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Review

Redox dependence of endoplasmic reticulum (ER) Ca^{2+} signaling

Arun Raturi, Carolina Ortiz-Sandoval and Thomas Simmen
Department of Cell Biology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

Summary. The endoplasmic reticulum (ER) is a multifunctional organelle that accommodates a large array of functions. Recent publications have shown that many of these functions are influenced by the ongoing oxidative folding of secretory and membrane proteins. Conversely, successful ER protein folding critically depends on the cellular redox state, but also the availability of Ca^{2+}. These findings suggest the existence of regulatory mechanisms that steer ER Ca^{2+} homeostasis according to the cellular redox state. Indeed, accumulating evidence demonstrates that ER Ca^{2+} uptake and release by sarco-endoplasmic reticulum Ca^{2+} transport ATPases (SERCAs), stromal interaction molecule 1 (STIM1), Orai1, inositol 1,4,5-trisphosphate (IP3) receptors (IP3Rs) and ryanodine receptors (RyR) depends on redox modifications of these channels and pumps. In addition, ER chaperones and oxidoreductases moonlight as regulators of ER Ca^{2+} channels and pumps. Discrete redox conditions of channels, pumps and oxidoreductases exist that allow for opening and closing. Through these functions, redox regulation of ER Ca^{2+} influences signaling mechanisms governing cell growth and migration, apoptosis and mitochondrial energy production. Therefore, pharmacological intervention based on ER redox or on ER redox-sensitive chaperones and oxidoreductases is a promising strategy to influence all metabolic syndromes including cancer and neurodegeneration.

Offprint requests to: Thomas Simmen, Department of Cell Biology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada. e-mail: Thomas.Simmen@ualberta.ca

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Introduction

Contrary to the historic view that the endoplasmic reticulum (ER) is nothing but the origin of protein secretion, this organelle has emerged over the past decade as a superorganelle that accommodates multiple functions within one continuous membrane system (Lynes and Simmen, 2011). Nevertheless, protein secretion that is preceded by the manufacture of secretory proteins via chaperone-mediated protein folding remains to be seen as a central determinant of many functions of the ER (Simmen et al., 2010). The cellular redox conditions largely regulate the progression of this mechanism (Merksamer et al., 2008). A similarly important connection occurs between the ER Ca^{2+} content and the progression of ER protein folding (Burdakov et al., 2005; Sammels et al., 2010). Importantly, the ER Ca^{2+} and ER redox conditions are tightly connected, as shown by the rapid reduction of the ER redox potential specifically upon loss of ER Ca^{2+}, which is, however, not observed after the mere accumulation of unfolded proteins (Avezov et al., 2013; Birk et al., 2013). While papers by us and others have demonstrated that ER protein folding chaperones can form a functional bridge between cellular redox conditions and ER Ca^{2+} content (Higo et al., 2005; Li et al., 2009; Lynes et al., 2013), ER Ca^{2+} import and release is also under the direct control of cellular redox

conditions, a link known for close to five decades (Yu et al., 1967). Similarly, early studies demonstrated that mitochondria-derived Ca^{2+}, another important determinant of cellular Ca^{2+}, is released depending on the redox state of mitochondrial nicotinamide (Lehninger et al., 1978; Lotscher et al., 1980). Redox controls operating at the level of the ER started to become unraveled with key experiments demonstrating that the presence of reduced, cytoplasmic glutathione restores Ca^{2+} import via sarco-endoplasmic reticulum Ca^{2+} transport ATPase (SERCA) into the ER upon oxidative stress (Jones et al., 1983; Orrenius et al., 1984). In contrast, oxidized glutathione maintains the release of Ca^{2+} from the ER through inositol 1,4,5-trisphosphate (IP3) receptors (IP3Rs) (Renard-Rooney et al., 1995). Similarly, the oxidation of ryanodine receptors also favors their opening and, hence, promotes Ca^{2+} release from the ER (Xia et al., 2000). The complexity of ER Ca^{2+} signaling has been nicely covered by several recent reviews (Berridge, 2009; Sammels et al., 2010; Stutzmann and Mattson, 2011). In this manuscript, we will focus on the redox regulation of this mechanism instead. By doing so, the redox regulation of ER Ca^{2+} signaling determines the amount of Ca^{2+} available in the cytoplasm and the mitochondria. ER Ca^{2+} content and release play a paramount role for cell growth and migration (Inesi et al., 1980), ER oxidative protein folding (Simmen et al., 2010), apoptosis (Giorgi et al., 2012) and mitochondria metabolism (Glancy and Balaban, 2012), extensively reviewed by us elsewhere (Raturi and Simmen, 2013). Therefore, the redox regulation of ER Ca^{2+} channels and pumps provides a direct mechanism that ties cellular redox conditions to these critical cell properties.

Redox regulation of SERCA

As a prerequisite for ER Ca^{2+} signaling, SERCAs import Ca^{2+} into the lumen of the ER at the expense of one mole of ATP per two moles of Ca^{2+} (Inesi et al., 1980). Energy for this activity is typically provided by mitochondria or alternatively by glycolysis (Florea and Blatter, 2010, 2012). Three human genes give rise to more than 10 different isoforms of these Ca^{2+} pumps through alternative splicing, all about 97-115 kDa transmembrane proteins (Periasamy and Kalyanasundaram, 2007). Of the 10 known isoforms of SERCA, the predominant housekeeping form of SERCA in non-muscle cells is SERCA2b, whereas in skeletal muscle and cardiac muscle, the dominant forms are SERCA1a and SERCA2a respectively (Periasamy and Kalyanasundaram, 2007). The SERCA3 pumps are restricted to hematopoietic cell lineages including platelets, mast cells, T cells, epithelial cells, fibroblasts, and endothelial cells (Periasamy and Kalyanasundaram, 2007).

The central regulatory mechanism of the activity of SERCAs is based on the redox state of a critical thiol, the conserved cysteine 674 (Tong et al., 2010). This residue, found in all SERCA isoforms within the ATP binding P domain (Autry et al., 2012), is very reactive and modulates pump activity (Bishop et al., 1988). Whereas mild oxidation leads to the glutathionylation of cysteine 674 and increases pump activity, chronic oxidation results in the oxidation of other cysteines, for instance the less reactive adjacent cysteine 669, and causes irreversible sulphonylation of cysteine 674 that completely shuts the ATPase pump (Adachi et al., 2004). This bell-shaped behavior of SERCA suggests that it determines ER Ca^{2+} signaling in a reactive oxygen species (ROS) dependent manner, which could critically impact the roles of SERCA, in particular during apoptosis. This important function of SERCA appears to be blunted in tumor cells, but can be rescued by lowering the level of ROS with N-acetyl-cysteine (Li et al., 2011). Lowering ROS levels also rescues SERCA amounts (Li et al., 2011), which are frequently low in tumor cells (Papp et al., 2004; Brouland et al., 2005). In contrast, the administration of the malaria drug artemisinin inactivates SERCA in a ROS-dependent manner and acts as cytotoxic for tumor cells (Wondrak, 2009). Together, these findings suggest that a close control of SERCA activity via the pharmacological manipulation of cellular redox conditions is a potential approach to contain cancer (Denmeade and Isaacs, 2005; Denmeade et al., 2012).

In heart tissue, the activity of SERCA2b is under the control of nitric oxide (NO), which activates it through the specific oxidation of cysteine 674 (Tong et al., 2010). In this mechanism, NO requires the secondary generation of reactive nitrogen species such as NO^2, N_2O_3, NO^- or $ONOO^-$ (peroxynitrite), which generate S-glutathionylated (GSS-) SERCA2b at cysteine 674 (Adachi et al., 2004). As a consequence, the stimulation of SERCA by NO reduces intracellular Ca^{2+} levels in smooth muscle cells, leading to their relaxation (Adachi et al., 2004). Consistent with these functional connections between cardiomyocyte activity, ROS and SERCA, the exposure of cardiomyocytes to oxidative stress caused by 100 μm H_2O_2 inhibits SERCA (Qin et al., 1998). This, together with the activation of Na/Ca exchangers, leads to a phenotype that is characterized by i) reduced contractile amplitude; ii) reductions in systolic intracellular Ca^{2+} and in the amplitude of the Ca^{2+} transient, and iii) depletion of the sarcoplasmic reticulum Ca^{2+} store (Kuster et al., 2010). Interestingly, nitroxyl (HNO), the protonated form of NO, has a similar effect like peroxynitrite and increases Ca^{2+} cycling in cardiac myocytes by increasing the S-glutathionylation and, hence, activity of SERCA, as well (Lancel et al., 2009). Together, these findings suggest that the redox-dependent modulation of the SERCA activity is not restricted to one oxidant, but is rather a general phenomenon.

In addition to determining cardiomyocyte contractility, intracellular Ca^{2+} that is under the control of SERCA activity also inhibits smooth muscle cell migration (Ying et al., 2007). This process is triggered

by the presence of excess ROS and reactive nitrogen species (RNS), specifically NO, that occurs for instance from inflammation and interleukin 1ß production associated with hypertension, heart tissue injury or diabetes, and can induce cardiovascular pathology and reduced blood flow via restenosis (San Martin and Griendling, 2010). Interestingly, the intrinsic activation of iNOS by interleukin 1ß that normally promotes the migration of smooth muscle cells in the presence of wild type SERCA does not occur in smooth muscle cells that express a mutant C674S SERCA (Ying et al., 2007). The incubation of smooth muscle cells in high glucose medium triggers the hyperoxidation of SERCA, which also blocks NO from inhibiting migration (Tong et al., 2008), because this condition leads to the upregulation of NADPH oxidase that increases ROS production and irreversibly oxidizes cysteine 674 of SERCA (Tong et al., 2010). These findings provide an important link between the redox regulation of SERCA and the etiology and treatment of diabetes, where NO-mediated regulation of SERCA is expected to be largely non-functional. Moreover, the *in vivo* administration of tempol, an antioxidant, not only prevents the effect of high glucose, but also prevents restenosis observed in the fructose-induced Type 2 diabetic rat perhaps, in part, via its effects on SERCA (Tong et al., 2008). Similar treatment avenues could exist in the case of hypercholesterolemia, where the activity, but not the amount of SERCA is decreased in smooth muscle cells (Adachi et al., 2001). Similarly, wild type SERCA2b, but not its C674S mutant nullify the inhibitory effect of high glucose medium on smooth muscle cell migration (Tong et al., 2008). Recent publications have demonstrated increased oxidation of SERCA during aging that can be counteracted via the activation of antioxidant enzymes, which would propose this mechanism as a treatable factor in cardiovascular failure associated with aging (Babusikova et al., 2012; Mital et al., 2011).

While the cytosolic domains dominate in the regulation of SERCA activity (Fig. 1), also shown by the redox-independent regulatory mechanisms based on the small proteins phospholamban (Kranias and Hajjar, 2012) and Hax-1 (Simmen, 2011), luminal interactions of SERCA with ER chaperones and oxidoreductases can nevertheless also significantly modulate SERCA activity. The ER luminal soluble thioredoxin-related protein ERp57 has been proposed to interact with SERCA2b in the luminal L7-8 loop, where it promotes disulfide bond formation between two conserved cysteines (cysteines 875 and 887 in SERCA2) and leads to a decrease in the activity of SERCA in the presence of high luminal ER Ca^{2+} concentrations (Li and Camacho, 2004). Recently, based on genetic and molecular studies that demonstrate the inactivity of SERCA2b upon mutation of the very same cysteines, this observation has been challenged (Vandecaetsbeek et al., 2009). Nevertheless, ERp57 is found significantly upregulated upon heart failure, suggesting a potential role of this oxidoreductase in this pathology (Vitello et al., 2012). The role of calnexin as a luminal regulator of SERCA2b activity has been in flux over the years as well: whereas it had initially been proposed that calnexin associates with SERCA2b to inhibit this Ca^{2+} pump under conditions of high ER Ca^{2+} content (Roderick et al., 2000), our lab has recently published, using calnexin knockout cells, that calnexin performs an activating role on ER Ca^{2+} filling that depends on its interaction with SERCA2b (Lynes et al., 2013). Another study has demonstrated decreased ER Ca^{2+} uptake upon transfection with calnexin RNAi as well (Bousette et al., 2013). Interestingly, the calnexin-SERCA2b interaction is lost upon ER stress or a reducing environment inside this organelle, suggesting that the ER needs to be oxidizing to allow for full SERCA activity. Our findings demonstrate a subtle Ca^{2+} signaling phenotype in the absence of calnexin, which is characterized by a loss of stress responsiveness of ER-mitochondria Ca^{2+} transfer, but no difference in the accumulation of cytoplasmic Ca^{2+} upon inhibition of SERCA, as observed by others as well (Zuppini et al., 2002). In the heart, calnexin expression determines the stability of SERCA that then impacts on the viability of cardiomyocytes, albeit by currently unclear mechanisms (Bousette et al., 2013). In addition to interacting with SERCA, calnexin also localizes to the translocon (Lakkaraju et al., 2012), from where it may prevent passive Ca^{2+} leakage in a manner not involving SERCA (Van Coppenolle et al., 2004). Interestingly, the downregulation of calnexin is also associated with metastasis of melanoma, suggesting that inhibition of SERCA or increased passive Ca^{2+} leakage from the ER, associated with increased levels of cytosolic Ca^{2+}, could also play a role in tumor cell migration (Dissemond et al., 2004). In addition to interacting with ERp57 and calnexin, SERCA interacts with calreticulin, an interaction that is critical for heart development, but is apparently not directly redox-dependent (Michalak et al., 2004), although calreticulin augments the sensitivity of SERCA2a to oxidative stress (Ihara et al., 2005).

Redox regulation of the IP3R

An important component of ER Ca^{2+} signaling is the release of Ca^{2+} from the ER. The inositol 1,4,5-triphosphate receptor (IP3R), present as three isoforms in humans, is one of two major Ca^{2+} channels that regulate Ca^{2+} release from the ER and sarcoplasmic reticulum (SR). IP3Rs open in response to an increase in IP3 generated following the activation of G-protein or tyrosine kinase-linked receptors on the plasma membrane (Mikoshiba, 2007), as well as phospholipase C (PLC) downstream of Ras (van Rossum et al., 2004). Almost all cells express the three forms of IP3Rs to some extent (Bezprozvanny, 2005). Whereas neuronal and smooth muscle cells exhibit high amounts of IP3R1 (Furuichi et al., 1993), IP3R2 is found highly expressed in liver (Newton et al., 1994; Wojcikiewicz, 1995) and is the most abundant form in skeletal and cardiac muscle

(De Smedt et al., 1997). A critical property of IP3R-mediated Ca^{2+} release is that increased amounts of cytosolic Ca^{2+} promote it. This property of IP3Rs depends on the binding of Ca^{2+} to IP3Rs, which results in their opening (Finch et al., 1991). However, very high amounts of cytosolic Ca^{2+} above 250 nM inhibit IP3Rs (Bezprozvanny et al., 1991). The redox dependence of IP3R Ca^{2+} release is not as well known as the Ca^{2+}-mediated regulation of its activity. While oxidized glutathione can alter the binding properties of IP3 to its

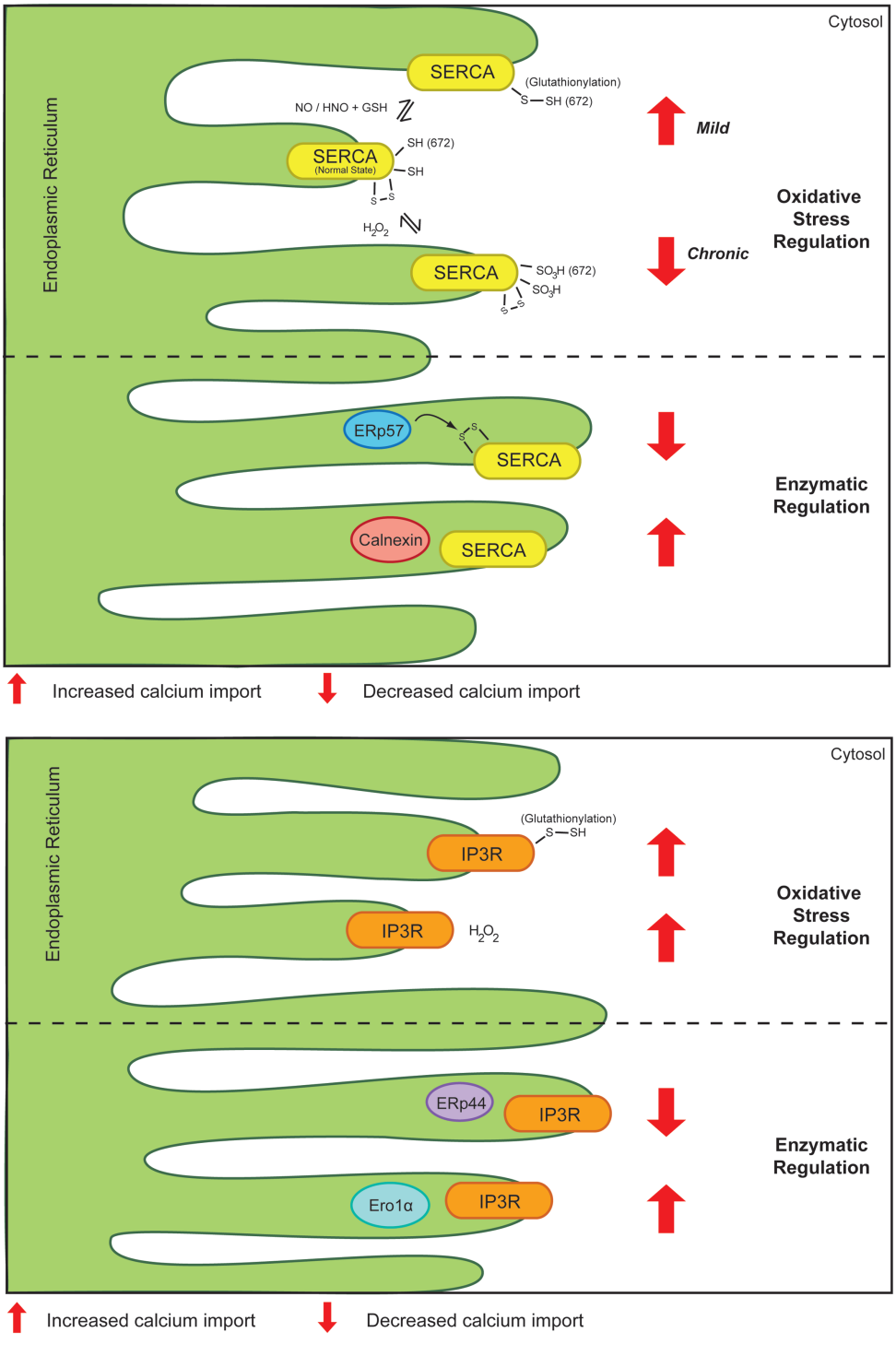

Fig. 1. Diagram of SERCA (top) and IP3R (bottom) redox regulation. Cytosolic glutathionylation of SERCA leads to a bell-shaped response, where mild oxidation acts as activating, whereas chronic activation acts inhibitory. Oxidative stress also regulates the IP3R. On the luminal side, ERp57 and calnexin act as inhibitors and activators of SERCA, respectively. Similar activities are perform by ERp44 (inhibitory) and Ero1α (activating), respectively.

receptor, this may be an indirect effect (Renard-Rooney et al., 1995). Alkylation by thimerosal can sensitize IP3R to IP3, an effect, which is blocked by DTT (Bootman et al., 1992). A recent study demonstrated that increased cytosolic H_2O_2 levels promote the glutathionylation of IP3R1, which subsequently increases its sensitivity to Ca^{2+}, reminiscent of glutathionylation-mediated regulation of SERCA (Lock et al., 2012). In contrast to SERCA (Fig. 1), the cysteine residue(s) responsible for this regulation are currently unknown, presumably due to their number exceeding 60 per molecule and about 24 of them being oxidized at resting conditions (Joseph et al., 2006; Kang et al., 2008). It is also currently unknown, whether this post-translational modification occurs on the cytoplasmic face or in the luminal region, where a glutathione-sensitive formation of a disulfide bond between cysteines 2456 and 2464 had been discovered earlier (Kang et al., 2008).

Similar to SERCA, redox regulation of IP3R also occurs via interaction of this Ca^{2+} release channel with ER luminal chaperones and oxidoreductases (Simmen et al., 2010). This regulatory mechanism is expected to be critical for apoptosis progression, since during this process, cytochrome c binding to IP3Rs dramatically accelerates cell death (Boehning et al., 2003). For instance, ERp44 directly inhibits the channel activity of the IP3R1 under reducing conditions (Higo et al., 2005). This interaction, which occurs on three conserved cysteines of the loop 3 region, blocks the progression of apoptosis. It has been also shown that an IP3R1-tetramer can sense ER stress through its interaction with the ER chaperone BiP/GRP78, thereby regulating ER stress-dependent neuronal cell death (Higo et al., 2010). In addition, ER oxidoreductin 1 α (Ero1α), another ER oxidoreductase, localizes to the ER-mitochondria interface in a cell stress-dependent manner (Gilady et al., 2010), where it can interact with IP3R1. This interaction is hypothesized to result in disulfide bond formation and in the opening of this Ca^{2+} channel, the promotion of Ca^{2+} signaling between the ER and mitochondria and thus, the acceleration of apoptosis (Li et al., 2009; Anelli et al., 2012).

Redox regulation of the ryanodine receptor

Human cells express three isoforms of the ryanodine receptor (RyR). They are known as RyR1, RyR2 and RyR3 (Lanner et al., 2010). In humans, each isoform has about 5000 amino acid residues, which are encoded by three different genes found on chromosomes 19, 1, and 15, respectively. The name of the receptor originates from the plant alkaloid ryanodine that specifically binds to the receptor (Valdivia and Coronado, 1989). RyR1 is primarily expressed in skeletal muscle, and in lower levels in cerebellum, spleen, ovary, testis and adrenal gland (Lanner et al., 2010). Conversely, RyR2 is predominantly found in skeletal and cardiac muscle, lung and brain (Takeshima et al., 1989; Zorzato et al., 1990), RyR3 is also found in the nervous system, heart and testis (Nakai et al., 1990; Otsu et al., 1990). These channels release Ca^{2+} from the SR/ER upon activation triggered by the binding of ions such as Ca^{2+} and Mg^{2+}, while their activity is modulated via phosphorylation by the kinases cAMP-dependent protein kinase (PKA) or Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) (Niggli et al., 2013). Each isoform of RyRs contain between 80 and 100 cysteines in one monomer, out of which many (about 25) are redox-sensitive, which makes RyRs suitabile candidates for redox modifications and oxidation (Xu et al., 1998). In 1994, Pessah and coworkers provided evidence of the existence of redox-sensitive cysteine residues on the RyR using a fluorogenic thiol-reactive probe and showed how this hyperactivity of cysteines plays a crucial role in regulating their gating (Liu et al., 1994). Specifically, the oxidation of RyR1 thiols located on the cytosolic face of the SR has multiple outcomes and affects i) the channel's gating properties ii) the ability of ions, nucleotides and caffeine to modulate RyR opening and iii) the ability of the RyRs to bind to calstabin and calmodulin, two proteins that determine Ca^{2+} from the SR via the RyR (Zhang et al., 1999; Aracena et al., 2005). Similar to the activities of SERCA and IP3R, RyR opening is regulated by the cellular redox state in a bell-shaped curve: whereas reducing conditions do not allow for RyR opening (Xu et al., 1998; Sun et al., 2008), mildly oxidizing conditions activate RyR Ca^{2+} release (Boraso and Williams, 1994) and can lead to RyRs to become glutathionylated (Aracena et al., 2005). Such conditions can also modulate the activity of RyRs indirectly via oxidation-mediated activation of CaMKII (Erickson et al., 2008). The oxidation of RyR cysteines is coupled to the cellular oxygen tension (Sun et al., 2013), but when oxidizing conditions become very high or chronic, RyR do not release Ca^{2+} (Xu et al., 1998).

RyR nitrosylation in the presence of peroxynitrite is thought to be another redox-dependent regulatory mechanism of RyR, since the inhibition of NOS blunts RyR activity (Petroff et al., 2001). The activity of NOS occurs via the formation of S-nitroso derivatives on cysteine 3635 (Sun et al., 2001); the redox state of other RyR cysteines is tied to the activity of NOS and oxygen tension (Eu et al., 2000). Consistent with its role in the regulation of Ca^{2+} release from the ER, also the RyR has to be functional for apoptosis to progress normally (Mariot et al., 2000). This property could be particularly critical in the presence of quinone drugs. These compounds, including etoposide and doxorubicin, directly activate the RyR by binding and oxidizing critical thiols of the receptor, thus triggering Ca^{2+} release from the ER (Feng et al., 1999; Fabisiak et al., 2000). Whether it is this property or other damaging effects of these drugs that ultimately triggers apoptosis is currently unclear. While the structure of the RyR shows homology to IP3R, suggesting overall similar mechanisms of regulation (Yuchi and Van Petegem, 2011), no mechanism has so far been discovered that recapitulates

the regulation of the IP3R using ER chaperones and oxidoreductases to determine the activity of the RyR, although the existence of such a mechanism appears highly likely.

Store-Operated Ca^{2+} Entry (SOCE)

The connection between ER oxidative protein folding and Ca^{2+} is very clear in the case of the recently described entry of Ca^{2+} into the ER occurring at the plasma membrane (Nunes and Demaurex, 2013). This mechanism is both redox-sensitive and also regulated by the luminal ER oxidoreductase ERp57. Store-operated Ca^{2+} entry (SOCE) is triggered when ER Ca^{2+} is depleted via the action of IP3Rs or RyRs (Cahalan, 2009). This mechanism depends on the loss of binding of Ca^{2+} to the ER single transmembrane protein stromal interaction molecule 1 (STIM1) to its EF hand domain (Roos et al., 2005). Unbound STIM1 undergoes a conformational change that leads to its translocation to the plasma membrane (Zhang et al., 2005). Here, STIM1 can interact with Orai1 Ca^{2+} entry channels that allow Ca^{2+} to enter the cell from the outside (Prakriya et al., 2006; Yeromin et al., 2006). Importantly, STIM1 remains associated with ER membranes during the entire process (Srikanth and Gwack, 2012). This allows the ER oxidoreductase ERp57 to interact with STIM1 on two conserved cysteines (49 and 56), which inhibits SOCE (Prins et al., 2011). Mild oxidative conditions lead to glutathionylation of STIM1 on Cys56, which is a prerequisite for its activation, thus explaining why mutants lacking these two cysteines are inactive (Hawkins et al., 2010). Therefore, one way of bypassing the ERp57-dependent regulation of STIM1 under oxidative stress could be prior modification of cysteine residues by either glutathionylation or S-nitrosylation that would make them inaccessible for the interaction. SOCE is under additional redox control at the level of Orai1, which are inhibited by hydrogen peroxide-mediated oxidation (Bogeski et al., 2010). The combination of the activating oxidation of STIM1 with the inhibitory action of oxidation on Orai1 likely results in a triphasic, bell-shaped activation curve of SOCE dependent on cellular redox conditions.

ER-mitochondria cross-talk

While ER Ca^{2+} release and uptake cross-regulate each other, another level of control of ER Ca^{2+} has emerged during the past decade. ER Ca^{2+} is also affected by redox regulation of mitochondrial Ca^{2+} concentrations. Inside mitochondria, the primary role of Ca^{2+} is to regulate oxidative phosphorylation by activating enzymes of the tricarboxylic acid (TCA) cycle such as pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase (McCormack and Denton, 1993) and by stimulating ATP synthase (Das and Harris, 1990), which together result in elevated ATP turnover. Therefore, elevated Ca^{2+} causes higher ATP production and has an overall positive effect on mitochondrial functions (Griffiths and Rutter, 2009; Tarasov et al., 2012). However, this activation of mitochondrial functions also results in higher consumption of molecular oxygen that leads to faster oxidative phosphorylation and more leakage of ROS. Not surprisingly, it has been shown that elevated ROS levels in mitochondria correlates with higher metabolic rate (Perez-Campo et al., 1998). Ca^{2+} is also a known activator of NOS and therefore, its elevated levels increase the concentration NO which, in turn, inhibits complex IV and further increase the amounts of ROS (Brookes and Darley-Usmar, 2002). Elevated ROS at mitochondria leads to stress that can lead to ER stress subsequently (Kuznetsov et al., 1996). Interestingly, however, Leadsham and co-workers recently showed in the yeast model that it is actually the ER, and not mitochondria, that is the major source of ROS generation after mitochondrial dysfunction (Leadsham et al., 2013), as previously proposed (Brown and Borutaite, 2012).

Conclusion

Together, our review depicts the tight connections between the release and uptake of Ca^{2+} from the ER and cellular redox conditions. Since the disease-relevant mechanisms of apoptosis, cell migration and mitochondrial energy production all are steered by the availability of Ca^{2+} from the ER, oxidant and/or antioxidant modulation of ER Ca^{2+} release and uptake is a very attractive pharmacological point of intervention in scenarios associated with metabolic syndromes. Modern medicine has accumulated a large inventory of redox-directed therapeutics that just await being tested for their mechanistic influence on ER Ca^{2+} housekeeping mediated by SERCAs, IP3Rs, STIM1, Orai1 and RyRs, with the aim to combat cancer (Wondrak, 2009) or neurodegeneration (Uttara et al., 2009).

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