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Organelles in focus

Organelle communication: Signaling crossroads between homeostasis and disease

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ABSTRACT

Cellular organelles do not function as isolated or static units, but rather form dynamic contacts between one another that can be modulated according to cellular needs. The physical interfaces between organelles are important for Ca^{2+} and lipid homeostasis, and serve as platforms for the control of many essential functions including metabolism, signaling, organelle integrity and execution of the apoptotic program. Emerging evidence also highlights the importance of organelle communication in disorders such as Alzheimer's disease, pulmonary arterial hypertension, cancer, skeletal and cardiac muscle dysfunction. Here, we provide an overview of the current literature on organelle communication and the link to human pathologies.

Organelle facts

Fact 1. Cell compartments engage in direct communication through specialized membrane domains in close proximity (20–40 nm) of one another.

Fact 2. Organelle interaction offers spatiality to cellular responses, serving as a platform that anchors molecular complexes to sub-cellular regions.

Fact 3. Organelle interfaces serve as nucleation sites for pathways such as stress signals, mitochondrial dynamics and autophagy.

Fact 4. Organelle communication regulates important cellular processes such as metabolism, cell death and organelle quality control.

1. Introduction

Compartmentalization of specific functions in organelles is a defining feature of eukaryotic cells. Although often conceived as separate, membrane-limited structures, several reports now indicate that organelles are not as "isolated" and static as originally thought. The first evidence for close proximity between two organelles, the ER and mitochondria was obtained using electron microscopy (Copeland and Dalton, 1959). Since then many additional experimental approaches, such as live cell confocal microscopy, subcellular fractionation and the use of genetically-engineered chimeras have confirmed the physical proximity and the functionality of such interorganellar communication sites. Lipid biosynthesis, Ca^{2+} handling, and degradation of cellular

structures are some examples of the many functions attributed to organelle coupling, suggesting a major role for these sites in general homeostasis.

Communication between organelles is a widespread phenomenon, involving ER, mitochondria, nucleus, PM, Golgi apparatus and other organelles. Although these organelle pairs form close contacts with reciprocal distances that range from 20 to 40 nm (Achleitner et al., 1999), they typically do not fuse their membranes, indicating that compartmentalization is always preserved. Moreover, organelle communication is also a dynamic process that allows adaptation to stress in a spatial and temporal fashion (Bravo et al., 2011). Of note, these processes rely on different protein entities, depending on the organelles involved.

In this review, we will focus on different types of interorganelle contacts, how they control cell metabolism, signaling and autophagy, and how they are linked to the development of pathologies.

2. Organelle communication function

2.1. Organelle interplay in Ca^{2+} homeostasis

The ER represents the main intracellular Ca^{2+} store and is crucial for cellular Ca^{2+} homeostasis. This extensive membranous network includes multiple sites in close proximity of the plasma membrane (PM). ER Ca^{2+} depletion is rapidly reversed by a mechanism known as Store-Operated Calcium Entry (SOCE). This process is initiated by stromal interaction molecule 1 (STIM1), a transmembrane protein that senses ER luminal Ca^{2+}. Decreases in Ca^{2+} levels induce STIM1 oligomerization and binding to acidic phosphoinositides at the PM (Muik et al., 2011). In these ER–PM contact sites, STIM1 recruits the Ca^{2+}-specific channel ORAI1, leading to Ca^{2+} entry into the ER (Prakriya et al., 2006). The formation of contacts between the ER and mitochondria is critical for this ER refilling mechanism, as SOCE requires a functional mitochondrial Na^+/Ca^{2+} exchanger (NCX) and the maintenance of the mitochondrial transmembrane potential ($\Delta\psi_{mt}$) (Naghdi et al., 2010).

The nuclear envelope (NE), which is continuous with the ER, can also communicate with the PM, leading to direct signaling from the extracellular space into the nucleus. The mechanism used by the NE also relies on Ca^{2+} signaling, and is able to trigger nuclear Ca^{2+} transients independently of the cytoplasm (Leite et al., 2003). Recently, we have shown that insulin-like growth factor 1 (IGF-1) generates fast and autonomous nuclear Ca^{2+} signaling in cardiomyocytes. This response is achieved through activation of IGF-1 receptor (IGF-1R) localized to perinuclear invaginations of the PM called T-tubules, resulting in local production of inositol 1,4,5-triphosphate ($InsP_3$), which diffuses into the nucleus to activate IP_3 receptors ($InsP_3R$), bypassing the ER (Ibarra et al., 2013).

Ca^{2+} transfer from the ER to mitochondria also requires regions of apposition between the organelles, which comprise ~5–20% of the total mitochondrial surface (Rizzuto et al., 1998). Ca^{2+} is released at the ER surface via $InsP_3R$, which is physically linked to the voltage-dependent anion channel isoform 1 (VDAC1) at the mitochondrial outer membrane (OMM) (Szabadkai et al., 2006). Ca^{2+} readily passes through VDAC1 and then enters to the mitochondrial matrix via the mitochondrial Ca^{2+} uniporter (MCU). MCU is highly selective for Ca^{2+}, but its low affinity results in its dependence on the elevated Ca^{2+} microdomains formed at the ER–mitochondria interface thanks to the $InsP_3R$-VDAC1 apposition. MCU modulators include: the $\Delta\psi_{mt}$ and the accessory proteins mitochondrial Ca^{2+} uptake 1 (MICU1) and MCU regulator 1 (MCUR1) (Mallilankaraman et al., 2012). Efficient ER storage filling by SERCA calcium pumps is a prerequisite for efficient ER–mitochondria calcium flux and its modulation
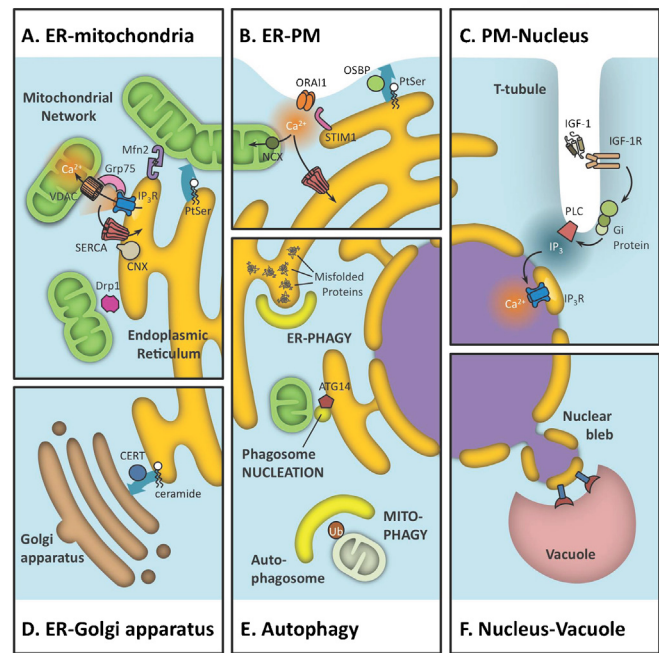

Fig. 1. Different types of organelle interaction. A: Mfn2 tethers ER and mitochondria together. Apposition allows direct Ca^{2+} transfer through VDAC1 and IP3R channels bridged by Grp75, as well as PtSer transfer. This interface also serves as recruitment site for the mitochondrial constriction GTPase Drp1. B: STIM1 at the ER surface recruits ORAI1 to the PM, stimulating Ca^{2+} entry from the extracellular medium to ER and mitochondria. PtSer transfer from ER to PM is mediated by OSBP in zones of close proximity. C: In cardiomyocytes, PM invaginations position the membrane in close proximity of the nucleus. This enables IGF-1 signaling to locally activate Phospholipase C (PLC), directly delivering IP3 to the nucleus, inducing intranuclear Ca^{2+} release. D: Ceramide transfer from ER to Golgi apparatus are mediated by CERT at contact sites between both organelles. E: Autophagosome nucleation occurs at the ER–mitochondria interface. During their expansion phase, autophagosomes selectively interact with and engulf damaged portions of the ER as a protective mechanism against protein misfolding (ER-phagy). They can also recognize ubiquitylated proteins at the surface of depolarized mitochondria, leading to their sequestration and degradation (Mitophagy). F: In yeast, vacuoles degrade portions of the nucleus via direct interaction, through specialized nucleus-vacuole junction proteins.

by the ER chaperone calnexin determines the ability of the ER to transmit a stress-dependent Ca^{2+} signal to mitochondria (Lynes et al., 2013). Other proteins implicated in mitochondrial Ca^{2+} uptake are Grp75, mitofusin-2 (Mfn2), PACS-2, Sigma-1 Receptor and Presenilins (for a more comprehensive review see reference Bravo-Sagua et al., 2013).

Also, peroxisomes and the Golgi apparatus are known to respond differentially with respect to uptake or release Ca^{2+} in response to agonists (Lasorsa et al., 2008; Wong et al., 2013). However, whether these processes are orchestrated by contact sites remains to be determined (Figs. 1 and 2).

2.2. Organelle interaction in lipid traffic

The ER–mitochondria interface, termed mitochondria-associated ER membranes (MAM), consists of a series of proteins that physically connect both organelles and regulate the flux of metabolites between ER and mitochondria. Another function of the MAM is the biosynthesis and transport of phospholipids due to the localization of essential enzymes for lipid metabolism within this domain of the ER (Rusiñol et al., 1994). Portions of the MAM might be enriched in cholesterol and raft-like microdomains, since cholesterol depletion decreases ER–mitochondria association and alters phosphatidylserine (PtSer) and phosphatidylethanolamine synthesis (Fujimoto et al., 2012).
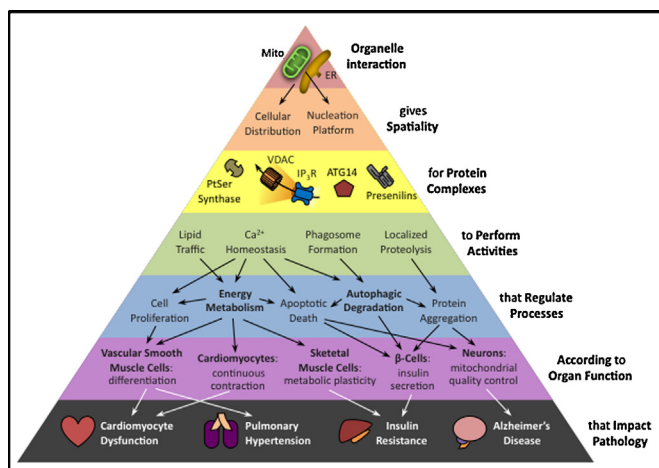
Fig. 2. Physiopathological implications of organelle interaction. The ER–mitochondria interface harbors many cellular processes, defining their localization within the cell and providing a nucleation platform for complex formation. Lipid biosynthetic enzymes (PtSer Synthase), Ca^{2+}-handling machinery (VDAC1-IP3R), autophagosome-seeding proteins (ATG14) and protease complexes (Presenilins), among others, regulate key functions whose interaction determines both homeostasis and disease.

Non-vesicular cholesterol transport also takes place at membrane contact sites, especially at the ER–PM and ER–Golgi interfaces. This process is mediated by cytosolic proteins such as oxysterol-binding protein (OSBP) and ceramide transfer protein (CERT), which bind both surfaces simultaneously via FFAT and PH domains (Levine and Loewen, 2006).

3. Cell physiology

3.1. Organelle contact sites form a signaling platform

Extensive cross-regulation of organelle function has been demonstrated to occur in organelle contact sites, especially between the ER and mitochondria. For example, Mfn2 silencing causes a loss of ER–mitochondria interaction sites, alterations in Ca^{2+} signaling, and both ER and mitochondrial dysfunction. These disturbances lead to the engagement of stress signals such as hydrogen peroxide elevation, JNK activation and ER stress, all of them linked to insulin resistance (Sebastián et al., 2012). Highlighting one of the MAM-associated signaling mechanisms, Gp78, a ubiquitin ligase involved in ER-associated degradation (ERAD), induces degradation of the mitochondrial fusion proteins Mitofusin-1 (Mfn1) and Mfn2, and leads to mitochondria fragmentation (Shankar et al., 2013). A different MAM-localized mechanism promoting mitochondria fragmentation is attributed to the constriction GTPase Drp1, a mediator of mitochondria fission (Friedman et al., 2011). The activity of Drp1 on the MAM depends on the ER-associated Rab32, which binds to PKA in order to inactivate Drp1 (Bui et al., 2010). The ER can also regulate Drp1 expression via the ER-residing BCL2/adenovirus E1B interacting protein 1 (BNIP1) (Ryu et al., 2012).

Autophagosome formation is another process dependent on organelle interaction. A recent study found that the ER–mitochondria interface serves as the site of autophagosome nucleation. After starvation, the pre-autophagosome markers ATG14 and ATG5 relocate to ER–mitochondria junctions. Loss of ER–mitochondria contact partially prevents autophagosome formation, suggesting that other sites can serve as the point of origin of autophagosome nucleation (Hamasaki et al., 2013).

3.2. ER and mitochondria at the edge between life and death

ER–mitochondria tethering provides locally elevated Ca^{2+} concentrations, allowing an efficient influx toward mitochondria. This Ca^{2+} influx is essential for cell bioenergetics, since it is required for Krebs cycle activity and ATP synthesis (Cárdenas et al., 2010). The importance of this mechanism is also seen under adverse conditions, such as ER stress, where it provides the necessary energy to restore homeostasis (Bravo et al., 2011). On the other hand, this local Ca^{2+} transfer, if deregulated, can lead to cell death. Excessive Ca^{2+} at the ER–mitochondria interface stimulates the opening of the mitochondrial permeability transition pore (MPTP), cytochrome c release, caspase activation and finally apoptosis (Bravo-Sagua et al., 2013).

3.3. Autophagosomes as executors of organelle quality control

The homeostatic role of autophagy involves both non-selective degradation, which supports basal turnover of cytoplasmic components, and selective degradation, which removes surplus or damaged structures. This second process requires selective targeting of organelles as well as their recognition and interaction with vacuoles or autophagosomes.

Pexophagy (Hutchins et al., 1999) and nucleophagy (Mijaljica et al., 2012) are the vacuolar degradation systems for peroxisomes and nucleus, respectively, however their molecular details in mammalian cells are not well understood yet. Mitophagy and ER-phagy occur via organelle sequestration into compartments called autophagosomes. This engulfment process requires mitochondria-autophagosome and ER-autophagosome interaction through adaptor molecules. Targeted mitochondrial degradation can occur either via ubiquitylation by the ubiquitin ligases Parkin or Mul1, or via depolarization mediated by the BH3-only proteins Nix or BNIP3 (Lokireddy et al., 2012; Ding and Yin, 2012). ER-phagy uses several autophagy genes induced by ER stress. Normally, stress in the ER leads to an increase in ER volume, in order to inhibit protein–protein aggregation. ER-phagy is the compensatory mechanism, leading to degradation of damaged parts of the ER and misfolded protein aggregates that cannot be degraded by other means (Bernales et al., 2006).

4. Organelle pathology: organelle communication in disease

Dynamic organelle interaction controls cell bioenergetics, substrate transport and Ca^{2+} homeostasis among others. Alterations in such interorganelle contacts directly affect cellular physiology and, as expected, are associated with pathology (Fig. 2).

For instance, ER–mitochondria contacts are relevant in the pathogenesis of pulmonary arterial hypertension. In this disease, Nogo-B, a stress-induced regulator of the ER structure, disrupts ER–mitochondria coupling, thereby impairing transfer of Ca^{2+} and phospholipids between them. This deregulation leads to hyperproliferation of pulmonary artery smooth muscle cells, favoring lumen obstruction (Sutendra et al., 2011).

On the other hand, Alzheimer's disease has been recently related to an increase in ER–mitochondria contacts. Such increments explain many of the biochemical and morphological changes that affect dopaminergic neurons. The latter notion is supported by the localization of presenilin 1 and 2 at MAM, where the amyloid precursor protein is processed to generate β-amyloid peptide (Area-Gomez et al., 2012). In contrast, the phosphatase and tensin homolog (PTEN), the mammalian target of rapamycin complex 2 (mTORC2) and the promyelocytic leukemia (PML) protein (Betz et al., 2013; Bononi et al., 2013) use this location to promote

mitochondria metabolism, presumably in order to keep glycolysis low in normal tissue.

ER–PM contacts are also relevant in disease, due to their essential role in SOCE. Interestingly, it has been reported that Mfn2 participates in this mechanism by recruiting polarized mitochondria to ER–PM contact sites, thereby increasing their Ca^{2+} buffering potential, which stimulates Orai1 activation and prevents cytosolic Ca^{2+} accumulation (Singaravelu et al., 2011). In diseases like Charcot–Marie–Tooth type 2A (CMT2A), where Mfn2 is mutated (Züchner et al., 2004), organelle contacts are lost, and with them the communication of the mitochondrial polarization state. This in turn is expected to cause deregulation of Ca^{2+} influx in a manner relevant to the pathogenesis of CMT2A. Likewise, loss of Mfn2 in cardiomyocytes reduces the contact area between sarcoplasmic reticulum (ER of muscle cells) and mitochondria, leading to impaired protein association at MAM and subsequently to abnormal Ca^{2+} signaling and bioenergetics (Chen et al., 2012).

Together, the evidence provided implicates malfunction of organelle contact sites as an initial common mechanism, albeit in distinct cell types, for diseases like arrhythmia, heart failure and CMT2A. In fact, down-regulation of Mfn2 has been observed in cardiac hypertrophy in rats (Fang et al., 2007) and in skeletal muscles of patients with type 2 diabetes or obesity (Bach et al., 2005).

Despite the evident importance of interorganelle contacts and signaling for various diseases and disorders, further research is required to determine whether the alterations observed are the cause or a consequence of such pathologies.

5. Future outlook

Multiple diseases have been studied by analyzing individual organelles, pinpointing specially mitochondria or the ER as the sole cause for pathogenesis. Communication between organelles, however, has so far little attention in biomedicine. Nonetheless, emerging evidence suggests that we may have only detected the tip of the iceberg concerning the impact of interorganelle cross-talk in the etiology of numerous diseases ranging from neurodegenerative disorders, to cardiac and pulmonary failures, diabetes and cancer. Therefore, simpler, high-throughput indicators of physical and functional organelle interaction are needed to remedy this situation, as are also means to manipulate said interactions. The modulation of organelle contacts during processes such as aging and infectious diseases is another important area that needs to be investigated. To date pioneering studies have developed tools to measure ER–mitochondria apposition and Ca^{2+} concentrations at their interface (Csordás et al., 2010; Alford et al., 2012); nonetheless, they still require further refining, as well as extension to other organelle contacts in shaping Ca^{2+} signals. Autophagosome-, lysosome- and peroxisome-mediated contacts are unexplored facets that may be crucial in the mechanism of diseases like aggregopathies, microbial infections and metabolic disorders, where aforementioned organelles are of particular relevance. Furthermore, the development of molecules that target organelle interactions is also a field with potential impact in the treatment of diseases, particularly those that compromise cellular bioenergetics and organelle quality control.

Conflict of interest

None.

Acknowledgements

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