Endoplasmic-Reticulum Calcium Depletion and Disease

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The endoplasmic reticulum (ER) as an intracellular Ca^{2+} store not only sets up cytosolic Ca^{2+} signals, but, among other functions, also assembles and folds newly synthesized proteins. Alterations in ER homeostasis, including severe Ca^{2+} depletion, are an upstream event in the pathophysiology of many diseases. On the one hand, insufficient release of activator Ca^{2+} may no longer sustain essential cell functions. On the other hand, loss of luminal Ca^{2+} causes ER stress and activates an unfolded protein response, which, depending on the duration and severity of the stress, can reestablish normal ER function or lead to cell death. We will review these various diseases by mainly focusing on the mechanisms that cause ER Ca^{2+} depletion.

Cytosolic $[Ca^{2+}]$ ($[Ca^{2+}]_{cyt}$) is precisely regulated in time and space because Ca^{2+} controls essential cell functions like proliferation, differentiation, secretion, contraction, metabolism, trafficking, gene transcription and apoptosis, and in this way controls complex processes like development or learning behavior (Berridge et al. 2000). An abnormal $[Ca^{2+}]_{cyt}$ caused by disturbances of Ca^{2+} channels, Ca^{2+} transporters, Ca^{2+} pumps, and Ca^{2+}-binding proteins can induce multiple pathologies (Missiaen et al. 2000). Ca^{2+} channelopathies in the nervous system leading to paralysis, ataxia, or migraine can be caused by mutations in subunits of voltage-operated Ca^{2+} channels in the plasma membrane (Bidaud et al. 2006; Lorenzon and Beam 2008). Other channelopathies like malignant hyperthermia and central core disease in skeletal muscle, and some

tachycardias and tachyarrhythmias in the heart are because of mutations in Ca^{2+}-release channels or Ca^{2+}-binding proteins of the sarcoplasmic reticulum (SR) (Durham et al. 2007; Lorenzon and Beam 2008; Blayney and Lai 2009; Gyorke 2009). Deafness and skin diseases can also be because of mutations in Ca^{2+} pumps (Foggia and Hovnanian 2004; Van Baelen et al. 2004; Brini and Carafoli 2009). Ca^{2+} dysregulation may also lead to more complex diseases like Alzheimer and other neurodegenerative diseases (Bezprozvanny 2009; Berridge 2010; Supnet and Bezprozvanny 2010).

Disease states associated with a decreased $[Ca^{2+}]$ in the lumen of the ER ($[Ca^{2+}]_{ER}$) have thus far received less attention. The ER controls the synthesis, modification, folding, and export of proteins. An imbalance between the demand for protein synthesis and the capacity to handle

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them leads to the accumulation of misfolded or unfolded proteins, which is referred to as ER stress. An unfolded protein response (UPR) is initiated to reestablish normal ER function (Schroder and Kaufman 2005; Ron and Walter 2007). If the stress is too prolonged or severe to be corrected, the adaptive response triggered by the UPR will not overcome the ER stress and a cell-death program is triggered to eliminate the damaged cell. Many diseases affect the ER environment leading to ER stress, a UPR, and apoptosis (Xu et al. 2005; Lindholm et al. 2006; Kim et al. 2008). Some of them first deplete ER Ca^{2+}, with disturbed function of luminal proteins (Michalak et al. 2002). The decreased $[Ca^{2+}]_{ER}$, rather than the increased $[Ca^{2+}]_{cyt}$, then triggers apoptosis (Nakano et al. 2006; Yoshida et al. 2006).

We will review the diseases in which a decreased $[Ca^{2+}]_{ER}$ is an upstream event in the pathophysiology and show that ER stress often plays an essential role. We will first briefly review the mechanisms controlling the $[Ca^{2+}]_{ER}$, then focus on how ER stress leads to apoptosis, and finally review the mechanisms of ER Ca^{2+} depletion in the various diseases.

Ca^{2+} HOMEOSTASIS IN THE ER/SR

To function as an intracellular Ca^{2+} store, the ER/SR needs to express at least three different types of proteins (Pozzan et al. 1994): (1) Ca^{2+} pumps for uphill transport of Ca^{2+} from the cytosol to the lumen; (2) luminal Ca^{2+}-binding proteins for storing Ca^{2+}; and (3) Ca^{2+} channels for the controlled release of Ca^{2+} to the cytosol along its electrochemical gradient. Although the ER is generally assumed to form a continuous compartment, it can be heterogeneous at the level of its Ca^{2+}-handling proteins. A heterogeneous distribution allows on the one hand localized Ca^{2+} pumping and release, and on the other hand, the setting up of Ca^{2+} signals without disturbing Ca^{2+}-dependent processes within the ER lumen (Petersen et al. 2001; Berridge 2002; Papp et al. 2003).

Ca^{2+} pumps of the SERCA type (sarco/ endoplasmic-reticulum Ca^{2+}-ATPase) actively pump Ca^{2+} into the store (Fig. 1). They are encoded by three different genes, whereby each of them exists as various splice variants. SERCA2b has the highest Ca^{2+} affinity and is the most ubiquitous pump. Other isoforms have a more restricted expression pattern. Thapsigargin is a much-used specific inhibitor of the SERCA pumps. This sesquiterpene lactone irreversibly interacts with their M3-transmembrane helix. Phospholamban is the major endogenous regulator of SERCA pumps (at least for isoforms 1a, 2a, and 2b), but it is only expressed in muscle cells. This small protein decreases their Ca^{2+} affinity (Brini and Carafoli 2009; Vangheluwe et al. 2009).

Ca^{2+} in the lumen of the ER/SR is buffered by Ca^{2+}-binding proteins. Calsequestrin is the main Ca^{2+}-binding protein in skeletal and cardiac muscle (Beard et al. 2004). In other tissues Ca^{2+} binds to calreticulin (Michalak et al. 2002) and other Ca^{2+}-dependent chaperones like calnexin, 78-kDa glucose-regulated protein/ immunoglobulin heavy chain binding protein (GRP78/BiP), GRP94, and various protein-disulfide isomerases (PDI) (Papp et al. 2003). All these proteins combine at least two of the following three properties: Ca^{2+} binding, regulation of Ca^{2+} pumps or Ca^{2+}-release channels, and chaperone function (Berridge 2002; Papp et al. 2003), emphasizing the close interrelation between the $[Ca^{2+}]_{ER}$ and ER function.

The main Ca^{2+}-release channels in the ER/ SR belong to either the ryanodine-receptor (RyR) (Zalk et al. 2007) or the inositol 1,4,5-trisphosphate (IP_3)-receptor (IP_3R) (Foskett et al. 2007) families. In each family, three genes code for receptor subunits, which assemble to produce very large tetrameric Ca^{2+}-release channels ($\sim$2.2 MDa for the RyRs, $\sim$1.2 MDa for the IP_3Rs). Further diversity occurs by alternative splicing and by the formation of both homo- and, at least for the IP_3R, heterotetramers. The differences in channel and regulatory properties, and in subcellular localization, allow highly specific Ca^{2+} signals propagating through the cell. RyRs are predominantly expressed in muscles and neurons although they can also be present at low levels in other cells. Skeletal muscle expresses mainly RyR1, which is activated by direct interaction with L-type voltage-operated
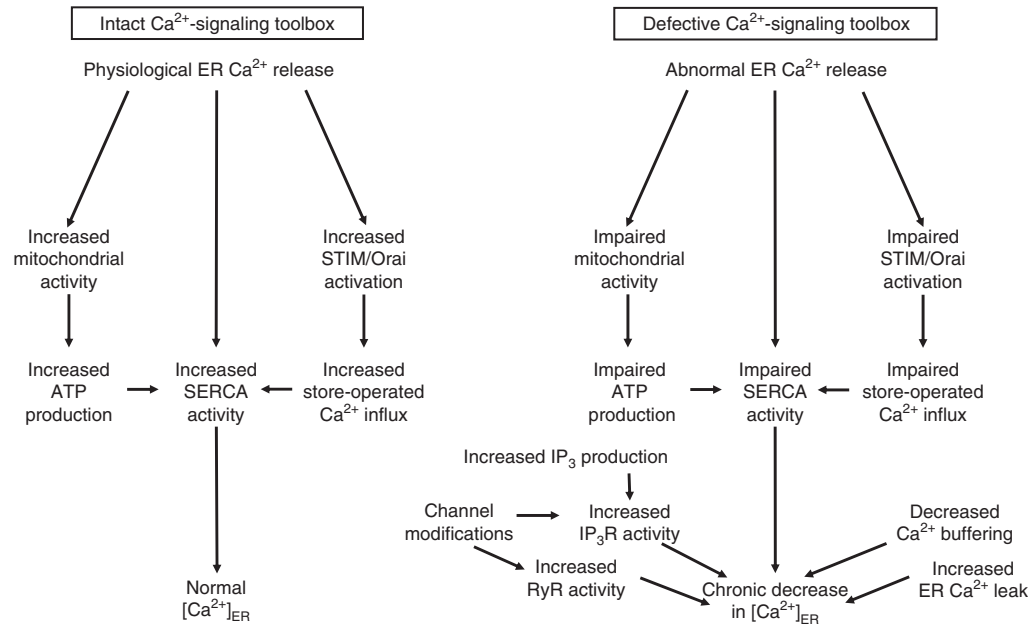
Figure 1. Normal and abnormal $[Ca^{2+}]_{ER}$. A tight coordination between ER Ca^{2+}-release and -refilling mechanisms enables proper Ca^{2+} signaling in response to physiological stimuli. Under these conditions, Ca^{2+} released from the ER stimulates mitochondrial activity and bioenergetics, leading to more ATP production. The initial decline in $[Ca^{2+}]_{ER}$ activates STIM, allowing for store-operated Ca^{2+} influx. Ca^{2+} is recycled via the SERCA pumps. Normal $[Ca^{2+}]_{ER}$ is restored and ER-related processes continue. In contrast, in pathological conditions, stress responses will occur and affect the Ca^{2+}-signaling toolbox in various ways. Impaired mitochondrial activity, store-operated Ca^{2+} influx, or SERCA activity may all cause failure in restoring normal $[Ca^{2+}]_{ER}$ in response to ER Ca^{2+}-signaling processes, and lead to a decreased $[Ca^{2+}]_{ER}$. A chronic decrease in $[Ca^{2+}]_{ER}$ may also be because of an imbalance between the Ca^{2+}-on and -off mechanisms as a result of increased IP_3R or RyR activity, decreased Ca^{2+} buffering, or increased ER Ca^{2+} leak.

Ca^{2+} channels, whereas the RyR2 in cardiac tissue and the RyR3 are activated by Ca^{2+} itself (Endo 2009). IP_3Rs on the other hand are expressed in all cell types. They generally become active when IP_3 is produced on cell stimulation by extracellular agonists. IP_3 binding at the amino terminus of the receptor induces channel opening at its carboxyl terminus (Bosanac et al. 2004). The further regulation of channel opening by cytosolic factors including Ca^{2+}, by regulatory proteins, and by phosphorylation/dephosphorylation, as well as their subcellular localization allow them to set up highly specific spatio-temporal Ca^{2+} signals (Vermassen et al. 2004; Foskett et al. 2007; Mikoshiba 2007; Vanderheyden et al. 2009).

In normal conditions, several mechanisms are operative to prevent ER Ca^{2+} depletion or overload, e.g., both Ca^{2+} channels and Ca^{2+} pumps are sensitive to luminal $[Ca^{2+}]$. The IP_3R becomes more sensitive to IP_3 when the $[Ca^{2+}]_{ER}$ increases (Irvine 1990; Missiaen et al. 1992) and also the RyR is stimulated by luminal Ca^{2+} (Nelson and Nelson 1990; Gyorke and Terentyev 2008). SERCA-mediated Ca^{2+} uptake into the ER is sensitive to $[Ca^{2+}]_{ER}$ (Takenaka et al. 1982). The release of Ca^{2+} from the ER during the generation of cytosolic Ca^{2+} signals should not decrease the $[Ca^{2+}]_{ER}$ to a level at which ER function and Ca^{2+} signaling become compromised (Sammels et al. 2010). A mechanism has evolved that couples ER Ca^{2+} depletion to an increase of Ca^{2+} entry into the cell. This phenomenon is known as "capacitative" (Putney 1986) or "store-operated" Ca^{2+} entry. STIM1 and STIM2 are ubiquitously expressed

single-pass transmembrane ER and, to some extent, plasma-membrane proteins with a luminal Ca^{2+} sensor (Stathopulos et al. 2008). Depending on the extent of ER depletion, either STIM1 or STIM2 oligomerize and interact with Orai1 proteins (Brandman et al. 2007). These tetrameric Ca^{2+} channels in the plasma membrane are then responsible for an increased Ca^{2+} entry (Cahalan 2009; Deng et al. 2009; Schindl et al. 2009).

ER STRESS AND APOPTOSIS

The ER not only fulfills a crucial role in Ca^{2+} signaling, but also provides a quality-control system for the proper folding of proteins and for sensing stress (Fig. 2). A plethora of ER-resident chaperones including calreticulin, calnexin, PDI, and GRP78/BiP bind unfolded or misfolded proteins via inappropriately exposed hydrophobic or hypo-glycosylated residues (Austin 2009). Calreticulin and calnexin bind to polypeptide chains entering the ER lumen through glycosylated residues, whereas PDI mediates the correct formation of disulfide bonds. GRP78/BiP undergoes cycles of binding and release of unfolded proteins until they are properly folded and hydrophobic residues are inaccessible. ER-resident chaperones like calreticulin, GRP78/BiP, and GRP94 need a high $[Ca^{2+}]_{ER}$ for their activity (Ma and Hendershot 2004) with Ca^{2+} binding to paired anionic amino acids (Lucero and Kaminer 1999). Moreover, several of the ER chaperones also act as Ca^{2+} buffers (Lievremont et al. 1997; Papp et al. 2003). Determination of the Ca^{2+} affinities suggests up to millimolar levels in the ER (Sambrook 1990), and depletion of ER Ca^{2+} by treating cells with a Ca^{2+} ionophore or thapsigargin can lead to inappropriate secretion, aggregation, and degradation of unassembled proteins (Gaut and Hendershot 1993).

The $[Ca^{2+}]_{ER}$ must be maintained in an environment of continuous intracellular Ca^{2+} signaling. Failure of this homeostatic mechanism, for example, by inhibition of SERCA with thapsigargin, triggers a UPR to either reestablish normal ER function or to eliminate the cell (Xu et al. 2005). The adaptive mechanisms initiated by the UPR involve reduced translation of misfolded proteins, enhanced translation of ER chaperones to increase the folding capacity of the ER, and degradation of misfolded proteins through ER-assisted degradation (ERAD) (Schroder and Kaufman 2005; Malhotra and Kaufman 2007). Global mRNA translation is inhibited for a few hours to reduce the influx of new proteins into the ER, whereas alarm signals involving the activation of mitogen-activated protein kinases (MAPK) are induced (Kim et al. 2008). The UPR involves three signaling pathways: PERK (PKR-like ER kinase), Ire1 (inositol-requiring enzyme 1), and ATF6 (activating transcription factor 6).

The recognition of misfolded proteins by the Ser/Thr kinase PERK leads to phosphorylation and inactivation of the eukaryotic initiation factor 2α (eIF2α). This shuts off mRNA translation, thereby preventing the accumulation of newly synthesized proteins in the ER (Harding et al. 1999), activates the transcription factor ATF4, which increases the level of chaperones such as GRP78/BiP and GRP94, and helps to restore the cellular redox homeostasis (Harding et al. 2000, 2003).

Ire1 has endoribonuclease and Ser/Thr-kinase activity. Its endoribonuclease activity degrades many mRNAs to reduce the protein load on the ER (Hollien and Weissman 2006). Ire1 removes an intron from the mRNA of X-box-binding protein 1 (XBP1), leading to the expression of XBP1. This transcription factor is involved in the expression of several UPR and ERAD genes (Rao and Bredesen 2004). The kinase activity of Ire1 is involved in apoptotic signaling via ASK1 (apoptosis signal-regulating kinase 1) and JNK (c-Jun N-terminal kinase). JNK activates the proapoptotic BH3-only protein Bim (Lei and Davis 2003; Putcha et al. 2003), and inactivates the antiapoptotic Bcl-2 protein (Yamamoto et al. 1999). Ire1 also recruits caspase 12 (Yoneda et al. 2001), which may play a role in ER stress-induced apoptosis (Szegezdi et al. 2003). However, caspase 12 is not present in humans, and although caspase 4, its close paralogue, may perform such function, it remains uncertain whether caspase 4 is vital for ER stress-induced apoptosis (Egger et al. 2003).
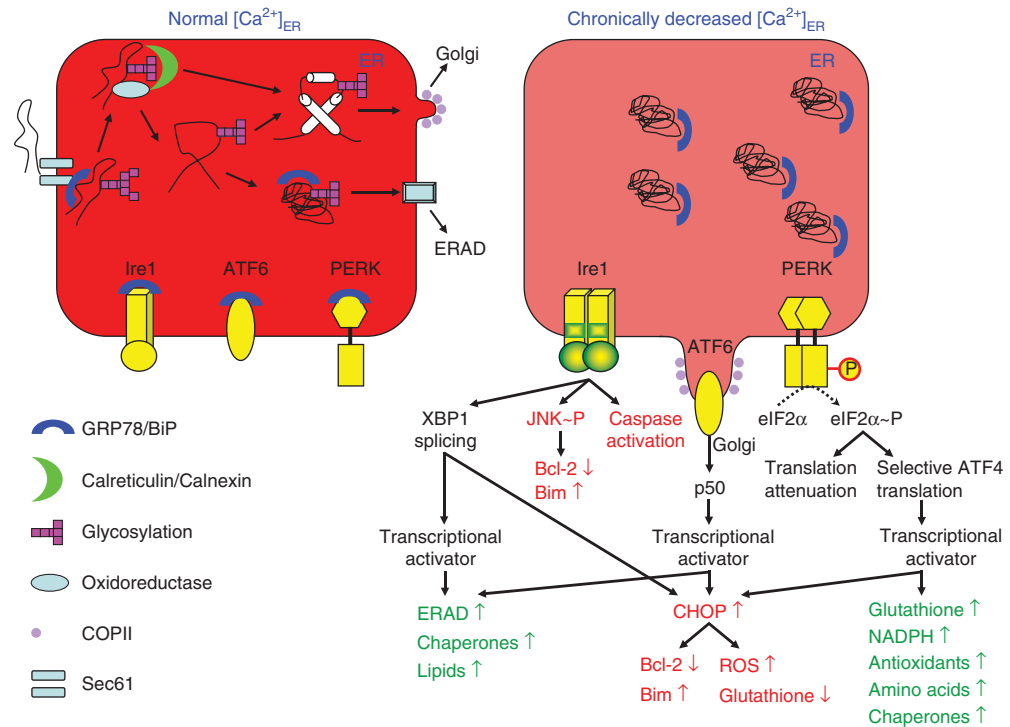
Figure 2. The UPR. At a normal $[Ca^{2+}]_{ER}$ the ER-stress sensors are scaffolded and inactivated by GRP78/BiP. Protein trafficking and quality-control mechanisms work normally. Polypeptides are translocated through Sec61 and glycosylated. This transport is facilitated by the molecular chaperone GRP78/BiP. Glucosidases then prepare the glycoprotein for binding to the ER lectins, calreticulin, and calnexin, whereas oxidoreductases catalyze disulfide-bond formation. ER-resident chaperones facilitate the proper folding of the nascent protein and prevent its aggregation. Further deglucosidation releases the ER lectins and once the protein is correctly folded and processed, the protein leaves the ER via the coat protein (COPII)-coated vesicles to the secretory pathway. Misfolded proteins, in contrast, associate with various chaperones, including GRP78/BiP, and are removed from the ER through ERAD.

In contrast, when the $[Ca^{2+}]_{ER}$ is chronically decreased, the function of chaperones becomes disturbed and unfolded proteins accumulate and act as a sponge for luminal GRP78/BiP. As a consequence, ER-stress sensors are devoid of GRP78/BiP and become activated, yielding early adaptive responses promoting survival (indicated in green) or late responses promoting apoptosis under conditions of severe or on-going ER stress (indicated in red). Ire1 undergoes dimerization and activation of its kinase and endoribonuclease activity, thereby splicing XBP1 mRNA and yielding a potent transcriptional activator that induces the expression of genes involved in ERAD, protein folding (like GRP78/BiP), and lipid synthesis. ATF6 goes to the Golgi compartment, where it is proteolytically cleaved to yield a cytosolic fragment (p50) that migrates to the nucleus and activates the transcription of UPR genes, like GRP78/BiP and CHOP. PERK dimerizes, autophosphorylates, and phosphorylates eIF2α, thereby suppressing its activity and reducing the rate of translation initiation, while increasing the rate of translation of ATF4, a potent transcription factor that augments the expression of genes involved in antioxidative stress, amino acid metabolism, and protein chaperoning. During on-going ER stress or irreparable ER damage, apoptotic pathways are activated. Ire1 phosphorylates JNK, leading to inhibition of Bcl-2 activity and activation of Bim, and recruits, releases, and activates procaspases in the cytosol. Induction of CHOP via XBP1, ATF6 or ATF4, down-regulates prosurvival Bcl-2-family members, increases prodeath proteins (like Bim) and ROS, and decreases the levels of glutathione, a ROS scavenger. In the presence of ROS, Ca^{2+} transfer to the mitochondria leads to the release of cytochrome *c*. The balance between proapoptotic and antiapoptotic Bcl-2-family members is disturbed, with activation of the intrinsic apoptotic pathway.

The transcription factor ATF6 is translocated to the Golgi during ER stress and is proteolytically activated. ATF6 stimulates ER-stress genes as a homodimer or as a heterodimer with other transcription factors like XBP1, whose transcription is also induced by ATF6 (Yoshida et al. 2001; Malhotra and Kaufman 2007). ATF6 is cytoprotective, possibly mediated by RCAN1 (regulator of calcineurin-1), an endogenous inhibitor of calcineurin (Belmont et al. 2008). This enzyme dephosphorylates the proapoptotic Bad (Bcl-2 antagonist of cell death), which then dimerizes and inhibits antiapoptotic family members such as Bcl-2 and Bcl-Xl (Wang et al. 1999).

ATF4, ATF6, and XBP1 all induce the transcription of the gene encoding CHOP (C/EBP homologous protein) (Kim et al. 2008). The Ire1-ASK1-p38-MAPK pathway enhances CHOP activity at a posttranscriptional level (Wang and Ron 1996). CHOP is involved in ER stress-induced apoptosis by down-regulating the antiapoptotic Bcl-2 (McCullough et al. 2001), and by inducing expression of the proapoptotic Bim (Puthalakath et al. 2007) and of ER oxidase 1α, thereby rendering the ER more oxidative and exacerbating ER stress (Marciniak et al. 2004). Misfolded proteins are eventually eliminated via proteins involved in the ERAD pathway, which are induced and controlled by both Ire1-XBP1 and ATF6 pathways (Yoshida et al. 2003).

No trigger for ER stress selectively elicits either adaptive responses or apoptosis. The switch between life and death is regulated by the complex interdependent UPR-signaling pathways that each may result in prosurvival or prodeath responses. The different time courses of the three main UPR branches may influence the cell fate (Lin et al. 2007a). The early termination of Ire1α activity is needed for cell death. Differential activation of PERK and Ire1α may lead to life or death (Lin et al. 2009). Cell death is induced by apoptosis and by caspase-independent necrosis. ER stress also induces autophagy (Ogata et al. 2006; Bernales et al. 2006; Hoyer-Hansen and Jaattela 2007). The PERK-ATF4 branch stimulates the expression of *ATG12*, an autophagy gene (Kouroku et al. 2007). This catabolic process removes unfolded proteins and their aggregates independently of the ubiquitin/proteasome system, thereby promoting cell survival. Ultimately, however, enhanced autophagic vacuolization may lead to non-apoptotic cell death (Levine and Kroemer 2008).

ER stress and cell death involve many Ca^{2+}-dependent processes (Kim et al. 2008) including phospholipases, scramblases, nitric-oxide (NO) synthases, calpains, calcineurin, FKBP38, fortilin, a putative modulator of Mcl-1 (myeloid cell leukemia sequence 1), death-associated protein kinase 1, mitochondrial fission, and Ca^{2+}-dependent pathways triggering autophagy. Some pathways require interplay between mitochondria and the ER in zones of close contact (Giorgi et al. 2008, 2009). These microdomains involve the close proximity of ER Ca^{2+}-release channels like the IP_3R and mitochondrial Ca^{2+}-transport mechanisms, like the voltage-dependent anion channel (VDAC) and the Ca^{2+} uniporter (Giorgi et al. 2009). Changes in ER Ca^{2+} homeostasis in this way affect mitochondrial Ca^{2+} signaling. Lowering of the $[Ca^{2+}]_{ER}$ by antiapoptotic proteins such as Bcl-2 has been described (Scorrano et al. 2003) and is expected to lower the sensitivity to apoptotic Ca^{2+} transfer from the ER to the mitochondria (Rizzuto et al. 2009). Bcl-Xl, a related antiapoptotic protein was found to induce prosurvival ER-to-mitochondria Ca^{2+} signaling by sensitizing the IP_3R to basal levels of IP_3 (White et al. 2005). ER-to-mitochondria Ca^{2+} signals can regulate cell survival by enhancing mitochondrial bioenergetics. Mitochondrial Ca^{2+} overload, on the other hand, by a larger or more persistent $[Ca^{2+}]$ rise was found to induce cell death (Rong and Distelhorst 2008). Cell death is characterized by mitochondrial outer membrane permeabilization (MOMP) and the loss of the mitochondrial transmembrane potential $\Delta\Psi_m$ (Kroemer et al. 2007). Mitochondrial Ca^{2+} overload can cause breakdown of $\Delta\Psi_m$ by activating the permeability transition pore (PTP). Loss of $\Delta\Psi_m$, however, seems to be a secondary event and not required for MOMP and the release of cytochrome *c* (Chipuk and Green 2008). Accordingly, PTP opening probably plays a role in necrosis but not apoptosis.

Deficiency of Bax and Bak confers resistance to apoptotic cell death induced by conventional anticancer therapies. SERCA inhibitors like thapsigargin, however, can efficiently kill Bax/Bak$^{-/-}$ MEFs by inducing mitochondrial Ca^{2+} overload, PTP opening and necrotic cell death (Janssen et al. 2009). In addition to PTP opening, the activation and oligomerization of the executioner proapoptotic Bcl-2-family members Bax and Bak induce MOMP in response to a variety of apoptotic triggers (Chipuk and Green 2008; Brunelle and Letai 2009). The activity of Bax/Bak is tightly controlled by proteins of the Bcl-2 family. The antiapoptotic Bcl-2-family members, including Bcl-2, Bcl-Xl and Mcl-1, neutralize and prevent oligomerization of Bax/Bak, whereas activator proapoptotic BH3-only proteins, including Bim, cleaved Bid and cytosolic p53, directly bind to Bax/Bak, causing a conformational change, membrane insertion, and oligomerization. In addition, sensitizer BH3-only proteins, including Bad, Noxa, and Puma, bind to the antiapoptotic Bcl-2-family members, neutralizing their antiapoptotic activity. Many of these proteins affect ER Ca^{2+} homeostasis by binding to the IP_3R and/or changing its phosphorylation, resulting in altered Ca^{2+}-flux properties of the channel (Oakes et al. 2005; White et al. 2005; Rong and Distelhorst 2008).

DIABETES MELLITUS

Intracellular Ca^{2+} signaling is perturbed in this chronic metabolic disease with hyperglycemia. Resting $[Ca^{2+}]_{cyt}$ increases, and stimulus-induced $[Ca^{2+}]_{cyt}$ increases in many tissues decrease (Levy 1999; Verkhratsky and Fernyhough 2008). The $[Ca^{2+}]_{ER}$ and SR $[Ca^{2+}]$ ($[Ca^{2+}]_{SR}$) decrease in the pancreatic ß-cell and in tissues affected by diabetic complications.

Pancreatic β-Cell

The progressive reduction in cell mass and eventually failure of the ß-cell is because of apoptotic cell death. ER stress is an important mechanism of apoptosis (Eizirik et al. 2008), at least in some types of diabetes (Akerfeldt

et al. 2008). The $[Ca^{2+}]_{ER}$ in the ß-cell is decreased, but the mechanism involved depends on the type of diabetes. The low $[Ca^{2+}]_{ER}$ impairs proinsulin processing and transport (Guest et al. 1997). The subsequently activated UPR can lead to apoptosis resulting in insufficient insulin secretion (Oyadomari and Mori 2004; Eizirik et al. 2008). The very high secretion rate of ß-cells makes them very sensitive to apoptosis induced by ER Ca^{2+} depletion (Araki et al. 2003; Cardozo et al. 2005; Tonnesen et al. 2009).

Type-1 diabetes is characterized by an auto-immune ß-cell destruction caused by over-production of NO (Gotoh and Mori 2006). Cytokines released from infiltrating T-cells and macrophages up-regulate inducible NO synthase in an NF-kB- and STAT-1-dependent manner (Eizirik et al. 2008). NO depletes ER Ca^{2+} in ß-cells by acting on SERCA and on the Ca^{2+}-release channels (Oyadomari et al. 2001). NO down-regulates SERCA2b expression (Cardozo et al. 2005), perhaps through inhibition of the Sp1 transcription factor (Pirot et al. 2008). NO also reacts with superoxide anion to form peroxynitrite, which inhibits SERCA by reacting with two tyrosine residues in the channel-like domain (Viner et al. 1999; Grover et al. 2003). Peroxynitrite also activates RyR2 by poly-S-nitrosylation of the channel (Xu et al. 1998). The cytokines also up-regulate death protein 5, a BH3-only protein that contributes to Ca^{2+} depletion and ER stress (Gurzov et al. 2009). This depletion mainly occurs when IP_3Rs and RyRs are stimulated (Luciani et al. 2009). Type-1 diabetes was furthermore associated with the single-nucleotide polymorphism *rs2296336* in the gene encoding IP_3R3 (Roach et al. 2006). Increased cholinergic tone with more acetylcholine-induced IP_3 production, and up-regulation of the IP_3R during hyperglycemia (Lee et al. 1999) therefore promote ER Ca^{2+} depletion. NO-induced ER stress in ß-cells does not activate the ATF6 branch of the UPR (Cardozo et al. 2005; Tonnesen et al. 2009). It is still debated whether cytokine-induced ER stress is a direct cause of ß-cell apoptosis or a parallel and/or downstream event (Akerfeldt et al. 2008).

Nonautoimmune type-1 diabetes in Wolfram syndrome is caused by mutations in the gene encoding the ER glycoprotein wolframin (Inoue et al. 1998; Strom et al. 1998). This genetic defect lowers $[Ca^{2+}]_{ER}$ in ß-cells (Takei et al. 2006) and activates the UPR and triggers the apoptotic pathway (Yamada et al. 2006). Reconstitution of this ER-resident transmembrane protein into planar lipid bilayers induces a cation-selective ion channel (Osman et al. 2003). Wolframin also prevents ER stress via other mechanisms, e.g., by negatively regulating ATF6α through the ubiquitin-proteasome pathway (Fonseca et al. 2010).

Type-2 diabetes is characterized by insulin resistance in liver, skeletal muscle and adipose tissue, and a failure of the ß-cell to compensate for the increasing demand. Insulin resistance in liver and adipose tissue may be because of ER stress (van der Kallen et al. 2009). ER Ca^{2+} depletion with thapsigargin leads to insulin resistance (Ozcan et al. 2004), but so far there are no studies linking peripheral insulin resistance to a decreased $[Ca^{2+}]_{ER}$. A high-fat diet or obesity often leads to the development of type-2 diabetes (Eizirik et al. 2008). Free fatty acids trigger ß-cell loss (Leonardi et al. 2003). One model of lipotoxicity proposes that palmitate activates the UPR in ß-cells (Eizirik et al. 2008). The mechanism may again involve ER Ca^{2+} depletion (Cunha et al. 2008; Gwiazda et al. 2009) by decreased expression (Roe et al. 1994; Evans-Molina et al. 2009) or activity of SERCA (Cunha et al. 2008). Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, which improve sensitivity to insulin, also restore SERCA expression and attenuate ER stress in the ß-cell (Evans-Molina et al. 2009). Despite variation in the gene encoding SERCA3 in type-2 diabetic patients (Varadi et al. 1999), insulin secretion and blood glucose levels were normal in SERCA3$^{-/-}$ mice (Arredouani et al. 2002), probably because of compensatory mechanisms.

Polymorphisms in the gene for insulin receptor substrate 1 (IRS-1) have been linked to type-2 diabetes (Almind et al. 1993). IRS-1 directly interacts with SERCA3 (Borge and Wolf 2003). Mice with deleted IRS-1 have reduced SERCA2b and 3 levels, more transient increases in $[Ca^{2+}]_{cyt}$ and less insulin secretion (Kulkarni et al. 2004).

Diabetic Cardiomyopathy

The remodeling of the SR resulting in a slower Ca^{2+} uptake, a lower $[Ca^{2+}]_{SR}$, and release of less activator Ca^{2+}, slows relaxation kinetics of the ventricle and eventually leads to systolic dysfunction, independently of vascular or valve disease (Rubler et al. 1972). Hyperglycemia causes these effects (Ren et al. 1997). The changes in SR Ca^{2+} handling depend on the type of diabetes, the experimental model, the degree of hyperglycemia, and the extent of disease progression. SR function is already abnormal at an insulin-resistant stage before the manifestation of overt type-2 diabetes (Dutta et al. 2002; Wold et al. 2005; Vasanji et al. 2006; Reuter et al. 2008).

Phospholamban, which inhibits SERCA2a, becomes up-regulated (Kim et al. 2001; Choi et al. 2002; Belke et al. 2004; Zhou et al. 2006) at an early stage of the disease (Zhong et al. 2001). Its phosphorylation by protein kinase A and Ca^{2+}/calmodulin-dependent protein kinase, which regulates the interaction with SERCA2a, and therefore stimulates Ca^{2+} uptake, decreases (Choi et al. 2002; Belke et al. 2004; Vasanji et al. 2004, 2006).

The activity and expression of SERCA2a decrease in the diabetic heart (Teshima et al. 2000; Kim et al. 2001; Trost et al. 2002; Choi et al. 2002; Belke et al. 2004; Vasanji et al. 2004; Wold et al. 2005; Zhang et al. 2008; Stolen et al. 2009; Wang et al. 2010). Reduced activity of SERCA2a is not only because of the effect on phospholamban, but also to increased formation of advanced glycation end products of SERCA2a (Bidasee et al. 2004), depressed activity of protein kinase A (Dutta et al. 2002), and sensory denervation leading to diminished production of NO and peroxynitrite, which at basal concentrations activate SERCA2a through S-nitrosylation of Cys-349 (Bencsik et al. 2008). The fact that peroxynitrite both stimulates (Adachi et al. 2004) and inhibits SERCA (Viner et al. 1999; Schmidt et al. 2003b) seems to

indicate that the effect is very much dependent on the experimental conditions or perhaps on the isoform studied. SERCA2a expression decreases in a later stage of the disease (Zhong et al. 2001), perhaps by increased O-glycosylation of the transcription factor Sp1 with β-*N*-acetylglucosamine because of the hyperglycemia (Clark et al. 2003), or by reduced expression and activity of SIRT1, a histone deacetylase (Sulaiman et al. 2010). RyR2 function changes by formation of disulfide bonds between adjacent sulfhydryl groups (Bidasee et al. 2003a), by increased glycation (Bidasee et al. 2003b), by decreased FKBP12.6 expression and binding (Belke et al. 2004; Shao et al. 2007), by hyperphosphorylation (Shao et al. 2007; Stolen et al. 2009), and by a reduced density of T-tubules (Stolen et al. 2009). Two RyR populations appear: one with enhanced responsiveness to Ca^{2+} and another being unresponsive (Shao et al. 2007). Dysfunctional RyR2 can cause dyssynchronous and diastolic Ca^{2+} releases, sometimes with ventricular arrhythmia (Shao et al. 2007). Spontaneous Ca^{2+} sparks representing aberrant RyR2 activation increase in frequency (Yaras et al. 2005; Shao et al. 2007). SR Ca^{2+} leak increases (Belke et al. 2004; Stolen et al. 2009). Expression of RyR2 decreases (Teshima et al. 2000; Choi et al. 2002; Guner et al. 2004; Pereira et al. 2006; Zhou et al. 2006; Reuter et al. 2008; Wang et al. 2010) at later stages of the disease (Zhong et al. 2001). IP$_3$R1, 2, and 3 become down-regulated, but these effects may be species related (Guner et al. 2004; Zhou et al. 2006). The roles of IP$_3$Rs in the heart are furthermore not entirely clear.

Some treatments directly affect the Ca^{2+} signal. Overexpression of SERCA2a protects the heart from contractile dysfunction (Trost et al. 2002; Vetter et al. 2002; Sakata et al. 2007) and reverses established cardiomyopathy (Suarez et al. 2008) and the transcriptional profile induced by diabetes (Karakikes et al. 2009). SERCA2a expression and cardiac function can be normalized by PPAR-γ agonists (Shah et al. 2005), total triterpene acids from *Cornus officinalis Sieb.* (Qi et al. 2008), and the SIRT1 activator resveratrol (Sulaiman et al. 2010). Breviscapine in Chinese medicine decreases phospholamban expression and increases that of SERCA2a and RyR2 (Wang et al. 2010). Exercise training also normalizes abnormal Ca^{2+} signaling (Shao et al. 2009; Stolen et al. 2009).

Vascular Disease

Diabetes lowers $[Ca^{2+}]_{ER}$ in the smooth-muscle cells, macrophages and platelets. These changes contribute to the vascular complications including atherosclerosis (Cooper et al. 2001).

In healthy smooth-muscle cells, basal levels of NO react with superoxide anion to form peroxynitrite, which together with glutathione reacts with Cys-674 of SERCA and increases its activity (Adachi et al. 2004). The hyperglycemia of diabetes induces high levels of oxidants that irreversibly oxidize Cys-674 leading to less *S*-glutathionylation-induced stimulation of SERCA2 (Adachi et al. 2004) and faster degradation (Ying et al. 2008). Insulin also inhibits SERCA via enhanced nitrotyrosine formation (Kobayashi et al. 2007). SERCA2 is also redistributed to a peri-nuclear pattern (Searls et al. 2010). The subsequently decreased $[Ca^{2+}]_{ER}$ stimulates plasma-membrane Ca^{2+} influx and induces migration of the smooth-muscle cell, which contributes to neointimal hyperplasia and atherosclerosis (Tong et al. 2008). Dedifferentiation of smooth-muscle cells precedes their migration from the media to the intima. The up-regulation of the secretory-pathway Ca^{2+}-ATPase 1 (SPCA1) in diabetes (Lai and Michelangeli 2009) probably reflects the change from a contractile to a secretory cell. Sp1 and YY1, transcription factors controlling SPCA1 transcription (Kawada et al. 2005), become more active in high glucose (Han and Kudlow 1997). The expression of IP$_3$R and RyR decreases (Ma et al. 2008; Searls et al. 2010).

Macrophages in type-2 diabetes express more CHOP and are therefore more susceptible to ER stress-induced apoptosis. CHOP induces ER oxidase 1α, with hyperoxidation of the ER lumen and disulfide-bond formation between two cysteines in IP$_3$R1. This causes dissociation of the disulfide isomerase-like protein ERp44 (Kang et al. 2008) and more IP$_3$-induced Ca^{2+}

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release (Li et al. 2009). These changes favor plaque necrosis.

Altered Ca^{2+} signaling in platelets makes them hyperreactive. Their increased adhesiveness and aggregability contribute to the development of the angiopathy (Knobler et al. 1998). The hyperglycemia causes oxidant stress in platelets (Vericel et al. 2004), which enhances tyrosine nitration of SERCA2 and in this way decreases SERCA2 function and, at least at high HbA_{1C} levels, expression in type-2 diabetic patients (Randriamboavonjy et al. 2008). PPAR-γ agonists decrease tyrosine nitration of SERCA and increase its expression. Increased levels of homocysteine in type-2 diabetic patients also release Ca^{2+} from agonist-sensitive Ca^{2+} stores (Zbidi et al. 2010). The direct stimulatory interaction of STIM1 with SERCA3 is impaired in type-2 diabetes (Lopez et al. 2008), which can explain the increased plasma-membrane Ca^{2+} entry, and the higher $[Ca^{2+}]_{cyt}$ at rest and during thrombin stimulation (Saavedra et al. 2004). SERCA3b was up-regulated in type-1 diabetes (Chaabane et al. 2007). This isoform is involved in cell adhesion (Chaabane et al. 2006) and its up-regulation can thus explain the increased adhesiveness in diabetic patients.

Diabetic Nephropathy

This complication is an important cause of end-stage renal disease. Apoptosis induced by ER stress also occurs in the diabetic kidney (Liu et al. 2008). In podocytes, advanced glycation end products release ER Ca^{2+} and trigger a UPR leading to apoptosis during the early stage of the nephropathy (Chen et al. 2008). The loss of podocytes is an important determinant in the progression of the disease. Tubulointerstitial cells also show ER stress (Lindenmeyer et al. 2008), probably induced by the hyperglycemia and the massive protein reabsorption as a result of the proteinuria, but possible changes in $[Ca^{2+}]_{ER}$ were not investigated. The activated UPR selectively enhances the prosurvival pathway of the response, suggesting that diabetic damage may occur independently of any terminal UPR process (Brosius and Kaufman 2008).

Decreased IP$_3$R1 expression in the afferent arteriole and mesangial cell leads to smaller $[Ca^{2+}]_{cyt}$ increases in response to vasoconstrictors, resulting in renal hyperfiltration and glomerular damage (Sharma et al. 1999).

Sensory Neuropathy

Diabetic neuropathy can produce prolonged changes in the nervous system, with pain, sensory loss, food ulceration, infection, gangrene and poor wound healing (Huang et al. 2002; Verkhratsky and Fernyhough 2008). The $[Ca^{2+}]_{ER}$ was decreased because of a decreased SERCA expression by a so far unidentified mechanism and by a decreased activity of the pump (Verkhratsky and Fernyhough 2008). The decreased activity of SERCA may be caused by impaired mitochondrial ATP production in diabetes because of reduced stimulation of insulin receptors (Fernyhough and Calcutt 2010). This effect on the mitochondria seems to be independent of the hyperglycemia. The decreased $[Ca^{2+}]_{ER}$ then affects protein synthesis, posttranslational modification and trafficking, which in turn diminish the supply of voltage-gated Ca^{2+} channels to the axons, thus resulting in the decrease of nerve-conductance velocity (Verkhratsky and Fernyhough 2008). Stimulus-induced $[Ca^{2+}]_{cyt}$ increases decrease (Kruglikov et al. 2004) as a result of the decreased $[Ca^{2+}]_{ER}$ and probably also as a result of decreased IP$_3$R function. Protein glycosylation with β-N-acetylglucosamine is increased in diabetes (Hu et al. 2005). Glycosylation of IP$_3$R1 by β-N-acetylglucosamine decreases its function (Rengifo et al. 2007).

Salivary Glands

Abnormal Ca^{2+} signaling in the salivary glands leads to dryness of the mouth, loss of taste sensation, sialosis, and other disorders of the oral cavity (Nicolau et al. 2009). SERCA is inhibited in the submandibular gland of streptozotocin-induced diabetic rats and therefore $[Ca^{2+}]_{ER}$ and IP$_3$-induced $[Ca^{2+}]_{cyt}$ increases decrease (Fedirko et al. 2006). The decreased $[Ca^{2+}]_{ER}$ results in improper posttranslational processing, folding, and exit of ER proteins. This could

explain the decreased saliva protein content and amylase activity.

NEUROLOGICAL DISEASES

Neural Ischemia

Ischemia depletes ER Ca^{2+}. Both the decreased $[Ca^{2+}]_{ER}$ (Paschen and Mengesdorf 2005) and the increased $[Ca^{2+}]_{cyt}$ (Verkhratsky 2005) contribute to cell death. The induced UPR may lead to apoptosis in the peri-infarct area (DeGracia et al. 2002). The release of Ca^{2+} amplifies the $[Ca^{2+}]_{cyt}$ increase evoked by ischemia-induced Ca^{2+} entry (Xiong et al. 2007). Inhibition of this release with dantrolene reduces cell injury (Wei and Perry 1996). The mechanism of ER Ca^{2+} depletion remains unclear. Cytosolic Ca^{2+} enhances NO synthesis, which inhibits mitochondrial electron transport, and augments the generation of reactive oxygen species (ROS) (Moncada and Erusalimsky 2002). SERCA becomes inhibited by excessive NO production (Doutheil et al. 2000), by ischemia-induced inhibition of the coupling of ATP hydrolysis to Ca^{2+} transport (Parsons et al. 1999), and by activated calpain by the increased $[Ca^{2+}]_{cyt}$ (French et al. 2006; Bevers and Neumar 2008). ER Ca^{2+}-release channels are affected during neural ischemia. RyR2 is activated by S-glutathionylation by NO and ROS (Bull et al. 2008), and by calpain-induced proteolysis (Rardon et al. 1990). Calpain causes proteolysis of the IP_3R resulting in decreased IP_3 binding, suggesting that site-specific cleavage decreases the affinity of the remaining protein species for IP_3 (Nagata et al. 1994; Dahl et al. 2000). Although this would indicate that calpain prevents Ca^{2+} release, it is also possible that the proteolysis simply removes the ligand regulation of the channel and leads to baseline Ca^{2+} release from the ER, contributing to Ca^{2+} overload (Bevers and Neumar 2008). Calpain also inhibits IP_3 metabolism by cleaving IP_3 kinase B (Pattni et al. 2003), allowing it to act longer on the IP_3R, thereby potentiating Ca^{2+} efflux from the ER (Bevers and Neumar 2008). Enhanced activity of phospholipase C and A_2 during ischemia liberates free fatty acids, which release ER Ca^{2+} (O'Neil et al. 1999).

Neurodegeneration

Ca^{2+} signaling is often abnormal in neurodegenerative diseases (Mattson 2007). Diseases with an increased $[Ca^{2+}]_{ER}$, like Alzheimer disease (Tu et al. 2006; Berridge 2010), fall outside the scope of this review. ER stress and the UPR also occur in Parkinson disease (Ryu et al. 2002), amyotrophic lateral sclerosis (Kanekura et al. 2009), and polyglutamate diseases (Lindholm et al. 2006), but the effects on $[Ca^{2+}]_{ER}$ are not well documented. We will focus on diseases with a decreased $[Ca^{2+}]_{ER}$.

Some lysosomal storage diseases lead to a decreased $[Ca^{2+}]_{ER}$. In neurons of G_{M1}-gangliosidosis, G_{M1} accumulates at the ER membrane and depletes ER Ca^{2+} stores (Tessitore et al. 2004) by interacting with the phosphorylated form of the IP_3R (Sano et al. 2009). The subsequent activation of the UPR leads to apoptosis (Sano et al. 2009). Silencing of IP_3R1 with siRNA reduces the number of apoptotic cells (Sano et al. 2009). Increased Ca^{2+} release from the ER in Gaucher disease is because of overactivation of the RyR (Korkotian et al. 1999; Pelled et al. 2005), because glucosylceramide, the lipid that accumulates in this disease, directly modulates the RyR (Lloyd-Evans et al. 2003). In Sandhoff disease, SERCA activity is inhibited by the accumulation of G_{M2}-ganglioside (Pelled et al. 2003), which depends on an exposed sialic-acid residue on G_{M2} (Ginzburg et al. 2008). The UPR is also activated by the accumulation of palmitoylated proteins in the infantile form of Batten disease, but ER Ca^{2+} handling was not investigated (Zhang et al. 2007). The decreased SERCA2 and IP_3R1 expression in Niemann-Pick A disease did not activate a UPR (Ginzburg and Futerman 2005). The suggestion that the UPR is a common mediator of apoptosis in neurodegenerative lysosomal storage diseases (Wei et al. 2008a) can therefore be questioned (Farfel-Becker et al. 2009). Increasing $[Ca^{2+}]_{ER}$ by inhibiting the RyR or by SERCA2b overexpression partially restored mutant-enzyme homeostasis in several lysosomal storage diseases (Ong et al. 2010).

Transmissible spongiform encephalopathies include Creutzfeldt-Jakob disease in humans,

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and bovine spongiform encephalopathy and scrapie in animals (Prusiner 1998). These diseases are associated with extracellular accumulation of a conformationally modified abnormal isoform of the prion protein, a widely expressed plasma membrane-associated glycoprotein with highest levels of expression on neurons and glia. This protein binds to the cell surface and sends a signal to the ER to release Ca^{2+} through the IP_3R and RyR (Hetz et al. 2003; Ferreiro et al. 2006, 2008). The subsequent decreased $[Ca^{2+}]_{ER}$ leads to a UPR and activates the ER-stress-induced apoptosis pathway. Dantrolene and xestospongin C, which are inhibitors of the RyR and IP_3R respectively, prevent neuronal death (Ferreiro et al. 2006, 2008).

Neuropathic Pain

Neuropathic pain is pain arising from nerve injury. The soma of sensory neurons is affected by injuring the peripheral axons. Spinal-nerve ligation depletes ER Ca^{2+} (Rigaud et al. 2009) by a loss of ER and therefore of SERCA (Gemes et al. 2009). Rigaud et al. (2009) suggested that this may trigger a UPR, but this was not directly shown. Depletion of ER Ca^{2+} stores thus contributes to the pathogenesis of neuropathic pain.

Anesthesia

General anesthesia may cause cognitive deficits after surgery (Moller et al. 1998). Inhalation anesthetics can overactivate the IP_3R, with excessive ER Ca^{2+} release leading to apoptosis (Wei et al. 2008b; Yang et al. 2008). Neurons with enhanced IP_3R activity, for example, in familial Alzheimer or Huntington disease, may be especially vulnerable.

CARDIOVASCULAR DISEASES

Atherosclerosis

Macrophages play a critical role in this chronic inflammatory disease (Fan and Watanabe 2003). They accumulate unesterified cholesterol in advanced lesions, which changes the fluidity of the ER membrane and in this way inhibits

SERCA (Li et al. 2004). Depletion of ER Ca^{2+} stores induces a UPR and apoptosis (Feng et al. 2003). Excessive apoptosis plays a key role in the progression of atherosclerosis. The UPR also sets up a positive feedback loop with more Ca^{2+} release via induction of ER oxidase 1α. Hyperoxidation of the ER lumen activates Ca^{2+} release (Li et al. 2009) by disulfide-bond formation between two cysteines in IP_3R1 and dissociation of the inhibitory ERp44 (Kang et al. 2008). This mechanism complements the increased ER Ca^{2+} leak through induction of a truncated variant of SERCA1 through the PERK pathway (Chami et al. 2008).

Homocysteine, a risk factor for cardiovascular disease, depletes ER Ca^{2+} in aortic smooth muscle, induces ER stress and in this way accelerates atherosclerosis (Dickhout et al. 2007). Also increased production of superoxide anion inhibits SERCA in blood vessels (Tong et al. 2009).

Endothelial dysfunction already occurs early during atherogenesis. Increased peroxynitrite formation in the endothelium inhibits SERCA, depletes ER Ca^{2+} and induces a UPR (Dickhout et al. 2005).

Chronic Heart Failure

Reduced $[Ca^{2+}]_{cyt}$ increases caused by a decreased SR Ca^{2+} content make the heart muscle too weak to pump sufficient blood through the body (Bers et al. 2003). Ca^{2+} pumping is reduced because of a decreased ratio of SERCA2a relative to phospholamban expression (Hasenfuss and Pieske 2002), or because phospholamban is either mutated with more inhibition of SERCA2a (Franz et al. 2001; Schmitt et al. 2003; Haghighi et al. 2006; Kranias and Bers 2007) or less phosphorylated (Frank et al. 2002; Bers et al. 2003; Yano et al. 2008) because of a more active protein phosphatase 1 (del Monte and Hajjar 2008). SERCA2 mutations have not been linked to heart failure (Schmidt et al. 2003a). SERCA3f, an isoform with a specific role in ER stress, becomes up-regulated (Dally et al. 2009). Enhanced Na^+-Ca^{2+} exchange leading to more extrusion of Ca^{2+} from the cell also depletes SR Ca^{2+} (O'Rourke et al. 1999).

Subconductance states of the RyR2 and decreased coupled gating of RyR2-channel clusters can increase SR Ca^{2+} leak during diastole (Reiken et al. 2003; Wehrens et al. 2003, 2005a, 2006; Lehnart et al. 2005, 2008; Huang et al. 2006; Zalk et al. 2007). Hyperactivation of RyR2 may arise from activated protein kinase A by sympathetic neurons and increased levels of catecholamines, and subsequent hyperphosphorylation of RyR2 at Ser-2809 and dissociation of FKBP12.6 (Marx et al. 2000) (but see Bers et al. 2003; Seidler et al. 2007; Yano et al. 2008). Enhanced Ca^{2+}/calmodulin-dependent protein kinase δ-dependent phosphorylation of RyR2 at Ser-2815 also increases diastolic Ca^{2+} leak and reduces SR Ca^{2+} load (Ai et al. 2005).

ß-blockers prevent the hyperphosphorylation of RyR2 by protein kinase A, normalize channel function and improve cardiac function (Reiken et al. 2001; Doi et al. 2002). Heart failure can also be prevented by JTV519, which inhibits the dissociation of FKBP12.6 from RyR2; thereby stabilizing the channel, enhancing cooperativity among the subunits, and promoting coupled gating (Yano et al. 2003; Wehrens et al. 2005b). Overexpression of SERCA2 (Inesi et al. 2008; Kawase and Hajjar 2008), of pseudophosphorylated phospholamban (Hoshijima et al. 2002), or of FKBP12.6 (Huang et al. 2006), gene transfer of a phospholamban-targeted antibody (Dieterle et al. 2005), and down-regulation of phospholamban (Andino et al. 2008) can correct in vivo cardiac function. Modification of SERCA/phospholamban activity/expression is a promising target for remediation of cardiac disease. Indeed, a clinical trial of SERCA2a-gene therapy is initiated (Jaski et al. 2009).

VIRUS INFECTION

Complete virions or viral proteins can decrease the $[Ca^{2+}]_{ER}$. Some viruses stimulate Ca^{2+} release via the IP_3R, often by increasing the $[IP_3]$ (Table 1). Other viruses release Ca^{2+} via an increased expression or function of the RyR. They may also decrease SERCA activity or expression, enhance the passive Ca^{2+} leak from the ER, or form pores in the ER membrane. Nef of human immunodeficiency virus type 1 directly interacts with the IP_3R and activates Ca^{2+} entry, without however inducing Ca^{2+} release (Foti et al. 1999; Manninen and Saksela 2002).

ER Ca^{2+} depletion may be apoptotic or antiapoptotic, depending on the virus, its life cycle, and the induced pathology (Chami et al. 2006; Zhou et al. 2009). Ca^{2+} depletion by, for example, enteroviruses and human cytomegalovirus, delays apoptosis, giving the virus more time for replication. These viruses reduce ER-mitochondrial Ca^{2+} fluxes and prevent opening of the PTP with less release of cytochrome c and less caspase activation (van Kuppeveld et al. 2005; Sharon-Friling et al. 2006). ER and also Golgi Ca^{2+} depletion by e.g., enteroviruses leads to the accumulation of ER/Golgi-derived vesicles, where viral RNA replication takes place (van Kuppeveld et al. 2005), and inhibits vesicular protein trafficking and so down-regulates immune responses of the ghost (de Jong et al. 2006). In contrast, ER Ca^{2+} depletion by hepatitis C virus in liver promotes apoptosis and facilitates virion release because of translocation of Bax to the mitochondria, depolarization of the mitochondrial membrane, release of cytochrome c, and activation of caspase 3 (Benali-Furet et al. 2005). Abnormal Ca^{2+} signaling by Gp120 and Tat causes neuronal apoptosis and dysfunction and eventually AIDS dementia (Haughey and Mattson 2002). The decreased SERCA expression and increased RyR expression in Borna disease lead to ER stress, activation of the UPR and apoptotic degeneration of the cerebellum and hippocampus (Williams and Lipkin 2006). ER Ca^{2+} depletion also increases $[Ca^{2+}]_{cyt}$ and therefore activates Ca^{2+}-dependent enzymatic processes and transcription factors, promoting virus replication and the induction of a variety of responses.

Some antiviral drugs directly affect the $[Ca^{2+}]_{ER}$. Human immunodeficiency virus-protease inhibitors induce the accumulation of free cholesterol in the ER of macrophages, deplete ER Ca^{2+}, and induce ER stress and apoptosis (Zhou et al. 2005). This may explain the increased incidence of atherosclerosis and

Table 1. Effects of complete virions or viral proteins on the $[Ca^{2+}]_{ER}$.

Target	Effect	Virus or viral protein	Reference
IP$_3$R	Increased IP$_3$R activity	p12^{I} of human T-cell lymphotropic virus type 1	Ding et al. 2002
		glycoproteins of human herpes simplex virus type 1 and type 2	Cheshenko et al. 2003
	Increased IP$_3$R activity because of increased IP$_3$ production	influenza A virus	Hartshorn et al. 1988
		Poliovirus	Guinea et al. 1989
		gp120 and Tat of human immunodeficiency virus type 1	Dayanithi et al. 1995
			Mayne et al. 2000
			Haughey and Mattson 2002
		nonstructural protein 4 of rotavirus	Tian et al. 1995
			Dong et al. 1997
			Seo et al. 2008
		gp86 of human cytomegalovirus	Keay et al. 1995
		G-protein coupled receptor and viral macrophage inflammatory protein-I and -II of human herpes virus 8	Arvanitakis et al. 1997
			Nakano et al. 2003
RyR	Increased RyR activity	Tat of human immunodeficiency virus type 1	Norman et al. 2008
		Poliovirus	Brisac et al. 2010
	Increased RyR expression	Borna disease virus	Williams and Lipkin 2006
SERCA	Decreased SERCA activity	core protein of hepatitis C virus	Benali-Furet et al. 2005
	Decreased SERCA expression	Borna disease virus	Williams and Lipkin 2006
		latent membrane protein-1 of Epstein-Barr virus	Dellis et al. 2009
Passive Ca^{2+} leak	Enhanced passive Ca^{2+} leak	nonstructural protein 5A of hepatitis C virus	Robinson and Marchant 2008
ER membrane	Pore formation	p7 and core protein of hepatitis C virus	Griffin et al. 2003
			Bergqvist et al. 2003
		2B and 2BC proteins of entero- and rhinoviruses	Aldabe et al. 1997
			de Jong et al. 2008
		nonstructural protein 4 of rotavirus	Zhou et al. 2009
		pUL37x1 protein of human cytomegalovirus	Sharon-Friling et al. 2006
			Zhou et al. 2009
		6K protein of alphavirus	Antoine et al. 2007

cardiovascular disease in patients treated with protease inhibitors. Lopinavir and ritonavir also deplete ER Ca^{2+} and activate the UPR in intestinal epithelial cells, thus disrupting the epithelial barrier integrity with drug-induced diarrhea as a frequent side effect (Wu et al. 2010).

Bacteria can also cause ER stress. For example, Shiga toxins of *Shigella dysenteriae* serotype 1 and some serotypes of *Escherichia coli* deplete ER Ca^{2+} and trigger a UPR with apoptosis (Lee et al. 2008).

LUNG DISEASES

Asthma

SERCA2 in airway smooth muscle is down-regulated in this chronic inflammatory disease with airway remodeling, leading to more

sustained $[Ca^{2+}]_{cyt}$ increases and enhanced cell motility, proliferation and secretion (Mahn et al. 2009). Decreased SERCA expression might be caused by enhanced cytokine production during airway inflammation (Sathish et al. 2009).

ORMDL3 is a genetic risk factor associated with asthma (Moffatt et al. 2007). The gene encodes an ER protein (Hjelmqvist et al. 2002) that binds to and inhibits SERCA, leading to a decreased $[Ca^{2+}]_{ER}$ and an UPR (Cantero-Recasens et al. 2010).

Toxicity

Chronic exposure to cadmium in humans is associated with lung, but also bone and renal damage. Cadmium stimulates the IP_3R through IP_3 production, and inhibits SERCA (Biagioli et al. 2008). The reduced $[Ca^{2+}]_{ER}$ leads to ER stress and ER-mediated apoptosis.

LIVER DISEASES

Nonalcoholic Fatty Liver

Triglycerides and free fatty acids accumulate in the liver of obese individuals. Palmitate and stearate deplete ER Ca^{2+} stores and activate the UPR leading to cell death (Wei et al. 2009).

Cholestatic Liver Disease

Intrahepatic accumulation of bile acids induces hepatocellular injury. Glycochenodeoxycholic acid depletes ER Ca^{2+} and induces a UPR and apoptosis (Tsuchiya et al. 2006). It is unclear to what extent the decreasing $[Ca^{2+}]_{ER}$ directly contributes to the pathology.

Burn Injury

Severe burn injury impairs liver function. Thermal skin injury in rats depletes ER Ca^{2+} in the liver (Jeschke et al. 2010). This effect is because of an activation of the IP_3R by released cytochrome *c* and an increased IP_3R expression. ER Ca^{2+} depletion activates the UPR leading to apoptosis.

SKELETAL-MUSCLE DISEASES

Brody Disease

Mutations in the gene of SERCA1 (Odermatt et al. 1996) leading to reduced Ca^{2+}-pump expression or activity and hence a prolonged $[Ca^{2+}]_{cyt}$ elevation cause muscle cramping and impaired relaxation during exercise (Brody 1969). Chianina cattle congenital pseudomyotonia (Drogemuller et al. 2008) and Belgian Blue cattle congenital muscular dystony (Charlier et al. 2008) are related pathologies. Until now, no evidence for a UPR leading to apoptosis has been provided, but the ongoing contracture in cattle may induce rhabdomyolysis (Sacchetto et al. 2009).

Autosomal Centronuclear Myopathy

Centronuclear myopathies are characterized by small myofibers with centrally placed nuclei. Mutations of the muscle-specific inositol phosphatase MIP/MTMR14 cause the dominant form of the disease (Tosch et al. 2006; Shen et al. 2009). Mice deficient in this phosphatase produce less contractile force, have prolonged relaxation, and show exacerbated fatigue. $PtdIns(3,5)P_2$ and $PtdIns(3,4)P_2$ accumulate and directly activate RyR1, resulting in an increased Ca^{2+} leak, a lower $[Ca^{2+}]_{SR}$ and a higher $[Ca^{2+}]_{cyt}$. This proposed effect of $PtdIns(3,5)P_2$ and $PtdIns(3,4)P_2$ on RyR1 still needs confirmation.

Central Core Disease

Some mutations in the gene for RyR1 lead to hypotonia, proximal-muscle weakness, and central cores on muscle biopsy (Zhang et al. 1993). They can lead to a leaky channel and a reduced $[Ca^{2+}]_{SR}$, with deleterious consequences for contractions (Brini et al. 2005).

SKIN DISEASE

Darier disease is an inherited skin disorder with less adhesion between epidermal cells and abnormal keratinization. Mutations in the gene encoding SERCA2 (Sakuntabhai et al. 1999) lower the $[Ca^{2+}]_{ER}$ in keratinocytes (Foggia

et al. 2006). ER stress may occur (Onozuka et al. 2006).

The fruit hull of mangosteen is used in Southeast Asia to treat skin infections and wounds (Mahabusarakam et al. 1987). α-mangostin inhibits SERCA, leading to a UPR and apoptosis (Sato et al. 2004).

CANCER

Malignant Transformation

Altered Ca^{2+} signaling may be involved in malignant transformation (Monteith et al. 2007). $[Ca^{2+}]_{ER}$ is often decreased, making the cell resistant to apoptosis. Subsequent Ca^{2+} entry increases $[Ca^{2+}]_{cyt}$ and changes gene expression, DNA repair, and cell-cycle regulation, resulting in cancer development (Korosec et al. 2006; Monteith et al. 2007; Lipskaia et al. 2009).

Human hepatitis B virus, an etiologic factor of hepatocellular carcinoma, integrates with its DNA into the gene for SERCA1 and *cis*-activates chimeric transcripts producing inactive proteins that deplete ER Ca^{2+} stores (Chami et al. 2000). Mice with a heterozygous deletion of the gene encoding SERCA2 (Liu et al. 2001) and some patients with Darier disease (Burge and Wilkinson 1992) develop squamous cell carcinomas. Neoplastic transformation has been linked to a down-regulated SERCA2 (Pacifico et al. 2003; Vanoverberghe et al. 2004; Bergner et al. 2009) or SERCA3 (Gelebart et al. 2002; Brouland et al. 2005), e.g., by somatic or germ-like mutations or epigenetic mechanisms involving promotor methylation (Endo et al. 2004; Korosec et al. 2006, 2008). ER Ca^{2+} depletion can also result from overexpression of Ca^{2+}-release channels. IP_3R3 is overexpressed in disseminated gastric cancer (Sakakura et al. 2003). The amplification of the gene for IP_3R2 increases in some tumors (Heighway et al. 1996). Increased IP_3R expression does not occur in all cancers (Bergner et al. 2009).

Anticancer Drugs

Most chemotherapeutic approaches kill tumor cells via the induction of MOMP. However, drugs that compromise the normal function and homeostasis of the ER may also induce programmed cell death or improve the therapeutic efficacy of existing anticancer drugs (Boelens et al. 2007). Some drugs primarily reduce the $[Ca^{2+}]_{ER}$ and in this way induce a UPR leading to apoptosis. Known SERCA blockers like thapsigargin and curcumin have anticancer activity (Denmeade et al. 2003; Anand et al. 2008; Bakhshi et al. 2008). Anticancer drugs like the stable analogue of the Bcl-2 antagonist HA 14-1 (Hermanson et al. 2009), artemisinin (Stockwin et al. 2009), amiloride analogues (Park et al. 2009), and 2,5-dimethyl-celecoxib (Johnson et al. 2002; Pyrko et al. 2007) also inhibit SERCA with ER stress as a result. SERCA2 expression decreases after photodynamic therapy with hypericin (Buytaert et al. 2006). ER Ca^{2+} stores are depleted by euplotin C through activated RyRs (Cervia et al. 2006), by paclitaxel through formation of Bax dimers in the ER (Liao et al. 2008), and by epigallocatechin gallate through inhibited protein processing at the level of glucosidase II (Magyar et al. 2009) and GRP78/BiP (Ermakova et al. 2006). Ca^{2+} depletion and ER stress are also induced by cisplatin (Nawrocki et al. 2005), dehydrocostuslactone (Hsu et al. 2009; Hung et al. 2010), honokiol (Chen et al. 2010), diaryl- and triaryl-methanes (Abdelrahim et al. 2006), inhibitors of heat shock protein 90 (Taiyab et al. 2009), n-3 long-chain polyunsaturated fatty acids (Jakobsen et al. 2008), rhein (Lai et al. 2009), cardiotoxin III (Chien et al. 2008), homoharringtonine (Jie et al. 2007), berberine (Lin et al. 2007b), diindolylmethane (Savino et al. 2006), the multi-kinase inhibitor sorafenib (Rahmani et al. 2007), the p210 bcr-abl tyrosine-kinase inhibitor STI571 (Pattacini et al. 2004), parthenolide (Zhang et al. 2004), photodynamic therapy with tetra-*S*-glycosylated porphyrin (Thompson et al. 2008), and by many other drugs. Edelfosine leads to Bax/Bak-mediated ER Ca^{2+} depletion and apoptosis, without inducing a UPR (Nieto-Miguel et al. 2007).

Ca^{2+} depletion-induced ER stress can also lead to autophagy, for example, in response to the tyrosine-kinase inhibitor imatinib (Bellodi et al. 2009), or to necrosis, for example, in

therapy-resistant tumors with down-regulated Bax or Bak (Janssen et al. 2009).

CONCLUDING REMARKS

Depletion of ER Ca^{2+} occurs in many diseases. The accompanying ER stress often triggers a UPR leading to apoptosis. The release of insufficient activator Ca^{2+} may compromise essential cell functions. We now begin to understand the molecular mechanisms that reduce the ER Ca^{2+} content. Some therapies already directly target the Ca^{2+}-signaling pathway. A better understanding of the defective Ca^{2+} signal and the development of better drugs targeting the proteins involved will eventually result in better treatments for these various diseases.

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