional splicing of the mRNA transcribed from the *XBP1* gene to a form that directs the translation of a stable and active transcription factor known as XBP1s.

In a recent paper, Carreras-Sureda et al. [3] reported that IRE1α is a structural component of mitochondria-associated membranes (MAM), which represent membrane contact sites (MCS) between ER and mitochondria [4] (Fig. 1). Using functional studies, they showed that IRE1α-deficient cells have decreased mitochondrial Ca^{2+} uptake and reduced ATP-dependent Ca^{2+} release to cytosol suggesting that IRE1α plays an important role in the mitochondrial import and export of Ca^{2+}. IRE1α reportedly forms a stable complex with inositol 1,4,5-trisphosphate receptors ($InsP_3R$) which is necessary for the localization of $InsP_3R$ at the MAM. Loss of IRE1α disrupts $InsP_3R$ distribution at the MAM and decreases activity of Ca^{2+}-regulated mitochondrial enzymes and energy metabolism. Accordingly, the authors propose that the presence of IRE1α/$InsP_3R$ at MAM serves to modulate cellular bioenergetics by supporting Ca^{2+} movement between ER and mitochondria.

The ER is the major component of the cellular reticular network (CRN), which is comprised of the membrane systems that spans the cell membrane and the nuclear envelop [5]. The membranes that make the different organelles representing discrete components of the CRN have distinct lipid and protein compositions and supply a wide array of specialized cellular functions necessary to maintain physiology [5]. Considering that most of these functions are energy-requiring, it is critical for the cell to regulate bioenergetics in order to maintain and coordinate multiple pathways occurring simultaneously within the CRN. A fundamental cause of cellular stress is attributable to loss of nutrient/energy homeostasis, which may be mitigated through transient activation of stress coping strategies to enable the cell to regain control of nutrient/energy metabolism. In some cases, the cell is able to circumvent cell stress and escape apoptosis through persistent modification of metabolic capacity, but this outcome results in a cellular function that no longer is responsive to physiologic homeostatic controls [6,7]. In this regard, the Ca^{2+} ion may play a key role as a signaling molecule and fine adjuster of enzymatic efficiency by virtue of its ability to serve as a cofactor, as this type of interaction can influence the conformation of protein-cofactor complexes. One way of ensuring rapid transport of signaling molecules, nutrients, metabolites and high-energy substrates within the CRN is to make use of MCS as portals connecting the different membrane systems (Fig. 1). Such structures have been observed to form between ER-mitochondria (i.e., MAM), ER-lysosomes, ER-peroxisomes, ER-Golgi as well as ER-plasma membrane [4].

MAM provides a physical and functional connection between ER and mitochondria [4]. Proteins enriched at MAM, such as phosphatidylserine synthases, $InsP_3R$, calnexin, PERK, Sigma-1, voltage-dependent anion channel 1 serve many functions such as lipid biosynthesis and transport between these two organelles, Ca^{2+} transfer,

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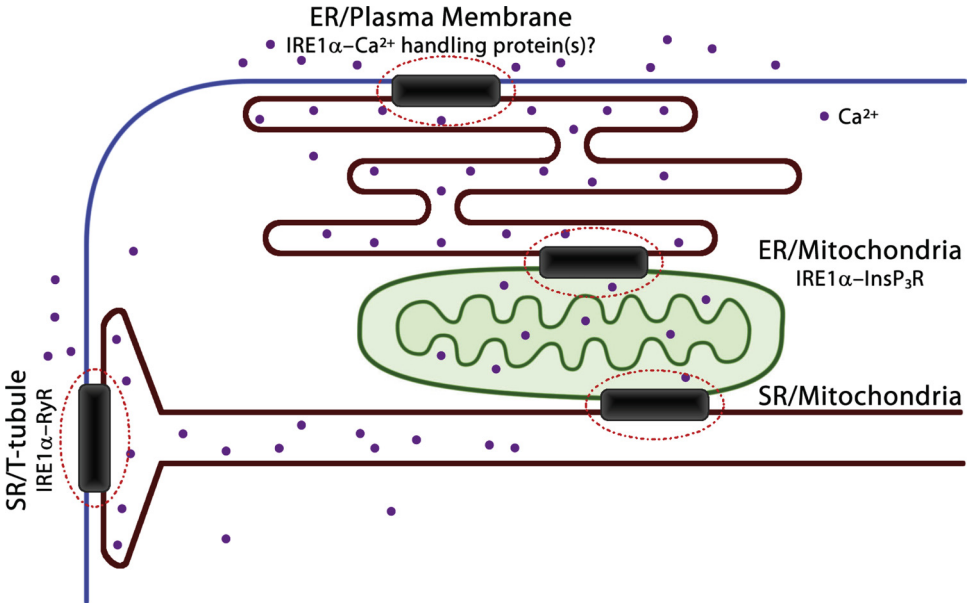

Fig. 1. IRE1α at the MCS. Membrane contact sites (MCS, black boxes) between different membrane systems are circled. RyR, ryanodine receptor; $InsP_3R$, inositol 1,4,5-trisphosphate receptors.

mitochondrial energetics, apoptosis, autophagy and mitochondrial fusion/fission [8]. Interestingly, interaction of Sigma-1 receptor with IRE1α influences IRE1α endonuclease activity [9]. PERK, another transmembrane ER stress sensor, is also enriched at MAM where, just like IRE1α, it too apparently plays a scaffolding role [10]. The presence of two ER sensors of the UPR, namely PERK and IRE1α, at the MCS may be a means to link ER stress coping mechanisms with cellular bioenergetics [6].

MCS are also formed between the ER and plasma membrane. For example, formation of an MCS due to interaction between ER Ca^{2+} sensor STIM and plasma membrane Ca^{2+} channel ORAI to drive store-operated Ca^{2+} entry for refilling of the ER Ca^{2+} stores [11] needed to support intracellular Ca^{2+} signalling. In muscle cells, MCS are also formed by interaction between ryanodine receptor/ Ca^{2+} channel of the junctional sarcoplasmic reticulum (SR) and dihydropyridine receptor/ Ca^{2+} channel of the T-tubules, which are extensions of the plasma membrane that penetrate into the muscle cells. This serves to synchronize Ca^{2+} release to initiate muscle contraction [12]. Noteworthy, MCS between SR and mitochondria have been reported [13]. Recently, IRE1α was identified at the MCS between junctional SR and the T-tubules where it interacts with calsequestrin, a junctional SR Ca^{2+} binding protein [14]. The binding of calsequestrin to IRE1α at the junctional SR prevents the activation of IRE1α despite the large fluctuations in Ca^{2+} concentrations in the SR [14]. It is interesting to note that IRE1α co-localizes with Ca^{2+} release channels at MCS (i.e., with InsP3R at the MAM [3] and with ryanodine receptor in the junctional SR [14]). In the muscle, IRE1α at the MCS formed between junctional SR and T-tubules likely serves to facilitate SR Ca^{2+} movement for E—C coupling.

That IRE1α displays functional versatility may not be surprising since it is involved in dictating the survival or death of the cell. In mice, global IRE1α deficiency is embryonic lethal at E9.5–11.5 due to placental malformation [15]. In contrast, mice with whole-body gene knockout of the *Xbp1* gene, which encodes the transcription factor induced by the "canonical" activation of IRE1α signaling, exhibit lethality at E12.5–14.5 due to impaired hepatocyte development and hepatic hypoplasia [16]. The molecular basis for these defects are not currently known, but the observed delay in the onset of lethality exhibited by whole-body Xbp1-deficient mice relative to the whole-body IRE1α-deficient mice suggest that IRE1α may be involved in regulating functions in addition to those associated with Xbp1s.

IRE1α is also capable of degrading selected mRNAs and microRNAs through a process referred as regulated IRE1α-dependent decay (RIDD), contributing to cell death, inflammation and other biological processes. Sustained IRE1α signaling leads to apoptosis and autophagy possibly resulting from uncontrolled RIDD, JNK activation, miRNA deregulation and other complementary mechanisms [2]. Furthermore, under stress conditions, IRE1α not only undergoes autophosphorylation but can also act as a kinase to phosphorylate Bcl2 [17]. Interestingly, recent studies show that IRE1α signaling is modulated through direct interaction of the IRE1α cytoplasmic domain with a variety of proteins, including phosphatases, kinases, apoptosis-related proteins and the cytoskeleton [2,6]. In the lumen of the ER, IRE1α activity is regulated by direct interactions with BiP [2,6], Hsp47 [18], PDIA6 [19], calsequestrin [14], and COX-2 [20]. Such an elaborate repertoire of interacting proteins suggests that IRE1α is involved intimately in the sensing and regulation of cellular homeostasis.

Evidently, IRE1α at the MCS has an important influence on Ca^{2+} movement within the CRN. It is apparent that IRE1α signaling is involved in many important cellular functions. Indeed, aberrant IRE1α signaling is prominent in the pathogenesis of many human diseases, including many types of neurological disorders, cancers as well as cardiovascular and metabolic diseases to name a few. We are just beginning to appreciate the multifaceted nature of IRE1α and the extent of its entrenchment in cellular homeostasis. It might be wise, therefore, to pay very close attention to what raises the ire of IRE1α.

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