Biochemical and Biophysical Research Communications 460 (2015) 114–121

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Review

Ca^{2+} homeostasis and endoplasmic reticulum (ER) stress: An integrated view of calcium signaling

Joachim Krebs [a, *], Luis B. Agellon [b], Marek Michalak [c]

[a] NMR-based Structural Biology, Max Planck Institute for Biophysical Chemistry, Göttingen, Germany
[b] School of Dietetics and Human Nutrition, McGill University, Ste. Anne de Bellevue, Quebec H9X 3V9, Canada
[c] Department of Biochemistry, University of Alberta, Edmonton, Alberta T6G 2H7, Canada

ARTICLE INFO

Article history:
Received 25 December 2014
Available online 18 May 2015

Keywords:
Ca^{2+} homeostasis
ER stress
Ca^{2+}-binding proteins
Calcium transport
Membrane contact sites
Unfolded protein response (UPR)
MicroRNAs

ABSTRACT

Cellular Ca^{2+} homeostasis is maintained through the integrated and coordinated function of Ca^{2+} transport molecules, Ca^{2+} buffers and sensors. These molecules are associated with the plasma membrane and different cellular compartments, such as the cytoplasm, nucleus, mitochondria, and cellular reticular network, including the endoplasmic reticulum (ER) to control free and bound Ca^{2+} levels in all parts of the cell. Loss of nutrients/energy leads to the loss of cellular homeostasis and disruption of Ca^{2+} signaling in both the reticular network and cytoplasmic compartments. As an integral part of cellular physiology and pathology, this leads to activation of ER stress coping responses, such as the unfolded protein response (UPR), and mobilization of pathways to regain ER homeostasis.

1. Introduction

Homeostasis is a mechanism to keep cells at balance, regulating themselves to maintain constant conditions. Ca^{2+} homeostasis is of pivotal interest for the cell, reflecting the central importance of Ca^{2+} as a second messenger, regulating a variety of cellular processes such as metabolism, protein phosphorylation and dephosphorylation, cell proliferation, division and differentiation, gene transcription, cell motility, muscle excitation-contraction and stimulus-secretion coupling, programmed cell death and neurotransmission [1]. To maintain Ca^{2+} homeostasis, the flow of Ca^{2+} into and out of cells and organelles has to be precisely regulated to be in balance, which is essential for cellular functions. High concentrations of cellular Ca^{2+} over a longer period of time can lead to cell death [2], therefore, a network of Ca^{2+} transport and buffering systems evolved in order to precisely control within the cell, the temporal and spatial fluxes and concentration of Ca^{2+} in the nanomolar range. The maintenance of Ca^{2+} homeostasis is a highly integrated process consisting of a number of hormonally controlled feedback loops and an elaborate system of Ca^{2+}-transporters, -channels, -exchangers, -binding/buffering proteins and -pumps. These include the Na^{+}/Ca^{2+}-exchanger of the plasma membrane (NCX) [3], a system of high capacity, but low affinity for Ca^{2+}; the plasma membrane Ca^{2+} pump (PMCA or ATP2B) [4] or the Ca^{2+} pump of the sarco/endoplasmic reticulum (SERCA or ATP1B) [5], which both have a high affinity, but low capacity for Ca^{2+}, pumping Ca^{2+} either out of the cell (PMCA) or into the endoplasmic reticulum (ER) and related reticular network (SERCA), respectively. They use ATP as energy source to pump Ca^{2+} against a steep ion gradient across the membrane. In cases of intracellular Ca^{2+} overflow, the mitochondrial Ca^{2+} uniporter (MCU) [6,7] or the NCX [8] can support regulation of the Ca^{2+} level, due to their high capacity. In this review, we will focus on the interplay between these Ca^{2+} regulating systems and their involvement in ER stress coping responses.

Abbreviations: ATF6, activating transcription factor 6; BiP, binding immunoglobulin protein; cADPR, cyclic ADP ribose; CCD, central core disease; CPVT, catecholaminergic polymorphic ventricular tachycardia; CRAC, calcium release activating calcium channel; CRT, calreticulin; CSQ, calsequestrin; ERAD, ER-associated degradation; ERMES, ER-mitochondria encounter structure; IP3, inositol-1,4,5-trisphosphate; IP3R, inositol-1,4,5-trisphosphate receptor; IRE, inositol-requiring enzyme; MCU, mitochondria calcium uniporter; MH, malignant hyperthermia; NCX, sodium/calcium exchanger; NMDA, *N*-methyl-D-aspartate receptor; PERK, protein kinase-like ER kinase; PDIA6, protein disulfide isomerase A6; PLC, phospholipase C; PMCA, plasma membrane calcium ATPase; R, receptor; RYR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum calcium ATPase; SOCE, store operated calcium entry; STIM, stromal interacting molecule; SARAF, SOCE-associated regulatory factor; TRPC, transient receptor potential channel; UPR, unfolded protein response; VOC, voltage operating calcium channel.

* Corresponding author. Fax: +41 44 825 2082.
E-mail addresses: jkrebs@nmr.mpibpc.mpg.de (J. Krebs), luis.agellon@mcgill.ca (L.B. Agellon), marek.michalak@ualberta.ca (M. Michalak).

http://dx.doi.org/10.1016/j.bbrc.2015.02.004
0006-291X/

Many excellent reviews have been published in the last few years focusing on many aspects of ER stress coping responses and the unfolded protein response (UPR) [9–12]. Here we focus on selected aspects of ER Ca^{2+} homeostasis, and its potential impact on ER stress and activation of ER stress coping responses.

2. Ca^{2+} buffers and Ca^{2+} sensors

Ca^{2+} signaling can be derived either through the uptake of extracellular Ca^{2+}, or the release of Ca^{2+} from intracellular stores, which results in changes in the free Ca^{2+} concentration. In the lumen of the intracellular stores, large amounts of Ca^{2+} are buffered by Ca^{2+} binding proteins such as calsequestrin or calreticulin, which are distinct from cytosolic Ca^{2+}-binding proteins such as parvalbumin, calbindin or the group of so-called S100 proteins [13]. The major difference between these two groups of Ca^{2+}-binding proteins is determined by their Ca^{2+} binding properties: the organellar Ca^{2+} buffers are considered low affinity but high capacity Ca^{2+}-binding proteins, in contrast to the cytosolic Ca^{2+} buffers, which have high affinity but low capacity Ca^{2+} binding properties. The latter group is also characterized as EF-hand domain containing proteins, originally characterized by Kretsinger, and based on the crystal structure of parvalbumin [14]. Although EF-hand containing proteins are predominantly found in the cytoplasmic compartment, several EF-hand containing proteins have also been identified in the lumen of the cellular reticular network (STIM1, ERC-55, FKBP65, calumenin, regulcalcin, CALNUC, and Cab45 to name a few) [15–20], but also associated with the mitochondria membrane [21]. The EF-hand motif is characterized as a helix-loop-helix structure and it is highly conserved [22]. EF-hands are not only typical for the cytosolic Ca^{2+} buffers, but they are also found in the so-called Ca^{2+} sensors such as calmodulin, troponinC or the neuronal Ca^{2+} sensor (NCS) family, which upon binding of Ca^{2+} undergo conformational changes enabling them to interact with targets. This differentiation between Ca^{2+} buffer and Ca^{2+} sensor proteins may however change, since newer results seem to indicate that some Ca^{2+} buffer proteins can also provide sensor functions, as well as calmodulin as the classical Ca^{2+} sensor might act as a fast intracellular buffer [23].

3. Ca^{2+} channels

Ca^{2+} can enter the cell down its electrochemical gradient through a variety of channels located in the plasma membrane. These include the voltage-gated Ca^{2+} channels in excitable cells Ca_{V1-3} [24], receptor-operated Ca^{2+} channels such as the *N*-methyl-D-aspartate receptor (NMDA) which is gated by glutamate [25], transient receptor potential channels (TRPC) [26], or store-operated Ca^{2+} entry (SOCE) channels such as ORAI [27,28] (Fig. 1). On the other hand, Ca^{2+} can be released from internal stores, the most important being the endoplasmic or the sarcoplasmic reticulum (ER/SR), through a variety of messengers such as inositol-1,4,5-trisphosphate (IP_3), cyclic ADPribose (cADPR), nicotinic acid adenine dinucleotide phosphate (NAADP) and others [1]. In response to the activation of cell surface receptors, IP_3 is generated through the stimulation of phopholipase C, which hydrolyzes the membrane lipid phosphatidylinositol 4,5-bisphosphate to gain IP_3 and diacylglycerol (DAG). Thus, IP_3 releases Ca^{2+} from the ER through the IP_3 receptor (IP_3R) which is an IP_3-gated Ca^{2+} release channel) [29–31] (Fig. 1). In mammalian organisms, three different genes code for the IP_3R, with additional spliced isoforms. The receptor, anchored in the ER by 6 transmembrane domains, can form homo- or hetero tetramers of 1.2 MDa. The IP_3R works like a scaffold protein, due to its interaction with numerous proteins like the IP_3R binding protein released with IP_3 (IRBIT) [32], calmodulin, FKBP12 and others, which may modulate the function of the IP_3R [33]. In addition, the function of the IP_3R can also be modulated by phosphorylation/dephosphorylation through various kinases and phosphatases [34]. Structural studies revealed the IP_3-binding core, and a suppressor domain at the N-terminus of the IP_3R [35]. They play a critical role in coupling between ligand binding and channel gating [36]. Even if the IP_3R is ubiquitously expressed, and the three different mammalian isoforms share 60–80% homology, the diversity in function and cellular distribution is quite significant. Type 1 receptor is mainly expressed in cerebellar Purkinje cells, type 2 mainly in cardiac myocytes, and type 3 in insulin-secreting β-cells. Numerous detailed studies revealed a remarkable complexity of the structural and functional properties of IP_3R, its diversity in regulation, gating behavior, tissue distribution and development [37,38]. A number of cardiac and neural diseases have been linked to the malfunction of the IP_3R [39].

Homologous to the IP_3R is the Ca^{2+}-release channel of the SR, the ryanodine receptor (RyR), which received its name due to the high affinity binding of the plant alkaloid ryanodine [40]. In muscle cells, the RyR is primarily located on the SR, in non-muscle cells it is expressed in the ER. Early electron microscopy studies discovered a unique junction between SR, transverse or T-tubules and the plasma membrane of skeletal muscles, which was later identified to be mediated by the interaction between the RyR of the SR and the dihydropyridine receptor, the L-type voltage-gated Ca^{2+} channel of T tubules [41]. This represents an early example of membrane contact sites, an area of research which gained increased interest recently, and will be documented later.

The RyR is a homotetramer with a molecular mass of 2.2 MDa and one of the largest membrane proteins known to date, consisting of over 5000 amino acids, [42,43]. Ca^{2+} is released from the RyR by the action of cADPR, which is generated from NAD by the cyclase CD38, a protein originally discovered in sea urchin eggs [44]. It is interesting to note that cADPR can greatly increase the sensitivity of RyR for the Ca^{2+}-induced Ca^{2+} release (CICR) mechanism, which is the basis for cardiac excitation–contraction (E–C) coupling [45]. In order to preserve the function of muscle contraction, Ca^{2+} levels are lowered by either the SR Ca^{2+} pump responsible for the reuptake of Ca^{2+} into the SR/ER, or by the NCX of the plasma membrane, to extrude Ca^{2+} from the cytoplasm (Fig. 1). Similar to the homologous IP_3R, there are also three different genes known for the RyR in mammals: RyR1 was first identified in skeletal muscles [43], RyR2 in the heart [46,47], and RyR3 in brain [48], but to date it is known these proteins are expressed in many different cell types. Similar to the IP_3R, RyRs also act as signal integrators, being modulated by a wide variety of different proteins [49]. In recent years, structural details of a number of domains of the RyR have been solved, leading to a better understanding of the structure–function relationship of the protein [49]. This is strongly supported by the high resolution structure of RyR1 determined by three different research groups who provided details on the channel pore architecture and identified paired EF-hands likely involved in a mechanism for channel gating by Ca^{2+} [50–52]. A number of genetic disorders have been linked to RyR mutations, such as malignant hyperthermia (MH) [53,54], central core disease (CCD) [55,56], or catecholaminergic polymorphic ventricular tachycardia (CPVT) [57], which can affect Ca^{2+} homeostasis due to store-overload Ca^{2+} release, or increased sensitivity to channel opening facilitation. Furthermore, recent evidence suggests that deregulation of RyR can lead to neurodegenerative diseases such as Alzheimer [58].

CD38 is also responsible for metabolizing NADP to gain NAADP, another messenger to mobilize Ca^{2+}. As suggested by the group of Galione [59], the receptor of NAADP is a two pore channel (TPC) located in lysosomes gating the release of Ca^{2+}. This concept has

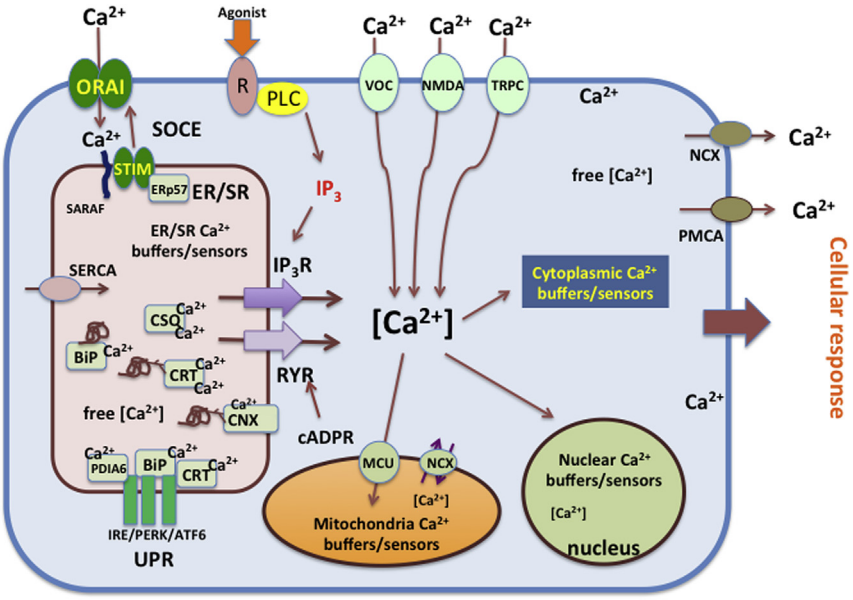

Fig. 1. Schematic cellular representation of the calcium-binding and transporting systems and proteins contributing to Ca^{2+} homeostasis and ER stress. Plasma membrane, reticular membrane network including ER, mitochondria and nuclear envelop contain many different Ca^{2+} transport molecules involved in control of Ca^{2+} movement in and out of the cells and in and out of intracellular organelles. The store-operated Ca^{2+} entry (SOCE) is activated in response to depleted ER Ca^{2+} stores where STIM plays a role of ER luminal Ca^{2+} sensor and Orai1 functions as a plasma membrane Ca^{2+} channel that allows for Ca^{2+} entry from the extracellular milieu into the cytoplasm. Different cellular compartments including ER, cytoplasm, mitochondria and the nucleus contain a pool of free Ca^{2+} and Ca^{2+} bound to Ca^{2+} buffering proteins. Ca^{2+} binding protein also affect function of SOCE (ERp57) and UPR (BiP, PDIA6). ATF6, activating transcription factor 6; BiP, Binding immunoglobulin protein; cADPR, cyclic ADP ribose; CNX, calnexin; CRT, calreticulin; CSQ, calsequestrin; IP_3, inositol-1,4,5-trisphosphate; IP_3R, Inositol-1,4,5-trisphosphate receptor; IRE, inositol-requiring enzyme; MCU, mitochondria calcium uniporter; NCX, sodium/calcium exchanger; NMDA, *N*-methyl-D-aspartate receptor; PERK, protein kinase-like ER kinase; PDIA6, protein disulfide isomerase A6; PLC, phospholipase C; PMCA, plasma membrane calcium ATPase; R, receptor; RYR, ryanodine receptor; SERCA, sarco/endoplasmic reticulum calcium ATPase; SOCE, store operated calcium entry; STIM, stromal interacting molecule; SARAF, SOCE-associated regulatory factor; TRPC, transient receptor potential channel; UPR, unfolded protein response; VOC, voltage operating calcium channel.

been challenged by Clapham and his co-workers [60], who demonstrated that the lysosomal TPCs are not NAADP sensitive Ca^{2+} channels, but ATP-sensitive Na^{+} channels complexed to the mammalian target of rapamycin (mTOR) [60].

4. Ca^{2+} pumps

The calcium pump of the ER/SR is responsible for the reuptake of Ca^{2+} into the lumen of the reticular network (Fig. 1). The SERCA pump belongs to the class of P-type ATPases [61,62], since it uses the energy of ATP to drive Ca^{2+} across the membrane against the ion gradient, by forming a high-energy intermediate acyl-phosphate with a stoichiometry of 2:1 Ca^{2+}/ATP. Based on the classical E1/E2 theory, high affinity binding of Ca^{2+} occurs in the E1 state, and faces the cytoplasm, whereas the low affinity site representing the E2 state, faces the luminal site of the SR/ER [63]. The seminal work of Toyoshima, Nissen and their co-workers, on the structure of the SERCA pump from skeletal muscles, provided us with detailed structural details of most of the different states during the reaction cycle and their functional consequences [5,64]. SERCA, coded by three different genes, is a transmembrane protein of approximately 100-kDa, with additional isoforms due to alternative splicing. The enzyme consists of 10 transmembrane helices, and like other P-type ATPases, can be divided into three functional domains facing the cytosol: the activator, the nucleotide binding and the phosphorylation domains [5]. To regulate the gating mechanism during the reaction cycle, structural details of the protein revealed large domain movements. Various mutations affect either the E2 to E1 transition, strongly reduce the Ca^{2+} affinity of the protein, which may lead to a genetic skin disorder such as Darier disease [64]. Phospholamban (PLN) is an important reversible regulator of cardiac SERCA activity, which is phosphorylated in a β-adrenergic response by either protein-kinase A or calmodulin-dependent kinase II, thereby activating the SERCA Ca^{2+} pump, whereas the dephosphorylated form of PLN inhibits the SERCA pump [65,66]. A similar regulation of the SERCA pump of skeletal muscles is carried out by sarcolipin (SLN), a membrane protein homologous to PLN [67,68]. Recent structural studies revealed that PLN and SLN bind to the Ca^{2+}-ATPase in their E1.Mg^{2+} state [69–71]. The cleft provided by transmembrane helices M2, M6 and M9 of SERCA is proposed to build the binding site for sarcolipin/phospholamban [70,71]. PLN is composed of two α-helices linked by a flexible loop [72], which was confirmed by studying the structure of PLN bound to SERCA, reconstituted in lipid bilayers using solid-state NMR methods [73].

The plasma membrane Ca^{2+} ATPase (PMCA) is responsible for fine tuning of the Ca^{2+} level in the cell. Ca^{2+} is pumped across the plasma membrane out of the cell at the expense of ATP, against a Ca^{2+} gradient with a 1:1 stoichiometry. PMCA activity is regulated in many ways [4,74]. Likely the most important regulator of PMCA is calmodulin, which directly interacts with PMCA [75]. Like the SERCA pump, PMCA also belongs to the class of P-type ATPases [61,62], forming an intermediate acyl-phosphate of high energy, at the expense of ATP consumption. Conformational changes occur during the reaction cycle, distinguishing at least two different conformational states, E1 and E2 [76], which were studied in much more detail for the homologous SERCA pump as mentioned previously [5,64]. Similar conformational changes may also exist for PMCA, as suggested by homology modeling, based on the structures of the SERCA pump, even if a high resolution structure of PMCA has not been solved yet [77]. Calmodulin is the major activator of PMCA, but in the absence of calmodulin, the calmodulin-binding domain interacts with two receptor sites within the catalytic domain of the pump, which keeps the enzyme in an inhibited state [78,79]. Detailed structural and biochemical studies of the interaction between calmodulin, PMCA and the binding domain of

the enzyme have been made, suggesting that the unique interaction between the C-terminal region of calmodulin and the pump not only would be necessary and sufficient to release the autoinhibitory state of the enzyme, but also sufficient to activate PMCA even at resting cell Ca^{2+} concentrations, important for the fine tuning of Ca^{2+} homeostasis [80–83]. cDNA encoding PMCA has been isolated from human [84] and rat [85] tissues, and its amino acid sequence determined. The protein consists of 10 transmembrane domains, the N-and C-terminus are both located in the cytosol and the major protein mass protrudes into the intracellular space. The enzyme is an essential component of all mammalian plasma membranes, and in mammals four different genes encode the plasma membrane Ca^{2+} pump [4]. Additional isoforms of the protein are produced by alternative splicing of the primary transcripts as first demonstrated by Strehler et al. [86], providing a great functional versatility, diverse tissue distribution, and differential membrane localization [74] important for the different requirements to regulate Ca^{2+} homeostasis. The importance of PMCA for regulating Ca^{2+} homeostasis is underlined by an increasing number of diseases linked to a malfunction of PMCA [87].

5. Store-operated calcium entry (SOCE)

The ER plays an essential role in the regulation of Ca^{2+} homeostasis. It remained long unanswered as to how the reticular membrane network senses the level of the luminal Ca^{2+} after Ca^{2+} was released from the system. Putney [88] proposed the store-operated Ca^{2+} entry (SOCE) model for receptor-regulated Ca^{2+} entry, where Ca^{2+} enters from the extracellular space after the reticular pool is depleted. The original capacitative model anticipated membrane contact sites, with the apposition of regions of the plasma membrane and the reticulum as a prerequisite for the regulation of SOCE, a view which was later supported by significant evidence [89]. These proposed SOCE channels were later electrophysiologically characterized as Ca^{2+} release-activated Ca^{2+} channels (CRAC) [90], but the molecular details remained unknown for a long time. Now, the molecular participants of the SOCE process have been identified as STIM (stromal interacting molecule) [91,92] and ORAI, an essential component of the CRAC channel [27,28,93] (Fig. 1). STIM is the ER-resident protein containing a single transmembrane domain and two EF-hands at the luminal N-terminus important for sensing the Ca^{2+} level [91,92]. ORAI (named according to greek mythology as a keeper of the gates to heaven [27], of which three isoforms have been identified in mammals, is a plasma membrane protein with four transmembrane domains, which provide the pore of the channel [27,28,93] which is supported by the recently solved structure of ORAI from *Drosophila melanogaster* [94]. This structure provided evidence that the Ca^{2+} channel is comprised of a hexameric assembly of ORAI subunits arranged around a central ion pore [94]. Detailed structural studies of STIM revealed both a canonical and non-canonical EF-hand, which together and in cooperation with the highly conserved so-called sterile α motif (SAM), sense changes of the luminal Ca^{2+} level of the ER [95]. In vertebrates, there are two STIM isoforms, STIM1 and STIM2, and both are ubiquitously expressed, but STIM2 is enriched in the nervous system, whereas STIM1 may play a more dominant role in regulating CRAC channels. Both isoforms of STIM contain 2 EF-hands, the SAM domain and several coiled-coil domains (CC1–3) at the cytosolic C-terminus of STIM, which are important for the interaction with ORAI. At resting ER Ca^{2+} levels, no interaction between STIM and ORAI can be observed, but upon depletion of the ER Ca^{2+}, STIM molecules oligomerize with the consequence that the conformation of the CC1 domain changes to enable the CRAC channel activating domain of STIM to recruit and gate the ORAI1-CRAC channel at the junction of the ER with the plasma membrane [96]. Recently, Palty et al. identified an ER integral membrane protein as a negative regulator of SOCE [97]. This protein, named SARAF (SOCE-associated regulatory factor), associates with STIM to facilitate slow Ca^{2+}-dependent inactivation to protect cells from Ca^{2+} overfilling [97]. Prins et al. [98] provided evidence for an interesting link between controlling Ca^{2+} homeostasis, protein quality control in the ER and induction of the unfolded protein response (UPR) due to ER stress. These authors showed that ERp57, an ER resident oxiodoreductase, which together with calreticulin and calnexin is involved in the quality control of protein folding [99] binds to the luminal domain of STIM1 (Fig. 1). ERp57 inhibits STIM1 induced SOCE via binding to two conserved cysteins closed to the N-terminus of STIM [98]. These finding indicate that ER-resident oxidoreductases are critical regulators of ER Ca^{2+} homeostasis [98]. In addition, recent results accumulated that Ca^{2+} fluxes across the ER membrane are modulated by a number of microRNAs which also regulate different branches of the unfolded protein response (for a review see Ref. [100]).

6. Membrane contact sites and Ca^{2+} signaling

As indicated earlier, recent accumulating evidence suggested that coordination of cellular activities often occurs by using a network of membrane contact sites (MCS) between different organelles [89]. Such contacts, established by tethering structures, create microdomains that enable the exchange of signals or metabolites between different membrane compartments. The ER is an important component of an extensive cellular reticular network, and it builds those contact sites with mitochondria, plasma membrane and other cellular organelles, which are considered especially important for the regulation of inter-organellar exchange of Ca^{2+} with wide-ranging consequences for Ca^{2+} dynamics. MCS between the ER and mitochondria play a major role in Ca^{2+} signaling due to the possible uptake of ER-released Ca^{2+} by mitochondria through the mitochondrial Ca^{2+} uniporter MCU [6], possibly mediated by mitofusin 2, a GTPase [101] and other proteins. A number of these conserved proteins have been identified by Kornmann, originally in yeast, as a protein complex named ER-mitochondria encounter structure (ERMES; [89]). The importance of MCS for the regulation of Ca^{2+} has been supported by the detection of high local Ca^{2+} concentrations at the MCS [102]. On the other hand, recent studies indicate that impairment of the ER-mitochondria contact sites might be involved in the pathology of several human neurodegenerative diseases [103]. In addition, many proteins involved in shaping the ER network are mutated in a number of common neural diseases, indicating their importance for ER network dynamics also involved in regulating Ca^{2+} signaling [104].

7. Ca^{2+} homeostasis and the unfolded protein response (UPR), an ER stress coping response

As pointed out before, the ER, as a component of the cellular reticular network, is a multifunctional organelle that plays a critical role in many cellular processes, including Ca^{2+} homeostasis (both in the ER lumen and other cellular compartments), lipid and protein biosynthesis, protein folding, and post-translational modification and regulation of gene expression [105]. Although in the ER lumen the majority of Ca^{2+} is bound to Ca^{2+} buffers the ER maintains a tightly controlled free Ca^{2+} concentration, which likely plays a critical role in ER Ca^{2+} signaling [106]. The multi-functional nature of the ER enables it to sense and integrate many of incoming signals, in particular the changes in free and bound Ca^{2+} concentrations in and outside of the ER compartment. More importantly,

the ER membrane can modulate its own luminal Ca^{2+} dynamics and generate appropriate signals to maintain balanced homeostasis. The majority of ER-associated proteins participate in maintaining ER Ca^{2+} homeostasis. For example, molecular chaperones such as calreticulin, GRP94 or BiP and folding enzymes (protein disulphide isomerase [PDI] family of enzymes) contribute to Ca^{2+} buffering in the ER lumen [107]. BiP is an especially important Ca^{2+}-binding protein as it is involved in sensing mis-folded protein accumulation in the ER and in conjunction with three other ER transmembrane proteins, ATF6, IRE1 and PERK, is responsible for the UPR [108]. BiP also plays an important role as a Ca^{2+} buffer in the lumen of ER. Association between BiP and nascent polypeptides is stabilized by high Ca^{2+} concentrations [109]. BiP may also be involved in Ca^{2+} transport from the ER to the mitochondria through transient associations with the ER membrane sigma-1 receptor (Sig-1R) [110]. In addition, BIP interacts with the translocon complex, contributes to the prevention of ER Ca^{2+} leakage, and helps to maintain ER homeostasis. PDI family proteins, ER associated oxidoreductases, catalyze disulfide bond formation, isomerization, and reduction of nascent proteins. PDIs directly bind Ca^{2+} to support their interaction with polypeptides and other chaperones. Clearly, protein folding and chaperone function both require Ca^{2+}, therefore, maintenance of balanced ER Ca^{2+} homeostasis is critical to virtually all ER-supported functions. Interestingly, ER and other components of the cellular reticular network contain a number of EF-hand proteins including STIMs that may play a role in luminal Ca^{2+} sensors for the reticular network [15–20].

Not surprisingly, disruption of Ca^{2+} homeostasis in the ER leads to activation of ER stress coping responses, one of which is the UPR [11,12]. Subtle disturbances of ER Ca^{2+} homeostasis have been linked to many human diseases such as cardiac disease or many neuropathies. It is critical, therefore, that cells mobilize corrective strategies and generate output signals in response to changes in cellular Ca^{2+} homeostasis. Activation of the UPR includes: (1) transcriptional activation of genes encoding chaperones, folding enzymes and other proteins involved in ER-associated degradation (ERAD); (2) translational attenuation to eliminate synthesis of new proteins into the ER; and (3) activation of apoptotic pathways if ER homeostasis cannot be restored [111,112]. The UPR is driven by three ER-associated integral membrane proteins: the ER kinase dsRNA-activated protein kinase-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1 (IRE1), in combination with the ER molecular chaperone BiP (immunoglobulin binding protein) [11]. In the UPR, PERK phosphorylates the eukaryotic translation initiation factor 2α (eIF2α), which attenuates translation of mRNA. The ATF6 is escorted to the Golgi where it is processed by site 1 and site 2 protease, releasing the DNA binding domain that functions as a transcription factor [113]. IRE1 has endoribonuclease activity that splices the mRNA encoding the transcription factor Xbp1 [114]. The spliced Xbp1 transcript is translated to produce a transcription factor that induces the expression of genes encoding molecular chaperones, folding enzymes and components of ERAD. Under prolonged and severe activation of the UPR, cells are eliminated by apoptosis [115]. Furthermore, UPR activated-autophagy may be induced, a controlled self-degradation process that can promote cell survival by eliminating damaged cellular components [116–119]. There is tight regulation of the three arms of the UPR with respect to temporal progression and amplitude of activation, which likely dictates the nature and elaboration of the cellular response.

Loss of nutrients/energy leads to the loss of ER homeostasis where Ca^{2+} signaling may play a role in recognizing disruption in reticular homeostasis, an important role impacting Ca^{2+} signaling. Experimentally, thapsigargin, an inhibitor of SERCA, and tunicamycin, an inhibitor of protein glycosylation, have been used as model drugs for disrupting the ER homeostasis-induced UPR [120]. Both drugs affect ER Ca^{2+} homeostasis, and therefore, contribute to activation of ER stress coping responses including the UPR [120]. Importantly, modulation of ER Ca^{2+} homeostasis affects mitochondria function and consequently energy metabolism including lipid turnover which is critically dependent on lipase maturation factor 1 (Lmf1), an ER chaperone [11,111,120,121]. Furthermore, depletion of the ER Ca^{2+} store activates SOCE involving the STIM1/Orai1 pathway that affects availability of cytoplasmic Ca^{2+} for intercellular signaling [122]. Depletion of the Ca^{2+} store leads to a rapid accumulation of mis-folded proteins, promoting dissociation of BiP from IRE1, PERK and ATF6 UPR components, thereby activating the UPR pathway. Activation of SOCE has also been associated with expression of specific microRNAs [100] and SOCE may indirectly influence ER luminal Ca^{2+}-dependent regulation of the UPR (IRE1 activity) [123].

Although the role of BiP as an essential component of the UPR activation is well established, other ER luminal Ca^{2+} buffers have recently been identified as regulators of the UPR [123,124]. Calreticulin, an ER resident Ca^{2+} buffer, associates with ATF6 in a carbohydrate-dependent way, and together with BiP, maintains ATF6 in an inactive state [124]. Upon ER stress, both BiP and calreticulin dissociate from ER membrane localized ATF6, promoting ATF6 trafficking to the Golgi where it is proteolytically processed [124]. Recently, PDIA6, an ER resident oxidoreductase, was identified as a regulator of IRE1 activity in response to depletion of the ER Ca^{2+} store [123]. PDIA6 interacts with the luminal domain of IRE1α in a cysteine-dependent manner to enhance IRE1 α activity. Interestingly, PDIA6 does not substantially affect the activity of the PERK pathway that mediates responses to ER stress, suggesting that each arm of the UPR may be responsive to different components of the ER lumen, depending on the nature of stress conditions. Importantly, ER store Ca^{2+} depletion and activation of SOCE reduces the abundance of the microRNA miR-322, which regulates PDIA6 mRNA stability and consequently IRE1 α activity [123]. This is the first documented case for ER luminal Ca^{2+}, which together with PDIA6, IRE1α and miR-322 function in a dynamic feedback loop modulating the UPR under conditions of disrupted ER Ca^{2+} homeostasis [123]. Other microRNAs have been shown to regulate components that maintain ER homeostasis, including channels to control Ca^{2+} fluxes across the ER membrane and, therefore, impact on ER Ca^{2+} homeostasis [100]. Expression of these microRNAs may be highly sensitive to changes in ER Ca^{2+} homeostasis [100]. The role of these microRNAs on the activation of ER stress coping responses and in disease pathogenesis remains to be established. Nevertheless, it is clear that the ER luminal environment (Ca^{2+} homeostasis, ER resident proteins) together with specific microRNAs interact to control the UPR coping response and reticular homeostasis.

In summary, cellular membranes contain many Ca^{2+}-transport and -binding molecules involved in control of Ca^{2+} movement in and out of the cells and in and out of cellular organelles. An important element of cellular Ca^{2+} signaling is the maintenance of free versus bound Ca^{2+} balance in all cellular compartments. Integration of Ca^{2+} signaling in the lumen of the cellular reticular network including the ER, in mitochondria, the nucleus and in the cytoplasm provide integrated mechanisms for responding to cellular stresses by activation of appropriate coping responses. The importance of maintaining Ca^{2+} homeostasis and appropriate adaptation to ER stress is underlined by the accumulating evidence that constant disturbing Ca^{2+} homeostasis and chronic ER stress could lead to neurodegenerative disorders [125], diabetes [126], cardiac hypertrophy [127] or cancer [128].

Conflicts of interest

The authors declare no conflict of interests.

Acknowledgments

This work was supported by grants to M.M. and L.B.A. from the Canadian Institutes of Health Research (CIHR, MOP-15291, MOP-15415, MOP-53050). J.K. acknowledges the support of the Max Planck Society.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.bbrc.2015.02.004.

References

[1] M.J. Berridge, M.D. Bootman, H.L. Roderick, Calcium signalling: dynamics, homeostasis and remodelling, Nat. Rev. Mol. Cell Biol. 4 (2003) 517–529.
[2] J. Krebs, The role of calcium in apoptosis, Biometals 11 (1998) 375–382.
[3] V. Sharma, D.M. O'Halloran, Recent structural and functional insights into the family of sodium calcium exchangers, Genesis 52 (2014) 93–109.
[4] M. Brini, T. Cali, D. Ottolini, E. Carafoli, The plasma membrane calcium pump in health and disease, FEBS J. 280 (2013) 5385–5397.
[5] C. Toyoshima, How Ca^{2+}-ATPase pumps ions across the sarcoplasmic reticulum membrane, Biochim. Biophys. Acta 1793 (2009) 943–946.
[6] D. De Stefani, A. Raffaello, E. Teardo, I. Szabo, R. Rizzuto, A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter, Nature 476 (2011) 336–340.
[7] J.M. Baughman, et al., Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter, Nature 476 (2011) 341–345.
[8] D.A. Nicoll, S. Longoni, K.D. Philipson, Molecular cloning and functional expression of the cardiac sarcolemmal Na^+-Ca^{2+} exchanger, Science 250 (1990) 562–565.
[9] E. Dufey, D. Sepulveda, D. Rojas-Rivera, C. Hetz, Cellular mechanisms of endoplasmic reticulum stress signaling in health and disease. 1. An overview, Am. J. Physiol. Cell. Physiol. 307 (2014) C582–C594.
[10] P. Walter, D. Ron, The unfolded protein response: from stress pathway to homeostatic regulation, Science 334 (2011) 1081–1086.
[11] J. Groenendyk, L.B. Agellon, M. Michalak, Coping with endoplasmic reticulum stress in the cardiovascular system, Annu. Rev. Physiol. 75 (2013) 49–67.
[12] J. Krebs, J. Groenendyk, M. Michalak, Ca^{2+}-signaling, alternative splicing and endoplasmic reticulum stress responses, Neurochem. Res. 36 (2011) 1198–1211.
[13] I. Marenholz, C.W. Heizmann, G. Fritz, S100 proteins in mouse and man: from evolution to function and pathology (including an update of the nomenclature), Biochem. Biophys. Res. Commun. 322 (2004) 1111–1122.
[14] R.H. Kretsinger, C.E. Nockolds, Carp muscle calcium-binding protein. II. Structure determination and general description, J. Biol. Chem. 248 (1973) 3313–3326.
[15] M. Yamaguchi, Role of regucalcin in maintaining cell homeostasis and function, Int. J. Mol. Med. 15 (2005) 371–389.
[16] P.B. Stathopulos, G.Y. Li, M.J. Plevin, J.B. Ames, M. Ikura, Stored Ca^{2+} depletion-induced oligomerization of stromal interaction molecule 1 (STIM1) via the EF-SAM region: an initiation mechanism for capacitative Ca^{2+} entry, J. Biol. Chem. 281 (2006) 35855–35862.
[17] K. Weis, G. Griffiths, A.I. Lamond, The endoplasmic reticulum calcium-binding protein of 55 kDa is a novel EF-hand protein retained in the endoplasmic reticulum by a carboxyl-terminal His-Asp-Glu-Leu motif, J. Biol. Chem. 269 (1994) 19142–19150.
[18] D. Yabe, T. Nakamura, N. Kanazawa, K. Tashiro, T. Honjo, Calumenin, a Ca^{2+}-binding protein retained in the endoplasmic reticulum with a novel carboxyl-terminal sequence, HDEF, J. Biol. Chem. 272 (1997) 18232–18239.
[19] P.E. Scherer, G.Z. Lederkremer, S. Williams, M. Fogliano, G. Baldini, H.F. Lodish, Cab45, a novel Ca^{2+}-binding protein localized to the Golgi lumen, J. Cell Biol. 133 (1996) 257–268.
[20] M. Ozawa, T. Muramatsu, Reticulocalbin, a novel endoplasmic reticulum resident Ca^{2+}-binding protein with multiple EF hand motifs and a carboxyl-terminal HDEL sequence, J. Biol. Chem. 268 (1993) 699–705.
[21] G. Hajnoczky, et al., Reliance of ER-mitochondrial calcium signaling on mitochondrial EF-hand Ca^{2+} binding proteins: Miros, MICUs, LETM1 and solute carriers, Curr. Opin. Cell. Biol. 29 (2014) 133–141.
[22] H. Kawasaki, S. Nakayama, R.H. Kretsinger, Classification and evolution of EF-hand proteins, Biometals 11 (1998) 277–295.
[23] B. Schwaller, The regulation of a cell's Ca^{2+} signaling toolkit: the Ca^{2+} homeostasome, Adv. Exp. Med. Biol. 740 (2012) 1–25.
[24] E.S. Piedras-Renteria, C.F. Barrett, Y.-Q. Cao, R.W. Tsien, Voltage-gated calcium channels, calcium signaling and channelopathies, in: J. Krebs, M. Michalak (Eds.), Calcium: a Matter of Life or Death, Elsevier, Amsterdam, 2007, pp. 127–166.
[25] G.E. Hardingham, H. Bading, Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders, Nat. Rev. Neurosci. 11 (2010) 682–696.
[26] H.L. Ong, L.B. de Souza, K.T. Cheng, I.S. Ambudkar, Physiological functions and regulation of TRPC channels, Handb. Exp. Pharmacol. 223 (2014) 1005–1034.
[27] S. Feske, et al., A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function, Nature 441 (2006) 179–185.
[28] M. Prakriya, S. Feske, Y. Gwack, S. Srikanth, A. Rao, P.G. Hogan, Orai1 is an essential pore subunit of the CRAC channel, Nature 443 (2006) 230–233.
[29] H. Streb, R.F. Irvine, M.J. Berridge, I. Schulz, Release of Ca^{2+} from a non-mitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate, Nature 306 (1983) 67–69.
[30] T. Furuichi, S. Yoshikawa, A. Miyawaki, K. Wada, N. Maeda, K. Mikoshiba, Primary structure and functional expression of the inositol 1,4,5-trisphosphate-binding protein, Nature 342 (1989) 32–38.
[31] N. Maeda, M. Niinobe, K. Mikoshiba, A cerebellar Purkinje cell marker P400 protein is an inositol 1,4,5-trisphosphate (InsP3) receptor protein. Purification and characterization of the InsP3 receptor complex, EMBO J. 9 (1990) 61–67.
[32] H. Ando, A. Mizutani, T. Matsu-Ura, K. Mikoshiba, IRBIT, a novel Inositol 1,4,5-trisphosphate (IP3) receptor-binding protein, is released from the IP3 receptor upon IP3 binding to the receptor, J. Biol. Chem. 278 (2003) 10602–10612.
[33] H. Ando, K. Kawaai, K. Mikoshiba, IRBIT: a regulator of ion channels and ion transporters, Biochim. Biophys. Acta 1843 (2014) 2195–2204.
[34] V. Vanderheyden, B. Devogelaere, L. Missiaen, H. de Smedt, G. Bultynck, J.B. Parys, Regulation of inositol 1,4,5-trisphosphate-induced Ca^{2+} release by reversible phosphorylation and dephosphorylation, Biochim. Biophys. Acta 1793 (2009) 959–970.
[35] I. Bosanac, et al., Structure of the inositol 1,4,5-trisphosphate receptor binding core in complex with its ligand, Nature 420 (2002) 696–700.
[36] J. Chan, H. Yamazaki, N. Ishiyama, M.D. Seo, T.K. Mai, T. Michikawa, K. Mikoshiba, M. Ikura, Structural studies of inositol 1,4,5-trisphosphate receptor: coupling ligand binding to channel gating, J. Biol. Chem. 285 (2010) 36092–36099.
[37] K. Mikoshiba, IP_3 receptor/Ca^{2+} channel: from discovery to new signaling concepts, J. Neurochem. 102 (2007) 1426–1446.
[38] J.K. Foskett, C. White, K.-H. Cheung, D.-O.D. Mak, Inositol trisphosphate receptor Ca^{2+} release channels, Physiol. Rev. 87 (2007) 593–658.
[39] M.J. Berridge, Calcium signalling remodelling and disease, Biochem. Soc. Trans. 40 (2012) 297–309.
[40] F. van Petegem, Ryanodine receptors: structure and function, J. Biol. Chem. 287 (2012) 31624–31632.
[41] C. Franzini-Armstrong, The sarcoplasmic reticulum and the control of muscle contraction, FASEB J. 13 (1999) S266–S270.
[42] M. Inui, A. Saito, S. Fleischer, Purification of the ryanodine receptor and identity with feet structures of junctional terminal cisternae of sarcoplasmic reticulum from fast skeletal muscle, J. Biol. Chem. 262 (1987) 1740–1747.
[43] H. Takeshima, et al., Primary structure and expression from complementary DNA of skeletal muscle ryanodine receptor, Nature 339 (1989) 439–445.
[44] A. Galione, H.C. Lee, W.B. Busa, Ca^{2+}-induced Ca^{2+} release in sea urchin egg homogenate: modulation by cyclic ADP-ribose, Science 253 (1991) 1143–1146.
[45] H.C. Lee, Cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate (NAADP) as messengers for calcium mobilization, J. Biol. Chem. 287 (2012) 31633–31640.
[46] J. Nakai, T. Imagawa, Y. Hakamata, M. Shigekawa, H. Takeshima, S. Numa, Primary structure and functional expression from cDNA of the cardiac ryanodine receptor/calcium release channel, FEBS Lett. 271 (1990) 169–177.
[47] K. Otsu, H. Willard, V. Khanna, F. Zorzato, N. Green, D. MacLennan, Molecular cloning of cDNA encoding the Ca^{2+} release channel (ryanodine receptor) of rabbit cardiac muscle sarcoplasmic reticulum, J. Biol. Chem. 265 (1990) 13472–13483.
[48] Y. Hakamata, J. Nakai, H. Takeshima, K. Imoto, Primary structure and distribution of a novel ryanodine receptor/calcium release channel from rabbit brain, FEBS Lett. 312 (1992) 229–235.
[49] F. Van Petegem, Ryanodine receptors: Allosteric ion channel giants, J. Mol. Biol. 427 (2015) 31–53.
[50] R. Zalk, et al., Structure of a mammalian ryanodine receptor, Nature 517 (2015) 44–49.
[51] R.G. Efremov, A. Leitner, R. Aebersold, S. Raunser, Architecture and conformational switch mechanism of the ryanodine receptor, Nature 517 (2015) 39–43.
[52] Z. Yan, et al., Structure of the rabbit ryanodine receptor RyR1 at near-atomic resolution, Nature 517 (2015) 50–55.
[53] J. Fujii, et al., Identification of a mutation in porcine ryanodine receptor associated with malignant hyperthermia, Science 253 (1991) 448–451.
[54] E.F. Gillard, et al., A substitution of cysteine for arginine 614 in the ryanodine receptor is potentially causative of human malignant hyperthermia, Genomics 11 (1991) 751–755.

[55] K.A. Quane, et al., Mutations in the ryanodine recepto gene in central core disease and malignant hyperthermia, Nat. Genet. 5 (1993) 51–55.
[56] J.C. Mulley, et al., Refined genetic localization for central core disease, Am. J. Hum. Genet. 52 (1993) 398–405.
[57] S.G. Priori, et al., Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia, Circulation 103 (2001) 196–200.
[58] D. Del Prete, F. Checler, M. Chami, Ryanodine receptors: physiological function and deregulation in Alzheimer disease, Mol. Neurodegener. 9 (2014) 21, http://dx.doi.org/10.1186/1750-1326-9-21.
[59] P.J. Calcraft, et al., NAADP mobilizes calcium from acidic organelles through two-pore channels, Nature 459 (2009) 596–600.
[60] C. Cang, et al., mTOR regulates lysosomal ATP-sensitive two-pore Na^+ channel to adapt to metabolic state, Cell 152 (2013) 778–790.
[61] P.L. Pedersen, E. Carafoli, Ion motive ATPases. I. Ubiquity, properties, and significance for cell function, Trends Biochem. Sci. 12 (1987) 146–150.
[62] P.L. Pedersen, E. Carafoli, Ion motive ATPases. II. Energy coupling and work output, Trends Biochem. Sci. 12 (1987) 186–189.
[63] L. de Meis, A.L. Vianna, Energy conversion by the Ca^{2+}-dependent ATPase of the sarcoplasmic reticulum, Annu. Rev. Biochem. 48 (1979) 275–292.
[64] M. Bublitz, et al., Ion pathways in the sarcoplasmic reticulum Ca^{2+} ATPase, J. Biol. Chem. 288 (2013) 10759–10765.
[65] D.H. MacLennan, E.G. Kranias, Phospholamban: a crucial regulator of cardiac contractility, Nat. Rev. Mol. Cell. Biol. 4 (2003) 566–577.
[66] E.G. Kranias, R.J. Hajjar, Modulation of cardiac contractility by the phospholamban/SERCA2a regulatome, Circ. Res. 110 (2012) 1646–1660.
[67] A. Odermatt, S. Becker, V.K. Khanna, K. Kurzydlowski, E. Leisner, D. Pette, D.H. MacLennan, Sarcolipin regulates the activity of SERCA1, the fast-twitch skeletal muscle sarcoplasmic reticulum Ca^{2+}-ATPase, J. Biol. Chem. 273 (1998) 12360–12369.
[68] N.C. Bal, et al., Sarcolipin is a newly identified regulator of muscle-based thermogenesis in mammals, Nat. Med. 18 (2012) 1575–1579.
[69] C. Toyoshima, F. Cornelius, New crystal structures of PII-type ATPases: excitement continues, Curr. Opin. Struct. Biol. 23 (2013) 507–514.
[70] C. Toyoshima, S. Iwasawa, H. Ogawa, A. Hirata, J. Tsueda, G. Inesi, Crystal structures of the calcium pump and sarcolipin in the Mg^{2+}-bound E1 state, Nature 495 (2013) 260–265.
[71] A.-M.L. Winther, et al., The sarcolipin-bound calcium pump stabilizes calcium sites exposed to the cytoplasm, Nature 495 (2013) 265–270.
[72] S. Lamberth, H. Schmid, M. Muenchbach, T. Vorherr, J. Krebs, E. Carafoli, C. Griesinger, NMR solution structure of phospholamban, Helv. Chim. Acta 83 (2000) 2141–2152.
[73] K. Seidel, O.C. Andronesi, J. Krebs, C. Griesinger, H.S. Young, S. Becker, M. Baldus, Structural characterization of Ca^{2+}-ATPase-bound phospholamban in lipid bilayers by solid-state nuclear magnetic resonance (NMR) spectroscopy, Biochemistry 47 (2008) 4369–4376.
[74] E.E. Strehler, A.G. Filoteo, J.T. Penniston, A.J. Caride, Plasma-membrane Ca^{2+} pumps: structural diversity as the basis for functional versatility, Biochem. Soc. Trans. 35 (2007) 919–922.
[75] P. James, M. Maeda, R. Fischer, A.K. Verma, J. Krebs, J.T. Penniston, E. Carafoli, Identification and primary structure of a calmodulin binding domain of the Ca^{2+} pump of human erythrocytes, J. Biol. Chem. 263 (1988) 2905–2910.
[76] J. Krebs, M. Vasak, A. Scarpa, E. Carafoli, Conformational differences between the E1 and E2 states of the calcium adenosinetriphosphatase of the erythrocyte plasma membrane as revealed by circular dichroism and fluorescence spectroscopy, Biochemistry 26 (1987) 3921–3926.
[77] J. Krebs, V. Helms, C. Griesinger, E. Carafoli, The regulation of the calcium signal by membrane pumps, Helv. Chim. Acta 86 (2003) 3875–3888.
[78] R. Falchetto, T. Vorherr, J. Brunner, E. Carafoli, The plasma membrane Ca^{2+}-pump contains a site that interacts with its calmodulin-binding domain, J. Biol. Chem. 266 (1991) 2930–2936.
[79] R. Falchetto, T. Vorherr, E. Carafoli, The calmodulin binding site of the plasma membrane Ca^{2+} pump interacts with the transduction domain of the enzyme, Protein Sci. 1 (1992) 1613–1621.
[80] D. Guerini, J. Krebs, E. Carafoli, Stimulation of the purified erythrocyte Ca^{2+} ATPase by tryptic fragments of calmodulin, J. Biol. Chem. 259 (1984) 15172–15177.
[81] Z.H. Gao, J. Krebs, M.F. VanBerkum, W.J. Tang, J.F. Maune, A.R. Means, J.T. Stull, K. Beckingham, Activation of four enzymes by two series of calmodulin mutants with point mutations in individual Ca^{2+} binding sites, J. Biol. Chem. 268 (1993) 20096–20104.
[82] B. Elshorst, et al., NMR solution structure of a complex of calmodulin with a binding peptide of the Ca^{2+} pump, Biochemistry 38 (1999) 12320–12332.
[83] N. Juranic, E. Atanasova, A.G. Filoteo, S. Macura, F.G. Prendergast, J.T. Penniston, E.E. Strehler, Calmodulin wraps around its binding domain in the plasma membrane Ca^{2+} pump anchored by a novel 18-1 motif, J. Biol. Chem. 285 (2010) 4015–4024.
[84] A.K. Verma, et al., Complete primary structure of a human plasma membrane Ca^{2+} pump, J. Biol. Chem. 263 (1988) 14152–14159.
[85] G.E. Shull, J. Greeb, Molecular cloning of two isoforms of the plasma membrane Ca^{2+}-transporting ATPase from rat brain. Structural and functional domains exhibit similarity to Na+, K+- and other Cation transport ATPases, J. Biol. Chem. 263 (1988) 8646–8657.
[86] E.E. Strehler, M.-A. Strehler-Page, G. Vogel, E. Carafoli, mRNAs for plasma membrane calcium pump isoforms differing in their regulatory domain are generated by alternative splicing that involves two internal donor sites in a single exon, Proc. Natl. Acad. Sci. U.S.A. 86 (1989) 6908–6912.
[87] J. Krebs, The plethora of PMCA isoforms: alternative splicing and differential expression, Biochim. Biophys. Acta (2015), http://dx.doi.org/10.1016/j.bbamcr.2014.12.020 (–).
[88] J.W. Putney Jr., A model for receptor-regulated calcium entry, Cell Calcium 7 (1986) 1–12.
[89] S.C.J. Helle, G. Kanfer, K. Kolar, A. Lang, A.H. Michel, B. Kornmann, Organization and function of membrane contact sites, Biochim. Biophys. Acta 1833 (2013) 2526–2541.
[90] A.B. Parekh, J.W. Putney Jr., Store-operated calcium channels, Physiol. Rev. 85 (2005) 757–810.
[91] J. Roos, et al., STIM1, an essential and conserved component of store-operated Ca^{2+} channel function, J. Cell. Biol. 169 (2005) 435–445.
[92] J. Liou, et al., STIM is a Ca^{2+} sensor essential for Ca^{2+}-store-depletion-triggered Ca^{2+} influx, Curr. Biol. 15 (2005) 1235–1241.
[93] A.V. Yeromin, S.L. Zhang, W. Jiang, Y. Yu, O. Safrina, M.D. Cahalan, Molecular identification of the CRAC channel by altered ion selectivity in a mutant of Orai, Nature 443 (2006) 226–229.
[94] X. Hou, L. Pedi, M.M. Diver, S.B. Long, Crystal structure of the calcium release-activated calcium channel Orai, Science 338 (2012) 1308–1313.
[95] P.B. Stathopulos, L. Zheng, M. Ikura, Stromal interaction molecule (STIM)1 and STIM2 calcium sensing regions exhibit distinct unfolding and oligomerization kinetics, J. Biol. Chem. 284 (2009) 728–732.
[96] P.B. Stathopulos, M. Ikura, Structural aspects of calcium-release activated calcium channel function, Channels 7 (2013) 344–353.
[97] R. Palty, A. Raveh, I. Kaminsky, R. Meller, E. Reuveny, SARAF inactivates the store operated calcium entry mechanism to prevent excess calcium refilling, Cell 149 (2012) 425–438.
[98] D. Prins, J. Groenendyk, N. Touret, M. Michalak, Modulation of STIM1 and capacitative Ca^{2+} entry by the endoplasmic reticulum luminal oxidoreductase ERp57, EMBO Rep. 12 (2011) 1182–1188.
[99] P.-A. Koenig, H.L. Ploegh, Protein quality control in the endoplasmic reticulum, F1000Prime Rep. 6 (2014) 49, http://dx.doi.org/10.12703/P6-49.
[100] F. Finger, T. Hoppe, MicroRNAs meet calcium: joint venture in ER proteostasis, Sci. Signal 7 (2014) re11.
[101] O.M. de Brito, L. Scorrano, Mitofusin 2 tethers endoplasmic reticulum to mitochondria, Nature 456 (2008) 605–610.
[102] R. Rizzuto, P. Pinton, W. Carrington, F.S. Fay, K.E. Fogarty, L.M. Lifshitz, R.A. Tuft, T. Pozzan, Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca^{2+} responses, Science 280 (1998) 14097–14104.
[103] J.E. Vance, MAM (mitochondria-associated membranes) in mammalian cells: lipids and beyond, Biochim. Biophys. Acta 1841 (2014) 595–609.
[104] U. Goyal, C. Blackstone, Untangling the web: mechanisms underlying ER network formation, Biochim. Biophys. Acta 1833 (2013) 2492–2498.
[105] R. Bravo, et al., Endoplasmic reticulum and the unfolded protein response: dynamics and metabolic integration, Int. Rev. Cell. Mol. Biol. 301 (2013) 215–290.
[106] E.F. Corbett, M. Michalak, Calcium, a signaling molecule in the endoplasmic reticulum? Trends Biochem.. Sci. 25 (2000) 307–311.
[107] D. Prins, M. Michalak, Organellar calcium buffers Cold Spring Harb, Perspect. Biol. 3 (2011).
[108] J.D. Malhotra, R.J. Kaufman, The endoplasmic reticulum and the unfolded protein response, Semin. Cell Dev. Biol. 18 (2007) 716–731.
[109] C.K. Suzuki, J.S. Bonifacino, A.Y. Lin, M.M. Davis, R.D. Klausner, Regulation the retention of T-cell receptor alpha chain variants within the endoplasmic reticulum Ca^{2+}-dependent association with BiP, J. Cell. Biol. 114 (1991) 189–205.
[110] J. Dudek, J. Benedix, S. Cappel, M. Greiner, C. Jalal, L. Müller, R. Zimmermann, Functions and pathologies of BiP and its interaction partners, Cell Mol. Life Sci. 66 (2009) 1556–1569.
[111] C. Hetz, The biological meaning of the UPR, Nat. Rev. Biol. Cell. Biol. 14 (2013) 404.
[112] J. Groenendyk, P.K. Sreenivasaiah, H. Kim Do, L.B. Agellon, M. Michalak, Biology of endoplasmic reticulum stress in the heart, Circ. Res. 107 (2010) 1185–1197.
[113] H. Yoshida, K. Haze, H. Yanagi, T. Yura, K. Mori, Identification of the cis-acting endoplasmic reticulum stress response element responsible for transcriptional induction of mammalian glucose-regulated proteins. Involvement of basic leucine zipper transcription factors, J. Biol. Chem. 273 (1998) 33741–33749.
[114] H. Yoshida, T. Okada, K. Haze, H. Yanagi, T. Yura, M. Negishi, K. Mori, Endoplasmic reticulum stress-induced formation of transcription factor complex ERSF including NF-Y (CBF) and activating transcription factors 6alpha and 6beta that activates the mammalian unfolded protein response, Mol. Cell. Biol. 21 (2001) 1239–1248.
[115] H. Urra, E. Dufey, F. Lisbona, D. Rojas-Rivera, C. Hetz, When ER stress reaches a dead end, Biochim. Biophys. Acta 1833 (2013) 3507–3517.
[116] R. Clarke, et al., Endoplasmic reticulum stress, the unfolded protein response, autophagy, and the integrated regulation of breast cancer cell fate, Cancer Res. 72 (2012) 1321–1331.
[117] S. Bernales, K.L. McDonald, P. Walter, Autophagy counterbalances endoplasmic reticulum expansion during the unfolded protein response, PLoS Biol. 4 (2006) e423.

[118] S. Bernales, S. Schuck, P. Walter, ER-phagy: selective autophagy of the endoplasmic reticulum, Autophagy 3 (2007) 285–287.
[119] A.B. Gustafsson, R.A. Gottlieb, Recycle or die: the role of autophagy in cardioprotection, J. Mol. Cardiol. 44 (2008) 654–661.
[120] H.Z. Mao, et al., Lipase maturation factor 1 (Imf1) is induced by endoplasmic reticulum stress through activating transcription factor 6α (Atf6α) signaling J, Biol. Chem. 289 (2014) 24417–24427.
[121] S.H. Back, R.J. Kaufman, Endoplasmic reticulum stress and type 2 diabetes, Annu. Rev. Biochem. 81 (2012) 767–793.
[122] J. Soboloff, B.S. Rothberg, M. Madesh, D.L. Gill, STIM proteins: dynamic calcium signal transducers, Nat. Rev. Mol. Cell. Biol. 13 (2012) 549–565.
[123] J. Groenendyk, et al., Interplay between the oxidoreductase PDIA6 and microRNA-322 controls the response to disrupted endoplasmic reticulum calcium homeostasis, Sci. Signal. 7 (2014). Sci.Signal.ra54.
[124] M. Hong, S. Luo, P. Baumeister, J.M. Huang, R.K. Gogia, M. Li, A.S. Lee, Underglycosylation of ATF6 as a novel sensing mechanism for activation of the unfolded protein response, J. Biol. Chem. 279 (2004) 11354–11363.
[125] V. Tadic, T. Prell, J. Lautenschlager, J. Grosskreutz, The ER mitochondria cycle and ER stress response as therapeutic targets in amyotrophic lateral sclerosis, Front. Cell. Neurosci. 8 (2014) 147.
[126] A. Guerrero-Hernandez, A. Verkhratsky, Calcium signalling in diabetes, Cell. Calcium 56 (2014) 297–301.
[127] H.E. Collins, X. Zhu-Mauldin, R.B. Marchase, J.C. Chatham, STIM/Orai 1-mediated SOCE: current perspectives and potential roles in cardiac function and pathology, Am. J. Physiol. Heart Circ. Physiol. 305 (2013) H446–H458.
[128] W.A. Wang, J. Groenendyk, M. Michalak, Endoplasmic reticulum stress associated responses in cancer, Biochim. Biophys. Acta 1843 (2014) 2143–2149.