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Review

Calcium trafficking integrates endoplasmic reticulum function with mitochondrial bioenergetics☆

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ABSTRACT

Calcium homeostasis is central to all cellular functions and has been studied for decades. Calcium acts as a critical second messenger for both extracellular and intracellular signaling and is fundamental in cell life and death decisions (Berridge et al., 2000) [1]. The calcium gradient in the cell is coupled with an inherent ability of the divalent cation to reversibly bind multiple target biological molecules to generate an extremely versatile signaling system [2]. Calcium signals are used by the cell to control diverse processes such as development, neurotransmitter release, muscle contraction, metabolism, autophagy and cell death. "Cellular calcium overload" is detrimental to cellular health, resulting in massive activation of proteases and phospholipases leading to cell death (Pinton et al., 2008) [3]. Historically, cell death associated with calcium ion perturbations has been primarily recognized as necrosis. Recent evidence clearly associates changes in calcium ion concentrations with more sophisticated forms of cellular demise, including apoptosis (Kruman et al., 1998; Tombal et al., 1999; Lynch et al., 2000; Orrenius et al., 2003) [4–7]. Although the endoplasmic reticulum (ER) serves as the primary calcium store in the metazoan cell, dynamic calcium release to the cytosol, mitochondria, nuclei and other organelles orchestrate diverse coordinated responses. Most evidence supports that calcium transport from the ER to mitochondria plays a significant role in regulating cellular bioenergetics, production of reactive oxygen species, induction of autophagy and apoptosis. Recently, molecular identities that mediate calcium traffic between the ER and mitochondria have been discovered (Mallilankaraman et al., 2012a; Mallilankaraman et al., 2012b; Sancak et al., 2013)[8–10]. The next questions are how they are regulated for exquisite tight control of ER–mitochondrial calcium dynamics. This review attempts to summarize recent advances in the role of calcium in regulation of ER and mitochondrial function. This article is part of a Special Issue entitled: Calcium signaling in health and disease. Guest Editors: Geert Bultynck, Jacques Haiech, Claus W. Heizmann, Joachim Krebs, and Marc Moreau.

1. Introduction

In 1883, Ringer recognized that addition of calcium (Ca^{2+}) to heart cultures caused their contraction [2,11] which spawned a new field regarding how Ca^{2+} controls cellular function. Now it is recognized that the ubiquitous second messenger Ca^{2+} is intricately involved in a wide spectrum of physiological functions, including signal transduction, muscle contraction, secretion of proteins and hormones and gene expression. About 50 years ago it was recognized that energized mitochondria rapidly uptake Ca^{2+} in response to an acute increase in the cytosolic $[Ca^{2+}]_c$ [12,13]. The discovery of Ca^{2+} probes that measure local Ca^{2+} concentrations within single cells provided new tools to study Ca^{2+} signaling, including the Ca^{2+} sensitive jellyfish aequorin which is engineered to target subcellular organelles, in response to a variety of physiological stimuli [14–16]. We now know that cytosolic Ca^{2+} concentrations $[Ca^{2+}]_c$ can vary by several orders of magnitude and trigger cascades of cellular events including contraction of myofilaments, secretion of hormones and neurotransmitters, induction of various forms of cell death (necrosis, apoptosis and autophagy) and, more recently neurodegenerative pathways. Under resting conditions cytosolic $[Ca^{2+}]_c$ is finely tuned at ~100 nM by the coordinated activity of Ca^{2+} pumping mechanisms that include plasma membrane Ca^{2+} ATPases and the Na^+/Ca^{2+} exchanger that actively mobilize Ca^{2+} from internal to external stores [1]. Within the cell, Ca^{2+} is stored in specialized compartments mainly in the endoplasmic reticulum (ER) and sarcoplasmic reticulum (SR, a specialized ER counterpart in muscle cells) as well as in other membrane-bound compartments, including the Golgi apparatus, lysosomes and endosomes [3,17]. The fine-tuning of $[Ca^{2+}]_c$ is accomplished through pumps, channels and buffering proteins that are located within the cytosol and in the ER/SR that coordinately regulate cellular Ca^{2+} homeostasis and signaling. Exquisite regulation of the Ca^{2+} concentration in different subcompartments of the cell is essential for cell function considering the fact that the

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extracellular medium has an unlimited Ca^{2+} reservoir, ~1 mM, and intracellular subcompartments (also known as Ca^{2+} stores) may have $[Ca^{2+}]$ of ~100 μM that facilitate rapid release through channels and reuptake through Ca^{2+} pumps. With the observation of the close juxtaposition of ER and mitochondria [18], interest grew in the mechanisms that drive local Ca^{2+} uptake from subdomains of the ER/SR to the mitochondrial matrix. The activities of pumps and channels that regulate the luminal ER $[Ca^{2+}]_{ER}$ are also regulated by the $[Ca^{2+}]_{ER}$. Here, we discuss the precise role of the ER and mitochondria in Ca^{2+} homeostasis and allude to the significance of ER–mitochondria cross-talk in further facilitating Ca^{2+} trafficking to regulate bioenergetics, production of reactive oxygen species (ROS), ER protein folding and induction of apoptosis and autophagy.

2. ER Ca^{2+} homeostasis

The ER is now recognized as the major Ca^{2+} storage organelle of the metazoan cell (Fig. 1). The ER regulates Ca^{2+} homeostasis through the presence of many Ca^{2+} binding proteins that function as buffers by having a low-affinity and large capacity for Ca^{2+} binding. These proteins, of which the most abundant are the protein chaperones calreticulin (CRT), calnexin (CNX), BiP/GRP78, GRP94 and protein disulfide isomerase (PDI), are responsible for maintaining ER Ca^{2+} concentration within a physiological range of ~100–200 μM. Ca^{2+} binding to molecular chaperones BiP, GRP94, PDI and ERP57 also regulates their chaperone activities [19,20]. As a consequence, alterations in $[Ca^{2+}]_{ER}$ can disrupt protein folding, cause accumulation of misfolded proteins and initiate signaling of the unfolded protein response [21,19,22]. BiP functions in the ER as a peptide-dependent ATPase and utilizes ATP to prevent protein aggregation [23,24]. BiP hydrolysis of ATP may deplete luminal ATP and initiate a signal to release Ca^{2+} to stimulate oxidative phosphorylation to maintain the ATP/ADP ratio. CRT and CNX are molecular chaperones that interact with specific glycoforms on asparagine-linked glycans to promote proper disulfide bond formation through interaction with the thiol-disulfide isomerase ERP57 [25] and direct protein trafficking and ER-associated protein degradation [26,27]. Finally, PDI and ERO1 provide an electron transport pathway from thiol residues to molecular oxygen during disulfide bond formation [28]. In addition to molecular chaperones, calsequestrins and chromogranins also buffer $[Ca^{2+}]_{ER}$.

Ca^{2+} accumulation in the ER lumen is mediated by the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA). The SERCAs are encoded by three genes (SERCA1, SERCA2, and SERCA3), but their variety and activity is diversified by the existence of splice variants [29]. The SERCAs have four domains: a nucleotide binding domain, a phosphorylation

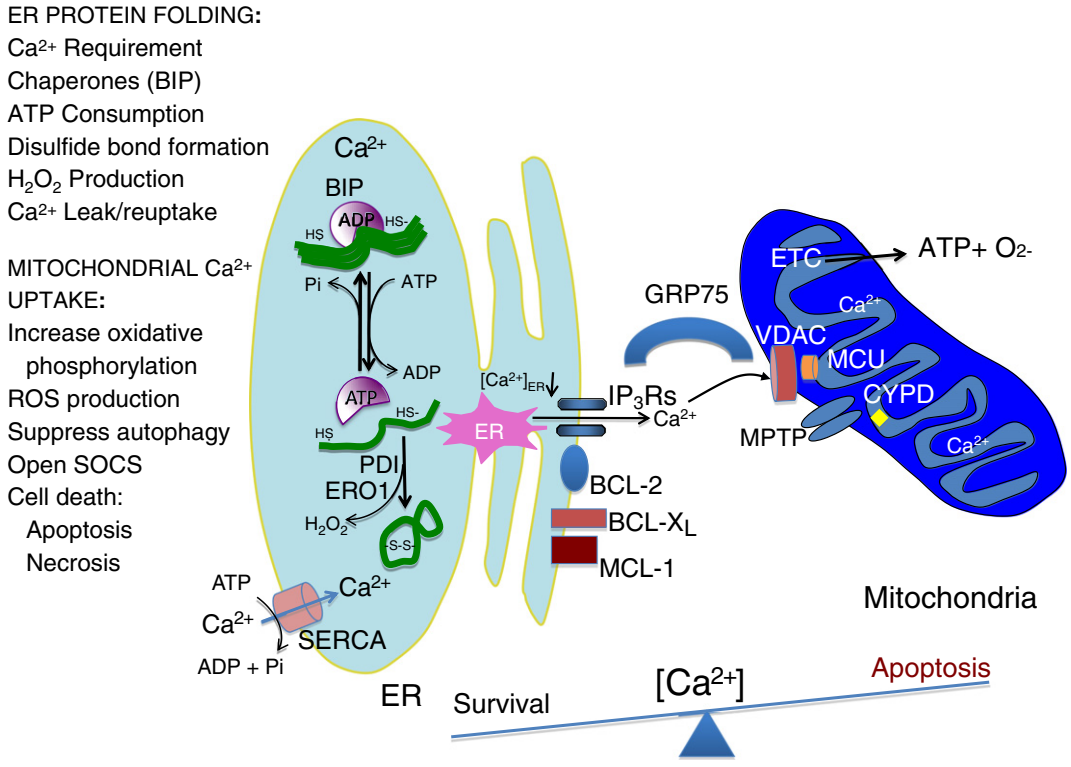

Fig. 1. Schematic representing how protein folding in the ER modulates mitochondrial ATP and ROS production. Mitochondria and ER are tethered by the actions of the MFNs, of which MFN2 is localized to the mitochondrial-associated membrane (MAM), that promotes efficient Ca^{2+} transfer from the ER to the mitochondria. Ca^{2+} loading in the ER is mediated by the abundance of Ca^{2+}-binding proteins, including CNX, CRT, as well as the protein chaperones BiP and PDI. Protein folding in the ER requires Ca^{2+} and ATP for chaperone function, proper glycosylation, and correct disulfide bond formation. Misfolded proteins may sequester protein chaperones which facilitate the opening of Ca^{2+} channels to initiate Ca^{2+} transfer to mitochondria to stimulate oxidative phosphorylation. Ca^{2+} transfer occurs through the activity of several Ca^{2+} channels that include the ER localized inositol-1,4,5-triphosphate receptors (IP_3Rs), as well as the ryanodine receptors (RyRs) and the mitochondrial-localized voltage-dependent anion channel (VDAC) and the mitochondrial Ca^{2+} uniporter complex MCU (MCU, including MICU1, MICU2, MCUR1 and EMRE). The IP_3Rs enriched at the MAMs are linked to VDAC on the OMM by the protein chaperone GRP75. VDAC tightly controls Ca^{2+} permeation into mitochondria by IP_3R-mediated Ca^{2+} signals. Once Ca^{2+} transverses the OMM it can subsequently cause depolarization of the inner mitochondrial permeability transition pore (MPTP) and induction of apoptotic stimuli. Conditions that prevent Ca^{2+} transfer from the ER to mitochondria include overexpression of anti-apoptotic proteins such as BCL-2 and BCL-XL and constitute survival signaling. A number of mechanisms have been proposed to cause Ca^{2+} leak from the ER and are depicted as red identities on the ER membrane (SEC61, SERCA1T, BCL-2, BCL-XL, MCL-1, BI-1 and IP_3Rs). As Ca^{2+} accumulates in mitochondria, cells are predisposed to disruption of the electron transport chain (ETC) to produce ROS, MPTP, mitochondrial swelling, disruption of the OMM, release of cytochrome *c* and apoptosome components leading to caspase activation and apoptosis. Mechanisms that limit mitochondrial loading of Ca^{2+} include MPTP itself, and the mitochondrial Ca^{2+} exchangers NCLX and HCX. In addition to protein synthesis, ATP-utilizing processes include chaperone (BiP)-assisted protein folding in the ER lumen, SERCA-mediated Ca^{2+} reuptake into the ER and possibly hydrolysis of ATP by the F_1/F_0 ATP synthase upon collapse of the IMM electro-chemical potential. Finally, in addition to superoxide production from the ETC, disulfide bond formation mediated by the protein thiol-disulfide isomerases (PDI, ERP57) and ER oxidase 1 (ERO1) generates hydrogen peroxide upon electron transport to molecular O_2 as the acceptor. The balance between the amount of Ca^{2+} stored in the ER lumen and the amount loaded into the mitochondrial matrix may be a determinant in the decision between survival and death.