Organellar Calcium Handling in the Cellular Reticular Network

Wen-An Wang,[1,3] Luis B. Agellon,[2] and Marek Michalak[1]

[1]Department of Biochemistry, University of Alberta, Edmonton, Alberta T6G 2S7, Canada

[2]School of Human Nutrition, McGill University, Ste. Anne de Bellevue, Quebec H9X 3V9, Canada

Correspondence: luis.agellon@mcgill.ca; marek.michalak@ualberta.ca

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Ca^{2+} is an important intracellular messenger affecting diverse cellular processes. In eukaryotic cells, Ca^{2+} is handled by a myriad of Ca^{2+}-binding proteins found in organelles that are organized into the cellular reticular network (CRN). The network is comprised of the endoplasmic reticulum, Golgi apparatus, lysosomes, membranous components of the endocytic and exocytic pathways, peroxisomes, and the nuclear envelope. Membrane contact sites between the different components of the CRN enable the rapid movement of Ca^{2+}, and communication of Ca^{2+} status, within the network. Ca^{2+}-handling proteins that reside in the CRN facilitate Ca^{2+} sensing, buffering, and cellular signaling to coordinate the many processes that operate within the cell.

INTRACELLULAR Ca^{2+} DYNAMICS AND THE CELLULAR RETICULAR NETWORK

Ca^{2+} is a universal signaling ion involved in the regulation of numerous processes throughout the lifetime of the cell and the organism (Krebs et al. 2015; Berridge 2016). Inside the cell, the resting free Ca^{2+} concentration and Ca^{2+}-signaling pathways must be tightly regulated because of the integral role of Ca^{2+} in nearly all aspects of cell physiology (Baumann and Walz 2001; Groenendyk et al. 2013; Krebs et al. 2015; Nunes-Hasler and Demaurex 2017; Prudent and McBride 2017). Cytoplasmic Ca^{2+} is maintained at a resting concentration that is two to three orders of magnitude lower than the extracellular free Ca^{2+} concentration (Krebs et al. 2015; Berridge 2016). This markedly lower cytoplasmic free Ca^{2+} concentration is maintained by action of Ca^{2+}-handling proteins and the reticular network of intracellular membrane systems (Fig. 1) that comprise the endoplasmic reticulum (ER), sarcoplasmic reticulum (SR), Golgi apparatus, lysosomes, membranous components of the endocytic pathway, peroxisomes, and nuclear envelope (Prins and Michalak 2011; Krebs et al. 2015; Berridge 2016). This intracellular network of specialized membrane systems, the cellular reticular network (CRN), is linked together to facilitate and coordinate cellular function. The organelles of the CRN accumulate and store Ca^{2+} and maintain the Ca^{2+} stores at a higher concentration (mM) than that of cytoplasmic Ca^{2+}. The ER is the dominating com-

[3]Present address: Department of Cellular Physiology and Metabolism, Faculty of Medicine, University of Geneva, CH-1211 Geneve 4, Switzerland.

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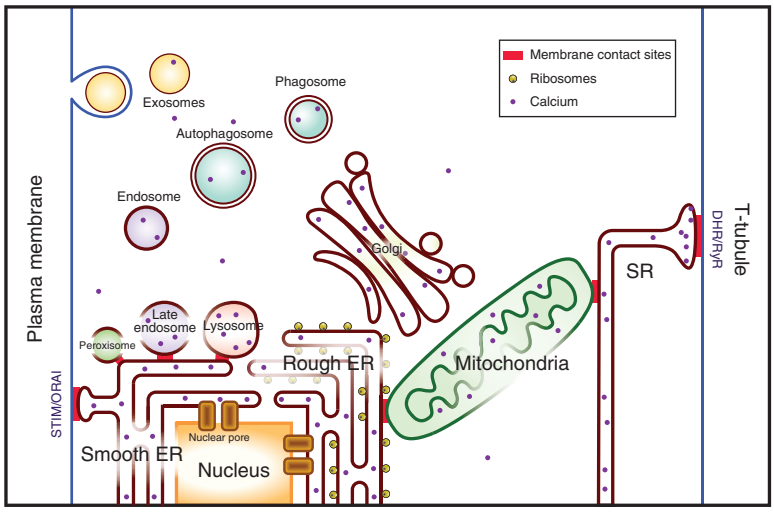

Figure 1. The cellular reticular network. Intracellular organelles are organized into the cellular reticular network that is linked by membrane contact sites ([MCSs], in red) allowing for rapid exchange of molecules between component of the network. DHR, Plasma membrane dihydropyridine Ca^{2+} channel receptor; RyR, ryanodine receptor/Ca^{2+} channel; $InsP_3R$, inositol 1,4,5-trisphosphate receptor; STIM, ER Ca^{2+} sensor; ORAI, plasma membrane Ca^{2+} channel; ER, endoplasmic reticulum.

ponent of the CRN and is the major Ca^{2+} store of the cell. Importantly, Ca^{2+} movement between components of the CRN plays an important role in regulation of cellular functions such as gene transcription (Zhang et al. 2009), cellular stress-coping strategies (Groenendyk et al. 2013; Dicks et al. 2015; Jung et al. 2017), and mitochondrial oxidative metabolism (Griffiths and Rutter 2009; De Stefani et al. 2016). This is achieved, at least in part, through membrane contact sites (MCSs) (Fig. 1), which are formed between closely apposed organellar membranes including the plasma membrane (Prinz 2014; Filadi and Pozzan 2015; Penny et al. 2015; Phillips and Voeltz 2016; Agellon and Michalak 2017; Barneda and Christian 2017; Joshi et al. 2017; Nunes-Hasler and Demaurex 2017; Prudent and McBride 2017). The organelles that make up the CRN contain specialized proteins responsible for the sensing, transport, and storage of intracellular Ca^{2+}, and in orchestrating Ca^{2+} dynamics within the lumen of the network that are necessary to exert this cation's regulatory role (Corbett and Michalak 2000). For example, ER luminal Ca^{2+} dictates many functions of the ER, including protein synthesis and modification, protein folding and quality control, activation of unfolded protein responses (UPRs), interchaperone interactions, lipid synthesis, and cholesterol metabolism (Sambrook 1990; Corbett et al. 2000; Groenendyk et al. 2013; Wang et al. 2017).

ENDOPLASMIC RETICULUM

The ER is a major component of the CRN and a main Ca^{2+} storage organelle with a tightly regulated total (i.e., free and bound Ca^{2+}) intraluminal Ca^{2+} concentration in excess of 2 mM. The free Ca^{2+} concentration in the lumen of ER is maintained at the 10–500 μM range (Corbett and Michalak 2000; Yu and Hinkle 2000; Solovyova et al. 2002). Ca^{2+} is released from the ER via the inositol 1,4,5-trisphosphate receptor/Ca^{2+} channel ($InsP_3R$) or ryanodine receptor/Ca^{2+} channel (RyR) (Krebs et al. 2015; Berridge 2016). The resulting increase in cytoplasmic Ca^{2+} level regulates many cellular processes, including cell proliferation, metabolism, and apoptosis (Berridge et al. 2000). The depletion of ER Ca^{2+} triggers Ca^{2+} entry from the extracellular space via store-operated Ca^{2+} entry

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(SOCE), which further sustains cytoplasmic Ca^{2+} signal and, most importantly, supplies Ca^{2+} for refilling of the ER Ca^{2+} store (Berridge et al. 2000; Roos et al. 2005). Stromal interaction molecule 1 (STIM1) is an ER membrane type I transmembrane protein that acts as an ER Ca^{2+} sensor (Liou et al. 2005; Roos et al. 2005; Zhang et al. 2005). The EF-hand of STIM1 binds Ca^{2+} (K_d = ~0.2–0.6 mM) within the lumen of the ER (Stathopulos et al. 2006; Zheng et al. 2008) and on ER Ca^{2+} depletion, STIM1 extends its conformation, clusters, moves toward the plasma membrane, and binds to the cytosolic domain of Orai1, a plasma membrane Ca^{2+} channel, to form MCS between the ER and the plasma membrane (Feske et al. 2006; Peinelt et al. 2006; Stathopulos et al. 2006; Muik et al. 2008; Park et al. 2009; Bhardwaj et al. 2016; Phillips and Voeltz 2016; Nwokonko et al. 2017). The interaction between STIM1 and Orai1 at the MCS causes oligomerization of Orai1 Ca^{2+} channel and the consequence of influx of Ca^{2+} (Peinelt et al. 2006; Prakriya et al. 2006; Mignen et al. 2008; Penna et al. 2008; Hou et al. 2012). The sarco-ER Ca^{2+} ATPase (SERCA) pumps Ca^{2+} from the cytosol into the ER to refill Ca^{2+} stores (Krebs et al. 2015; Berridge 2016).

The ER also plays a central role in managing cellular stress via mobilization of ER stress-coping responses, such as the UPR. The UPR involves three unique ER transmembrane signaling proteins: the inositol-requiring 1 (IRE1), ER kinase dsRNA-activated protein kinase-like ER kinase (PERK), and activating transcription factor 6 (ATF6) (Groenendyk et al. 2013; Wang and Kaufman 2016; Hetz and Papa 2018). Activation of ER stress-induced UPR signaling pathways result in translational attenuation and in transcriptional activation of genes encoding proteins involved in protein folding as well as genes for components of the ER-associated degradation pathway (Groenendyk et al. 2013; Wang and Kaufman 2016; Hetz and Papa 2018). Prolonged ER Ca^{2+} depletion is a potent activator of UPR (Mekahli et al. 2011; Groenendyk et al. 2013). ER luminal Ca^{2+}-binding proteins, notably BiP/GRP78 and PDIA6, regulate UPR signaling and illustrate the important link between ER Ca^{2+} homeostasis and ER stress responses (Higo et al. 2010; Groenendyk et al. 2013, 2014; Hetz and Papa 2018).

There are two categories of Ca^{2+}-handling proteins as defined by their Ca^{2+}-binding properties. The first binds Ca^{2+} with low affinity but high capacity. These proteins contribute to the Ca^{2+} storage and buffering capacity within organelles. The second binds Ca^{2+} with high affinity but low capacity. These proteins act as Ca^{2+} sensors as well as conveyors of Ca^{2+}-dependent events into downstream components of intracellular signaling pathways (Krebs et al. 2015). Additionally, there are a variety of Ca^{2+}-binding protein chaperones and folding enzymes localized within the lumen and membrane of the ER.

Calreticulin

Calreticulin is an ER luminal protein chaperone and a major Ca^{2+}-binding protein that is important for maintaining 50% of the total Ca^{2+} within the ER Ca^{2+} (Gelebart et al. 2005). Calreticulin is 400 amino acid and 46 kDa protein and is composed of three structural and functional domains. The highly conserved N-globular domain contains a disulfide-linkage and binding sites for polypeptides, carbohydrates, and Zn^{2+} (Baksh et al. 1995; Schrag et al. 2001; Leach et al. 2002; Kapoor et al. 2004). The P-domain is the proline-rich extended arm of calreticulin that contains a binding site for the thiol oxidoreductase ERp57/PDIA3 and a high-affinity (K_d = 1 μM) but low-capacity (1 mol of Ca^{2+}/mol of protein) Ca^{2+}-binding site (Baksh and Michalak 1991; Tjoelker et al. 1994; Ellgaard et al. 2001, 2002; Frickel et al. 2002). Together, the N- and P-domains comprise the protein chaperone unit of calreticulin (Nakamura et al. 2001). The C-domain contains many acidic residues and is the Ca^{2+}-binding unit of calreticulin, binding Ca^{2+} with low affinity (K_d = 2 mM) but at high capacity (20–30 mol of Ca^{2+}/mol of protein) (Tjoelker et al. 1994; Nakamura et al. 2001).

The role of calreticulin in maintaining ER homeostasis is illustrated in the effects of its loss- or gain-of-function on ER Ca^{2+}-signaling dynamics. Loss of calreticulin in mice is embry-

onically lethal owing to inadequate ER Ca^{2+} signaling. This is attributed to both the chaperone and Ca^{2+} storage function of calreticulin (Mesaeli et al. 1999). In the absence of calreticulin, ER Ca^{2+} stores, as measured by thapsigargin-induced total ER Ca^{2+} release, is reduced by 50% (Nakamura et al. 2001). Furthermore, calreticulin-deficient cells were no longer responsive to bradykinin-induced ER Ca^{2+} release, but permeabilized calreticulin-deficient cells remained responsive to $InsP_3$-induced ER Ca^{2+} release (Nakamura et al. 2001). The lack of response to bradykinin in calreticulin-deficient cells was caused by the absence of the chaperone function of calreticulin, which resulted in the misfolding of the plasma membrane bradykinin receptor and thus the loss of ability of cells to interact with bradykinin (Nakamura et al. 2001). This disrupted Ca^{2+} signaling from the ER caused by the absence of calreticulin led to insufficient activation of calcineurin and subsequent failure to stimulate transcription factors that induce the expression of responsive genes (Mesaeli et al. 1999; Guo et al. 2002; Lynch et al. 2005). In mice, calreticulin deficiency results in embryonic lethality owing to failure in cardiac development (Mesaeli et al. 1999). Remarkably, the lethality caused by calreticulin deficiency could be prevented by targeted expression of a constitutively active calcineurin solely in cardiac cells of mice with whole-body deficiency of calreticulin (Guo et al. 2002). On the other hand, overexpression of calreticulin increased total and free ER Ca^{2+} concentration (Bastianutto et al. 1995; Mery et al. 1996; Arnaudeau et al. 2002). This also led to a reduction in mitochondria Ca^{2+} causing mitochondrial damage and increasing cellular sensitivity to apoptosis (Arnaudeau et al. 2002). The increase in ER luminal Ca^{2+} concentration caused by calreticulin overexpression reduced STIM1 sensitivity to ER Ca^{2+}, thereby decreasing and delaying SOCE activity (Mery et al. 1996).

The expected discovery of hyperlipidemia in calreticulin-deficient mice rescued from embryonic lethality by cardiac-specific expression of constitutively active calcineurin suggested a link between Ca^{2+} and lipid homeostasis (Guo et al. 2002). It is now evident that the decrease in ER luminal Ca^{2+} caused by the loss of calreticulin (Mesaeli et al. 1999; Nakamura et al. 2001) shifts the distribution of intracellular unesterified cholesterol, resulting in the depletion of the regulatory pool of cholesterol that controls cholesterol biosynthesis (Wang et al. 2017).

Immunoglobulin-Binding Protein/Glucose-Regulated Protein 78 (BiP/GRP78)

The molecular chaperone BiP/GRP78 binds hydrophobic regions of nascent proteins through the carboxy-terminal domain (C chain) and facilitates proper protein folding at the expense of ATP, as it is also an ATPase with an ATP/ADP-binding site in the N-domain (A chain) (Gaut and Hendershot 1993; Awad et al. 2008). BiP/GRP78 is a key player in sensing ER stress through binding to accumulating misfolded proteins. However, it is also important for buffering 25% of total ER Ca^{2+} stores (Lievremont et al. 1997). The protein has four Ca^{2+} ion-binding acidic amino acid residues; two Ca^{2+} ions are accommodated in opposite chains by the coordination of His-252, Asp-257, and Gly-315; two other Ca^{2+} ions are held at the base of α-helix-6 by the hydroxyl group of His-252 and the carboxylate group of Glu-256 and Asp-257 (Wisniewska et al. 2010). Although BiP/GRP78 binds Ca^{2+} with low capacity (1–2 mol Ca^{2+}/mol of protein), it contributes to ER Ca^{2+} buffering owing to its high abundance in the lumen of the ER (~5-fold higher abundance than calreticulin) (Lievremont et al. 1997).

There is an intrinsic relationship between the chaperone and the Ca^{2+}-binding functions of BiP/GRP78. Stoichiometrically, the binding affinity of BiP/GRP78 to Ca^{2+} changes in the presence of ATP or ADP. It binds Ca^{2+} with a K_d of ~0.7 mM in the absence of ATP and ADP; a K_d of ~18 μM in the presence of ATP; and a K_d of ~0.8 μM in the presence of ADP (Lamb et al. 2006). The reverse is also true; in the presence of Ca^{2+}, the binding affinity of ATP to BiP/GRP78 increases ~11-fold and the binding of ADP increases ~930-fold (Lamb et al. 2006). Functionally, the ER Ca^{2+} level regulates the chaper-

one activity of BiP/GRP78 as reduction in ER Ca^{2+} levels causes dissociation of BiP/GRP78 from client proteins, and increases in ER Ca^{2+} level inhibits BiP/GRP78-associated ATPase activity (Kassenbrock and Kelly 1989; Suzuki et al. 1991). This interconnected relationship between ER Ca^{2+} store and signaling is a dynamic contributor to Ca^{2+} binding and chaperone activity of BiP/GRP78. Therefore, the abundance of BiP/GRP78 modulates ER–mitochondria Ca^{2+} flux and may play a protective role against mitochondria-induced apoptosis, depending on the level or duration of stress (Lievremont et al. 1997; Liu et al. 1997; Deniaud et al. 2008; Ouyang et al. 2011). Furthermore, BiP/GRP78 is responsible for selectively gating and closing of ribosome-associated Sec61 translocon to prevent Ca^{2+} leakage at ER–mitochondria MCS and induction of apoptosis from ER stress (Haigh and Johnson 2002; Van Coppenolle et al. 2004; Alder et al. 2005; Schauble et al. 2012; Hammadi et al. 2013; Gutiérrez and Simmen 2018).

Glucose-Regulated Protein

The glucose-regulated protein (GRP94) is an ER protein chaperone that is involved in the folding and secretion of membrane proteins (Marzec et al. 2012). GRP94 is a heat shock protein 90 (HSP90)-like protein that contains an ATP-binding domain within the amino-terminal region, a client-binding region, and a dimerization domain within the carboxyl terminus (Marzec et al. 2012). In addition, GRP94 has a peptide-binding region in its amino-terminal region (Biswas et al. 2007). This major chaperone is involved in the folding of immunoglobulins (Melnick et al. 1994) and Toll-like receptors (Randow and Seed 2001). The peptide-binding activity of GRP94 is important for the immune response during T-cell activation (Berwin et al. 2002; Li et al. 2005). GRP94 possesses four Ca^{2+}-binding sites with high affinity (K_d = ~2 μM) and 11 Ca^{2+}-binding sites with low affinity (K_d = ~600 μM) (Van et al. 1989), an EF-hand-like structure (Csermely et al. 1995), and is able to accommodate 16–28 mol of Ca^{2+}/mol of protein (Macer and Koch 1988; Van et al. 1989). In addition, the ER Ca^{2+} level affects the peptide-binding activity of GRP94; specifically, Ca^{2+} binding within the amino terminus (amino acids 266–355) induces a conformational change that favors peptide interaction (Van et al. 1989; Biswas et al. 2007).

The expression of GRP94 proteins is stimulated by induction of the UPR during ER stress, resulting from misfolding of proteins or perturbed ER Ca^{2+} homeostasis (Lee 1992). Depletion of GRP94 does not cause ER stress nor loss of ER Ca^{2+} homeostasis (Poirier et al. 2015); however, cells lacking GRP94 were more susceptible to thapsigargin-induced ER Ca^{2+} depletion and cell death (Biswas et al. 2007). Expression of GRP94, similar to BiP/GRP78, showed antiapoptotic properties and protected cells from Ca^{2+} depletion-induced stress and apoptosis (Little and Lee 1995). Furthermore, the cleavage or degradation of GRP94 is mediated through the activity of Ca^{2+}-dependent calpains during DNA damage–induced apoptosis (Reddy et al. 1999). Overexpression of GRP94 protected cardiomyocytes from intracellular Ca^{2+} overload and ischemia (Bando et al. 2003; Vitadello et al. 2003).

Protein Disulfide Isomerase

The protein disulfide isomerase (PDI) family of proteins were discovered in 1963 as ER proteins involved in co- and posttranslational modification of nascent synthesized proteins. Specifically, these proteins are important in the formation and cleavage of disulfide bonds (Goldberger et al. 1963), which is necessary for the proper folding of cysteine-containing proteins (Creighton et al. 1980). Subsequently, PDIs were identified as calsequestrin-like proteins of the ER (Oberdorf et al. 1988) and later glycoproteins with Ca^{2+}-binding properties (Lebeche and Kaminer 1992). Mammalian PDIs have been shown to bind Ca^{2+} at high capacity (averaging at 19 mol of Ca^{2+}/mol of protein) but with low affinity (K_d = 4.7 mM) (Lebeche et al. 1994). The Ca^{2+}-binding region of PDIs consists of a number of paired acidic residues within the carboxyl terminus of the protein (Freedman et al. 1994; Lucero et al. 1998). As PDIs contribute to the

Ca^{2+} store within the ER, the level of Ca^{2+} in the ER (1–5 mM) in turn affects their overall enzymatic activity (Lucero and Kaminer 1999).

Recent reports indicate that PDI family of proteins influence ER stress responses and impact on the ER and cellular Ca^{2+} homeostasis. For example, PDIA6 plays a role in regulation of IRE1α activity in response to ER Ca^{2+} depletion (Groenendyk et al. 2014). PDIA3 (ERp57) interacts with, and regulates, STIM1 activity, thereby impacting on SOCE and cytoplasmic Ca^{2+} signaling (Prins et al. 2011), in addition to its key role in the quality control of newly synthesized glycoproteins (Coe and Michalak 2010). Furthermore, PDIA3 modulates the redox state of ER-facing thiols in SERCA2b in a Ca^{2+}-dependent manner (Li and Camacho 2004) and PDIA10 (ERp44) modulates Ca^{2+} release by $InsP_3R$ (Higo et al. 2005).

SARCOPLASMIC RETICULUM

In some cells, the ER is further subspecialized into rough ER, such as in secretory cell types, and smooth ER, such as in cells that actively synthesize and metabolize lipids. In muscle cells, in addition to perinuclear rough and smooth ER, the ER is subspecialized into the SR (Fig. 1), which is responsible for the regulation of excitation–contraction–coupling to facilitate muscle contraction and relaxation (Bers 2014). The presence of highly specialized SR membrane networks in muscle cells supports mechanical functions requiring large fluxes of Ca^{2+}, without compromising other important Ca^{2+}-requiring cellular processes that are normally associated with ER (Michalak and Opas 2009). There are two well-defined structural and functional regions of the SR. The longitudinal SR, a membrane network around contractile myofibrils extending into the junctional SR, is a membrane network with multiple MCS with T-tubules formed from invaginations in the plasma membranes of muscle cells such as cardiomyocytes (Wray and Burdyga 2010; Bers 2014). The longitudinal SR is enriched with SERCA, and is responsible for rapid removal of Ca^{2+} from the cytoplasm to initiate muscle relaxation (Wray and Burdyga 2010; Bers 2014). The junctional SR contains the RyR, responsible for Ca^{2+} release to the cytoplasm to initiate muscle contraction, and calsequestrin, a major Ca^{2+}-binding protein of muscle (Rossi and Dirksen 2006; Wray and Burdyga 2010; Bers 2014). The SR luminal Ca^{2+}-binding proteins calsequestrin, histidine-rich calcium-binding protein, junctate, and sarcalumenin are responsible for Ca^{2+} storage, whereas RyR is responsible for Ca^{2+} release to trigger muscle contraction.

Calsequestrin

Calsequestrin is the major Ca^{2+}-binding protein within the SR, binding Ca^{2+} with high capacity (40–50 mol of Ca^{2+}/mol of protein) but low affinity (K_d = ~1 mM) (MacLennan and Wong 1971). Two isoforms of calsequestrin exist and are encoded by two distinct genes: skeletal muscle calsequestrin (*CASQ1*) and cardiac calsequestrin (*CASQ2*) (Györke et al. 2009; Knollmann 2009). Structurally, calsequestrin is composed of three thioredoxin-like domains linked together to form a monomer with a hydrophilic core and a carboxyl terminus that contains the majority of paired acidic residues for Ca^{2+} binding (Wang et al. 1998). These Ca^{2+}-binding sites have been termed the consecutive aspartate stretch at the carboxy-terminal domain (Kumar et al. 2013). The structure and oligomerization state of calsequestrin is dependent on the concentration of Ca^{2+} within the SR lumen (Ikemoto et al. 1974). Calsequestrin can dimerize and polymerize, and can exist as stable polymers at a Ca^{2+} concentration of 1 mM (the physiological stable level of Ca^{2+} within the SR lumen) (Franzini-Armstrong et al. 1987; Wang et al. 1998). The binding of calsequestrin monomers to Ca^{2+} mediates the oligomeric state of calsequestrin, as shown through crystallization studies (Sanchez et al. 2012). High Ca^{2+} concentration in the junctional SR supports calsequestrin polymerization (Wang et al. 1998; Beard et al. 2005), whereas Ca^{2+} depletion in the junctional SR causes calsequestrin depolymerization (Manno et al. 2017). The carboxyl terminus portion of calsequestrin contains a disordered region that is involved in the Ca^{2+}-dependent polymerization properties of these proteins

and accounts for the unique polymerization differences between calsequestrin 1 and 2 isoforms (Bal et al. 2015). These conformational changes are important for the role of calsequestrin in regulating Ca^{2+} storage and release.

Mice deficient in skeletal muscle calsequestrin (CASQ1) are viable but they show reduced Ca^{2+} release and Ca^{2+} transients (Paolini et al. 2007). Deficiency in cardiac calsequestrin (CASQ2) leads to an increased diastolic SR Ca^{2+} leak and development of catecholaminergic ventricular arrhythmias (Knollmann et al. 2006). Mutations in the *CASQ2* gene cause a severe form of catecholaminergic polymorphic ventricular tachycardia (CPVT) (Faggioni et al. 2012).

Histidine-Rich Ca^{2+}-Binding Protein

The histidine-rich Ca^{2+}-binding protein (HRC) was first discovered in 1989 as a 165 kDa Ca^{2+}-binding protein within the lumen of the SR (Campbell et al. 1983; Hofmann et al. 1989). HRC binds Ca^{2+} with high capacity (reported at 200 nmol of Ca^{2+}/mg of protein) but low affinity (K_d = 1.9 mM) (Picello et al. 1992). Overexpression of HRC in rat cardiomyocytes (Fan et al. 2004) and rat neonatal cardiomyocytes increased SR Ca^{2+} store content and prevented SR Ca^{2+} depletion induced by cyclopiazonic acid (Kim et al. 2003).

HRC has also been found to be important for Ca^{2+} cycling within the SR lumen. The conformation of HRC, and its interaction with other proteins, are Ca^{2+}-dependent. HRC can exist as a multimeric complex, which dissociates on Ca^{2+} binding (conditions of high Ca^{2+} concentration) caused by changes in conformation (Suk et al. 1999). Similar to calsequestrin, the HRC protein can bind to triadin, a junctional SR protein, through its carboxy-terminal region in a Ca^{2+}-dependent fashion (Lee et al. 2001; Sacchetto et al. 2001). Furthermore, HRC forms a complex with SERCA and triadin to modulate Ca^{2+} uptake and release from the SR (Gregory et al. 2006; Arvanitis et al. 2007). Mice deficient for HRC showed increases in Ca^{2+} signaling, cardiomyocyte contractility, and rate of SR Ca^{2+} uptake (Park et al. 2013). Therefore, HRC is integral to the maintenance of Ca^{2+} homeostasis within the SR.

Junctate

Junctate is a newly described protein that is expressed within the junctional SR. It is a 33-kDa single-pass integral SR membrane protein with the amino-terminal portion facing the cytoplasm and the carboxy-terminal portion within the SR lumen, and acts as a high-capacity/low-affinity Ca^{2+}-binding protein (Treves et al. 2000). The carboxy-terminal luminal portion of junctate is enriched in negatively charged amino acid residues and the protein is able to bind 21 mol of Ca^{2+}/mol of protein with an affinity of K_d = 217 μM (Treves et al. 2000). Junctate has a significant influence on SR Ca^{2+} store capacity. Specifically, overexpression of junctate in mouse skeletal muscle increased both the SR Ca^{2+} store content and Ca^{2+} release on induction (Divet et al. 2007). However, in cardiomyocytes isolated from transgenic mice, overexpression of junctate resulted in a reduced SR function and reduced abundance of SERCA and calsequestrin. This resulted in disrupted cardiac Ca^{2+} transients, inducing cardiac hypertrophy (Hong et al. 2008). On the other hand, the same investigators showed that overexpression of junctate in rat cardiomyocytes infected with junctate adenovirus system led to an increase in SERCA2a activity and Ca^{2+} uptake (Kwon and Kim 2009).

Additionally, junctate appears to play a major role in maintaining Ca^{2+} homeostasis in eukaryotic cells through the regulation of Ca^{2+} uptake/release and SOCE. Junctate was found to interact with SERCA2a, the cardiac SERCA isoform, in the SR of cardiomyocytes via its carboxy-terminal domain, and the luminal domain of SERCA2a (Kwon and Kim 2009). Junctate also regulates Ca^{2+} entry and stabilizes ER–plasma membrane junctions through complex interaction with $InsP_3R$ and transient receptor potential protein 3 (TRPC3) cation channels (Treves et al. 2004). Moreover, studies have implicated junctate as a component of the STIM1 and Orai1 complex that mediates SOCE (Srikanth et al. 2012; Guido et al. 2015). This

interaction was shown to be important in Ca^{2+} signaling within immune cells, specifically affecting Ca^{2+} dynamics at both ER–plasma membrane junctions (Srikanth et al. 2012) and ER-phagosome junctions (Guido et al. 2015).

Sarcalumenin

Sarcalumenin was discovered as the 160-kDa protein variant generated by alternative splicing of a messenger RNA (mRNA) transcript of a gene that encodes a 53-kDa SR glycoprotein (Leberer et al. 1989). The protein binds Ca^{2+} at high capacity (30–35 mol of Ca^{2+}/mol of protein) but with low affinity ($K_d = 300$ μM) (Leberer et al. 1990). The skeletal muscle of sarcalumenin-deficient mice showed delayed relaxation phase following contraction and reduced Ca^{2+} uptake into the SR (Yoshida et al. 2005). Similarly, the cardiac performance of sarcalumenin-deficient mice was impaired. Further analysis of sarcalumenin-deficient cardiomyocytes revealed slow contraction and relaxation along with disrupted Ca^{2+} signaling (Yoshida et al. 2005). These mice, however, showed an increase in SOCE and a resistance to muscle fatigue in response to treadmill exercise (Zhao et al. 2005). Furthermore, sarcalumenin-deficient mice displayed reduced cardiac function in the presence of biomechanical stress. This was attributed to the absence of sarcalumenin function in regulating SR Ca^{2+} handling through its interaction with SERCA (Shimura et al. 2008; Jiao et al. 2009, 2012).

MITOCHONDRIA

Mitochondrial Ca^{2+} uptake and accumulation are important components of cellular Ca^{2+} homeostasis and signaling. This process does not depend on any mitochondrial Ca^{2+}-buffering proteins, but rather on the membrane potential difference resulting from the electrochemical gradient generated by the H^+ ions pumped into the intermembrane space by the electron transport chain. This membrane potential drives Ca^{2+} from the cytoplasm through the outer and inner mitochondrial membranes. The outer mitochondrial membrane is ion permeable owing to the presence of large-conductance voltage-dependent anion channels, which are also permeable to Ca^{2+} ions (Rapizzi et al. 2002). Ca^{2+} transport across the ion impermeable inner mitochondrial membrane occurs through the mitochondrial Ca^{2+} uniporter complex (Kirichok et al. 2004), which allows rapid accumulation of Ca^{2+} into the mitochondrial matrix at a $V_{max} > 1400$ nmol of Ca^{2+}/mg of protein/min (Bragadin et al. 1979). Mitochondrial Ca^{2+} uptake occurs at ER–mitochondria MCS in proximity to ER membrane Ca^{2+}channels such as the $InsP_3R$ and the RyR, and depends on the high Ca^{2+} concentration hotspots at these microdomains (Rizzuto et al. 1993, 1998; Szalai et al. 2000).

In this sense, the generation of mitochondrial Ca^{2+} hotspots (Csordas et al. 2010; Giacomello et al. 2010), together with the rapid and large accumulation of Ca^{2+} within mitochondria on stimulation, suggests a role for mitochondria as a Ca^{2+}-buffer within the cell. This might also enable modulation of Ca^{2+} levels and thus Ca^{2+} signaling in the immediate proximity of mitochondria. The $InsP_3R$ activity is regulated by cytoplasmic Ca^{2+} concentrations (Bezprozvanny et al. 1991) and mitochondrial uptake or sequestering of Ca^{2+} during ER Ca^{2+} release suppresses Ca^{2+} feedback activation of $InsP_3R$ (Hajnoczky et al. 1999). Moreover, Ca^{2+} uptake by mitochondria can occur near Orai Ca^{2+} channels on the plasma membrane and thus modulate channel activity during SOCE (Hoth et al. 1997; Gilabert and Parekh 2000). Furthermore, Ca^{2+} uptake by mitochondria stimulates the tricarboxylic acid (TCA) cycle and oxidative phosphorylation and prevents induction of autophagy (Cardenas et al. 2016; Singh et al. 2017; Bootman et al. 2018; Morciano et al. 2018).

GOLGI APPARATUS

The Golgi apparatus accounts for up to 5% of the total cellular Ca^{2+} store (Chandra et al. 1991). The Golgi Ca^{2+} store is important for the optimal function of certain enzymes within the organelle (Oda 1992; Carnell and Moore 1994), retrograde transport (Ivessa et al. 1995;

Micaroni et al. 2010), and secretory protein sorting (Chanat and Huttner 1991; Micaroni et al. 2010). The Golgi Ca^{2+} store is sensitive to $InsP_3$ production as there are $InsP_3R$ in Golgi structures (Pinton et al. 1998). However, the Ca^{2+} released from $InsP_3R$ on Golgi membranes is functionally distinct from that originating from ER Ca^{2+} stores (Vanoevelen et al. 2004). The Golgi Ca^{2+} store is maintained via the activity of SERCA and the secretory pathway Ca^{2+} ATPase1 (SPCA1), which is able to pump Ca^{2+} from the cytoplasm into the Golgi (Wuytack et al. 2003; Micaroni et al. 2010; Vandecaetsbeek et al. 2011). Although Ca^{2+} is present within the lumen of the entire Golgi network (Pezzati et al. 1997), the handling of Ca^{2+} across the Golgi network is heterogeneous (Wong et al. 2013; Aulestia et al. 2015). There is a Ca^{2+} gradient within the Golgi apparatus whereby the Ca^{2+} concentration within the lumen of the Golgi is higher than that of *trans*-Golgi (but lower than that of the ER) (Wong et al. 2013). Furthermore, the *cis*-Golgi accumulates Ca^{2+} mostly from SERCA activity, whereas the *trans*-Golgi accumulates Ca^{2+} through the action of SPCA1 (Aulestia et al. 2015). In addition, Ca^{2+} release via $InsP_3R$ occurs only from the *cis*- and the second *trans*-Golgi portion, whereas Ca^{2+} release from all of Golgi can be induced by caffeine (Aulestia et al. 2015). The heterogeneity of Ca^{2+} concentration in the Golgi may reflect differing regulatory functions for Ca^{2+} within the different Golgi compartments.

CALNUC

CALNUC is a major Ca^{2+}-binding protein within the Golgi apparatus and is highly homologous to calreticulin (Lin et al. 1998). Structurally, it consists of a signal peptide, followed by a basic amino acid region, an acidic amino acid region that makes up two EF-hand motifs (de Alba and Tjandra 2004), and a leucine zipper motif (Miura et al. 1992; Lin et al. 1998). CALNUC binds Ca^{2+} with high affinity (K_d = 6.6 μM) but at low capacity (1.1 mol of Ca^{2+}/mol of protein) (Lin et al. 1999), and accounts for the majority of Golgi Ca^{2+} stores by virtue of its high abundance in this organelle (~3.8 μg of CALNUC/mg of total Golgi protein) (Lin et al. 1999). CALNUC has been recently implicated in the endosome-to-*trans*-Golgi retrograde transport of lysosomal receptors the recruitment of retromers to endosomes (Larkin et al. 2016).

Calumenin

Calumenin is also a part of the CREC (acronym derived from the four main family members: Cab45, reticulocalbin1, ERC-55, and calumenin; Yabe et al. 1998) family of EF-hand-containing proteins and is localized to both the ER and the Golgi (Vorum et al. 1998). The protein contains an amino-terminal signal sequence, an HDEF ER retrieval signal, and seven EF-hand motifs, each with low Ca^{2+}-affinity (K_d = 1.6 mM) (Vorum et al. 1998). Calumenin can be further processed and secreted by cultured cells (Vorum et al. 1999). Furthermore, it is highly expressed within the brain during development and may play a role in neuronal Ca^{2+}-signaling (Vasiljevic et al. 2012).

Cab45 was the first Ca^{2+}-binding luminal-resident protein of the Golgi apparatus to be discovered, and is a 45-kDa protein belonging to the superfamily of CREC proteins (Scherer et al. 1996; Honore and Vorum 2000). Cab45 is a soluble protein and contains an amino-terminal signal sequence and six EF-hand motifs (Scherer et al. 1996). The function of Cab45 includes sorting of secretory proteins within the *trans*-Golgi and occurs in a SPCA-1- and Ca^{2+}-dependent manner (von Blume et al. 2012). The binding of Ca^{2+} evokes an oligomerized state that enables Cab45 activity (Crevenna et al. 2016). Oligomerized Cab45 binds a variety of proteins destined for cellular secretion. Cab45 plays an important Ca^{2+}-dependent role in sorting cargo export at the *trans*-Golgi membrane through its association with SPCA-1 and actin (Blank and von Blume 2017).

p54/NEFA

The DNA-binding, EF-hand, acidic region (p54/NEFA) protein contains a basic region, two EF-hand motifs and a leucine zipper repeat (Karabinos et al. 1996). p54/NEFA is a resident

of medial Golgi and is retained within the ER through its amino-terminal Leu/Ile rich region (Nesselhut et al. 2001; Morel-Huaux et al. 2002).

ENDOSOME/LYSOSOME/PEROXISOME/PHAGOSOME

Endosomes and lysosomes have emerging roles in Ca^{2+} storage and signaling. As endosomes mature into late endosomes and subsequently fuse with lysosomes, the gradual acidification of the vesicles is accompanied by a concomitant increase in Ca^{2+} concentration (Gerasimenko et al. 1998; Pryor et al. 2000). The concentration of Ca^{2+} within the lumen of lysosomes is estimated to range from 400 μM to 600 μM (Christensen et al. 2002; Lloyd-Evans et al. 2008). Ca^{2+} release from the endosome/s/lysosomes shown to be sensitive to nicotinic acid adenine dinucleotide phosphate (NAADP) treatment is mediated by the RyR and TPC2 channels (Mojzisova et al. 2001; Hohenegger et al. 2002; Gerasimenko et al. 2003; Brailoiu et al. 2010; Lin-Moshier et al. 2014; Davis et al. 2015; Galione 2015; Hockey et al. 2015; Ruas et al. 2015) and is distinct from Ca^{2+} released from $InsP_3$-sensitive ER stores (Lee and Aarhus 1995; Genazzani and Galione 1996; Lopez-Sanjurjo et al. 2013). The transient receptor potential (TRPML) channels belonging to the mucolipin family and the two-pore channels are also involved in the release of Ca^{2+} from the acidic stores in these organelles (Patel and Muallem 2011; Kilpatrick et al. 2013, 2016; Penny et al. 2015; Atakpa et al. 2018).

Currently, the existence of endosomal/lysosomal Ca^{2+}-buffering proteins are unknown. The uptake and accumulation of Ca^{2+} within these acidic stores seem to be highly dependent on pH (Christensen et al. 2002; Morgan et al. 2013). Uptake of Ca^{2+} into lysosomes occurs through the H^+/Ca^{2+} exchanger, vacuolar (V)-type H^+-ATPase (Pryor et al. 2000), and Ca^{2+}/H^+ exchanger (CAX) (Melchionda et al. 2016). Furthermore, the Ca^{2+} storage and signaling capacity of the endosomal/lysosomal pathway is highly dependent on Ca^{2+} signaling and exchange with the ER at ER-endosomal/-lysosomal MCS (Penny et al. 2015; Ronco et al. 2015). Movement of Ca^{2+} between the ER and the endosomal/lysosomal pathway is important for the progression, maturation, fusion events of the endosomes/lysosomes, and autophagy (Huotari and Helenius 2011; Coen et al. 2012; Bootman et al. 2018).

Peroxisomes are capable of storing Ca^{2+} within their lumen at concentrations higher than that in cytoplasm (Lasorsa et al. 2008; Costa et al. 2013). However, it is not known how Ca^{2+} is stored or buffered in this organelle. It is thought that Ca^{2+} is involved in the regulation of autophagy, a process that delivers proteins and damaged organelles to the lysosome for breakdown to promote cell survival under conditions of nutrient deprivation (Decuypere et al. 2011; Tong and Song 2015). The fate of Ca^{2+} trapped during phagosomal formation and how it is stored in phagosome is not known.

SUMMARY

It is evident that there is rich variety of Ca^{2+}-handling proteins that bind the ion with differing affinities and capacities distributed throughout the cell, and especially within the organellar components that make up the CRN. Ca^{2+}-handling proteins that bind Ca^{2+} with high affinity but low capacity likely function as sensors or conveyors of Ca^{2+}-dependent signaling events, whereas those that bind Ca^{2+} with low affinity but high capacity are likely involved in storage or buffering of Ca^{2+} in the local milieu. The rapid movement of Ca^{2+} and communication of luminal Ca^{2+} status, among the different compartments of the CRN may be partly facilitated through MCS, which themselves are characterized by a unique set of accessory proteins, including specific Ca^{2+}-handling proteins, depending on the membranes involved in the formation of the MCS. A recent study illustrated that luminal ER Ca^{2+} status has a dramatic impact on the intracellular distribution of unesterified cholesterol, and thus alters the set point of the basal-sensing mechanism responsible for cholesterol homeostasis. In the years to come, it will be interesting to uncover how the diverse collection of Ca^{2+}-handling proteins within the cell are networked to coordinate the manifold

and simultaneous cellular processes that enable the cell to exist and carry out its functions.

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Wen-An Wang, Luis B. Agellon and Marek Michalak

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