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

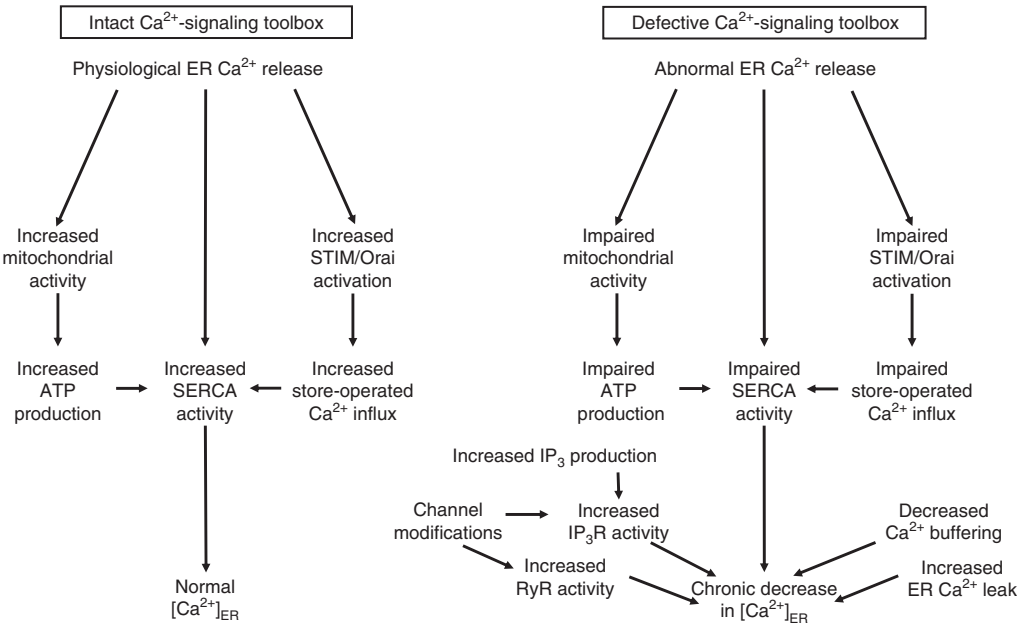

Figure 1. Normal and abnormal $[Ca^{2+}]_{ER}$. A tight coordination between ER Ca^{2+}-release and -refilling mechanisms enables proper Ca^{2+} signaling in response to physiological stimuli. Under these conditions, Ca^{2+} released from the ER stimulates mitochondrial activity and bioenergetics, leading 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).

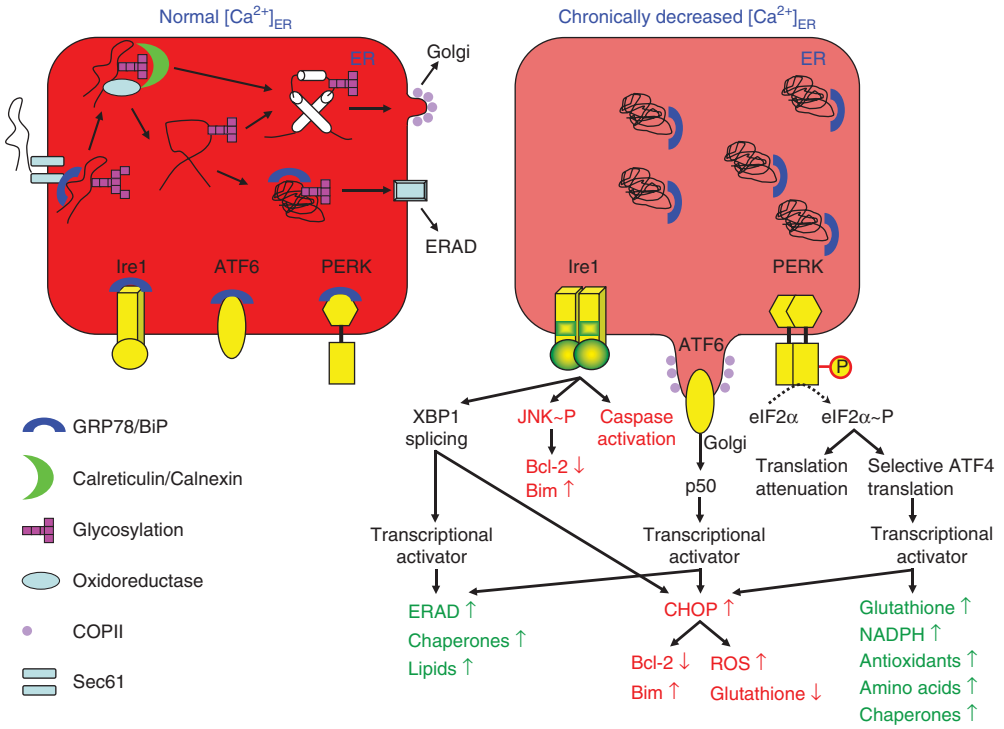

Figure 2. The UPR. At a normal $[Ca^{2+}]_{ER}$ the ER-stress sensors are scaffolded and inactivated by GRP78/BiP. Protein trafficking and quality-control mechanisms work normally. Polypeptides are translocated through Sec61 and glycosylated. This transport is facilitated by the molecular chaperone GRP78/BiP. 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 autoimmune ß-cell destruction caused by overproduction 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_3R1, 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_3Rs 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_3R 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_3R1. This causes dissociation of the disulfide isomerase-like protein ERp44 (Kang et al. 2008) and more IP_3-induced Ca^{2+}

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_3R1 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_3R function. Protein glycosylation with β-*N*-acetylglucosamine is increased in diabetes (Hu et al. 2005). Glycosylation of IP_3R1 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,

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_3R	Increased IP_3R 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_3R 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 downregulated 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 triarylmethanes (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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REFERENCES

Abdelrahim M, Newman K, Vanderlaag K, Samudio I, Safe S. 2006. 3,3'-diindolylmethane (DIM) and its derivatives induce apoptosis in pancreatic cancer cells through endoplasmic reticulum stress-dependent upregulation of DR5. *Carcinogenesis* **27:** 717–728.

Adachi T, Weisbrod RM, Pimentel DR, Ying J, Sharov VS, Schoneich C, Cohen RA. 2004. S-glutathiolation by peroxynitrite activates SERCA during arterial relaxation by nitric oxide. *Nat Med* **10:** 1200–1207.

Ai X, Curran JW, Shannon TR, Bers DM, Pogwizd SM. 2005. Ca^{2+}/calmodulin-dependent protein kinase modulates cardiac ryanodine receptor phosphorylation and sarcoplasmic reticulum Ca^{2+} leak in heart failure. *Circ Res* **97:** 1314–1322.

Akerfeldt MC, Howes J, Chan JY, Stevens VA, Boubenna N, McGuire HM, King C, Biden TJ, Laybutt DR. 2008. Cytokine-induced β-cell death is independent of endoplasmic reticulum stress signaling. *Diabetes* **57:** 3034–3044.

Aldabe R, Irurzun A, Carrasco L. 1997. Poliovirus protein 2BC increases cytosolic free calcium concentrations. *J Virol* **71:** 6214–6217.

Almind K, Bjorbaek C, Vestergaard H, Hansen T, Echwald S, Pedersen O. 1993. Aminoacid polymorphisms of insulin receptor substrate-1 in non-insulin-dependent diabetes mellitus. *Lancet* **342:** 828–832.

Anand P, Sundaram C, Jhurani S, Kunnumakkara AB, Aggarwal BB. 2008. Curcumin and cancer: an "old-age" disease with an "age-old" solution. *Cancer Lett* **267:** 133–164.

Andino LM, Takeda M, Kasahara H, Jakymiw A, Byrne BJ, Lewin AS. 2008. AAV-mediated knockdown of phospholamban leads to improved contractility and calcium handling in cardiomyocytes. *J Gene Med* **10:** 132–142.

Antoine AF, Montpellier C, Cailliau K, Browaeys-Poly E, Vilain JP, Dubuisson J. 2007. The αvirus 6K protein activates endogenous ionic conductances when expressed in Xenopus oocytes. *J Membr Biol* **215:** 37–48.

Araki E, Oyadomari S, Mori M. 2003. Impact of endoplasmic reticulum stress pathway on pancreatic β-cells and diabetes mellitus. *Exp Biol Med* **228:** 1213–1217.

Arredouani A, Guiot Y, Jonas JC, Liu LH, Nenquin M, Pertusa JA, Rahier J, Rolland JF, Shull GE, Stevens M, et al. 2002. SERCA3 ablation does not impair insulin secretion but suggests distinct roles of different sarcoendoplasmic reticulum Ca^{2+} pumps for Ca^{2+} homeostasis in pancreatic β-cells. *Diabetes* **51:** 3245–3253.

Arvanitakis L, Geras-Raaka E, Varma A, Gershengorn MC, Cesarman E. 1997. Human herpesvirus KSHV encodes a constitutively active G-protein-coupled receptor linked to cell proliferation. *Nature* **385:** 347–350.

Austin RC. 2009. The unfolded protein response in health and disease. *Antioxid Redox Signal* **11:** 2279–2287.

Bakhshi J, Weinstein L, Poksay KS, Nishinaga B, Bredesen DE, Rao RV. 2008. Coupling endoplasmic reticulum stress to the cell death program in mouse melanoma cells: effect of curcumin. *Apoptosis* **13:** 904–914.

Beard NA, Laver DR, Dulhunty AF. 2004. Calsequestrin and the calcium release channel of skeletal and cardiac muscle. *Prog Biophys Mol Biol* **85:** 33–69.

Belke DD, Swanson EA, Dillmann WH. 2004. Decreased sarcoplasmic reticulum activity and contractility in diabetic db/db mouse heart. *Diabetes* **53:** 3201–3208.

Bellodi C, Lidonnici MR, Hamilton A, Helgason GV, Soliera AR, Ronchetti M, Galavotti S, Young KW, Selmi T, Yacobi R, et al. 2009. Targeting autophagy potentiates tyrosine kinase inhibitor-induced cell death in Philadelphia chromosome-positive cells, including primary CML stem cells. *J Clin Invest* **119:** 1109–1123.

Belmont PJ, Tadimalla A, Chen WJ, Martindale JJ, Thuerauf DJ, Marcinko M, Gude N, Sussman MA, Glembotski CC. 2008. Coordination of growth and endoplasmic reticulum stress signaling by regulator of calcineurin 1 (RCAN1), a novel ATF6-inducible gene. *J Biol Chem* **283:** 14012–14021.

Benali-Furet NL, Chami M, Houel L, De Giorgi F, Vernejoul F, Lagorce D, Buscail L, Bartenschlager R, Ichas F, Rizzuto R, et al. 2005. Hepatitis C virus core triggers apoptosis in liver cells by inducing ER stress and ER calcium depletion. *Oncogene* **24:** 4921–4933.

Bencsik P, Kupai K, Giricz Z, Gorbe A, Huliak I, Furst S, Dux L, Csont T, Jancso G, Ferdinandy P. 2008. Cardiac capsaicin-sensitive sensory nerves regulate myocardial relaxation via *S*-nitrosylation of SERCA: role of peroxynitrite. *Br J Pharmacol* **153:** 488–496.

Bergner A, Kellner J, Tufman A, Huber RM. 2009. Endoplasmic reticulum Ca^{2+}-homeostasis is altered in small and non-small cell lung cancer cell lines. *J Exp Clin Cancer Res* **28:** 25. doi:101186/1756-9966-28-25.

Bergqvist A, Sundstrom S, Dimberg LY, Gylfe E, Masucci MG. 2003. The hepatitis C virus core protein modulates T cell responses by inducing spontaneous and altering T-cell receptor-triggered Ca^{2+} oscillations. *J Biol Chem* **278:** 18877–18883.

Bernales S, McDonald KL, Walter P. 2006. Autophagy counterbalances endoplasmic reticulum expansion during the unfolded protein response. *PLoS Biol* **4:** e423. doi:101371/journalpbio0040423.

Berridge MJ. 2002. The endoplasmic reticulum: a multifunctional signaling organelle. *Cell Calcium* **32:** 235–249.

Berridge MJ. 2010. Calcium hypothesis of Alzheimer's disease. *Pflugers Arch* **459:** 441–449.

Berridge MJ, Lipp P, Bootman MD. 2000. The versatility and universality of calcium signalling. *Nat Rev Mol Cell Biol* **1:** 11–21.

Bers DM, Eisner DA, Valdivia HH. 2003. Sarcoplasmic reticulum Ca^{2+} and heart failure: roles of diastolic leak and Ca^{2+} transport. *Circ Res* **93:** 487–490.

Bevers MB, Neumar RW. 2008. Mechanistic role of calpains in postischemic neurodegeneration. *J Cereb Blood Flow Metab* **28:** 655–673.

Bezprozvanny I. 2009. Calcium signaling and neurodegenerative diseases. *Trends Mol Med* **15:** 89–100.

Biagioli M, Pifferi S, Ragghianti M, Bucci S, Rizzuto R, Pinton P. 2008. Endoplasmic reticulum stress and alteration in calcium homeostasis are involved in cadmium-induced apoptosis. *Cell Calcium* **43:** 184–195.

Bidasee KR, Nallani K, Besch HR Jr, Dincer UD. 2003a. Streptozotocin-induced diabetes increases disulfide bond formation on cardiac ryanodine receptor (RyR2). *J Pharmacol Exp Ther* **305:** 989–998.

Bidasee KR, Nallani K, Yu Y, Cocklin RR, Zhang Y, Wang M, Dincer UD, Besch HR Jr. 2003b. Chronic diabetes increases advanced glycation end products on cardiac ryanodine receptors/calcium-release channels. *Diabetes* **52:** 1825–1836.

Bidasee KR, Zhang Y, Shao CH, Wang M, Patel KP, Dincer UD, Besch HR Jr. 2004. Diabetes increases formation of advanced glycation end products on sarco(endo)plasmic reticulum Ca^{2+}-ATPase. *Diabetes* **53:** 463–473.

Bidaud I, Mezghrani A, Swayne LA, Monteil A, Lory P. 2006. Voltage-gated calcium channels in genetic diseases. *Biochim Biophys Acta* **1763:** 1169–1174.

Blayney LM, Lai FA. 2009. Ryanodine receptor-mediated arrhythmias and sudden cardiac death. *Pharmacol Ther* **123:** 151–177.

Boelens J, Lust S, Offner F, Bracke ME, Vanhoecke BW. 2007. The endoplasmic reticulum: a target for new anticancer drugs. *In Vivo* **21:** 215–226.

Borge PD Jr, Wolf BA. 2003. Insulin receptor substrate 1 regulation of sarco-endoplasmic reticulum calcium ATPase 3 in insulin-secreting β-cells. *J Biol Chem* **278:** 11359–11368.

Bosanac I, Michikawa T, Mikoshiba K, Ikura M. 2004. Structural insights into the regulatory mechanism of IP_3 receptor. *Biochim Biophys Acta* **1742:** 89–102.

Brandman O, Liou J, Park WS, Meyer T. 2007. STIM2 is a feedback regulator that stabilizes basal cytosolic and endoplasmic reticulum Ca^{2+} levels. *Cell* **131:** 1327–1339.

Brini M, Carafoli E. 2009. Calcium pumps in health and disease. *Physiol Rev* **89:** 1341–1378.

Brini M, Manni S, Pierobon N, Du GG, Sharma P, MacLennan DH, Carafoli E. 2005. Ca^{2+} signaling in HEK-293 and skeletal muscle cells expressing recombinant ryanodine receptors harboring malignant hyperthermia and central core disease mutations. *J Biol Chem* **280:** 15380–15389.

Brisac C, Teoule F, Autret A, Pelletier I, Colbere-Garapin F, Brenner C, Lemaire C, Blondel B. 2010. Calcium flux between the endoplasmic reticulum and mitochondria contributes to poliovirus-induced apoptosis. *J Virol* **84:** 12226–12235.

Brody IA. 1969. Muscle contracture induced by exercise: a syndrome attributable to decreased relaxing factor. *N Engl J Med* **281:** 187–192.

Brosius FC III, Kaufman RJ. 2008. Is the ER stressed out in diabetic kidney disease? *J Am Soc Nephrol* **19:** 2040–2042.

Brouland JP, Gelebart P, Kovacs T, Enouf J, Grossmann J, Papp B. 2005. The loss of sarco/endoplasmic reticulum calcium transport ATPase 3 expression is an early event during the multistep process of colon carcinogenesis. *Am J Pathol* **167:** 233–242.

Brunelle JK, Letai A. 2009. Control of mitochondrial apoptosis by the Bcl-2 family. *J Cell Sci* **122:** 437–441.

Bull R, Finkelstein JP, Galvez J, Sanchez G, Donoso P, Behrens MI, Hidalgo C. 2008. Ischemia enhances activation by Ca^{2+} and redox modification of ryanodine receptor channels from rat brain cortex. *J Neurosci* **28:** 9463–9472.

Burge SM, Wilkinson JD. 1992. Darier-White disease: a review of the clinical features in 163 patients. *J Am Acad Dermatol* **27:** 40–50.

Buytaert E, Callewaert G, Hendrickx N, Scorrano L, Hartmann D, Missiaen L, Vandenheede JR, Heirman I, Grooten J, Agostinis P. 2006. Role of endoplasmic reticulum depletion and multidomain proapoptotic BAX and BAK proteins in shaping cell death after hypericin-mediated photodynamic therapy. *FASEB J* **20:** 756–758.

Cahalan MD. 2009. STIMulating store-operated Ca^{2+} entry. *Nat Cell Biol* **11:** 669–677.

Cantero-Recasens G, Fandos C, Rubio-Moscardo F, Valverde MA, Vicente R. 2010. The asthma-associated ORMDL3 gene product regulates endoplasmic reticulum-mediated calcium signaling and cellular stress. *Hum Mol Genet* **19:** 111–121.

Cardozo AK, Ortis F, Storling J, Feng YM, Rasschaert J, Tonnesen M, Van Eylen F, Mandrup-Poulsen T, Herchuelz A, Eizirik DL. 2005. Cytokines down-regulate the sarcoendoplasmic reticulum pump Ca^{2+} ATPase 2b and deplete endoplasmic reticulum Ca^{2+}, leading to induction of endoplasmic reticulum stress in pancreatic β-cells. *Diabetes* **54:** 452–461.

Cervia D, Martini D, Garcia-Gil M, Di Giuseppe G, Guella G, Dini F, Bagnoli P. 2006. Cytotoxic effects and apoptotic signalling mechanisms of the sesquiterpenoid euplotin C, a secondary metabolite of the marine ciliate Euplotes crassus, in tumour cells. *Apoptosis* **11:** 829–843.

Chaabane C, Corvazier E, Bredoux R, Dally S, Raies A, Villemain A, Dupuy E, Enouf J, Bobe R. 2006. Sarco/endoplasmic reticulum Ca^{2+}ATPase type 3 isoforms (SERCA3b and SERCA3f): distinct roles in cell adhesion and ER stress. *Biochem Biophys Res Commun* **345:** 1377–1385.

Chaabane C, Dally S, Corvazier E, Bredoux R, Bobe R, Ftouhi B, Raies A, Enouf J. 2007. Platelet PMCA- and SERCA-type Ca^{2+}-ATPase expression in diabetes: a novel signature of abnormal megakaryocytopoiesis. *J Thromb Haemost* **5:** 2127–2135.

Chami M, Oules B, Paterlini-Brechot P. 2006. Cytobiological consequences of calcium-signaling alterations induced by human viral proteins. *Biochim Biophys Acta* **1763:** 1344–1362.

Chami M, Gozuacik D, Saigo K, Capiod T, Falson P, Lecoeur H, Urashima T, Beckmann J, Gougeon ML, Claret M, et al. 2000. Hepatitis B virus-related insertional mutagenesis implicates SERCA1 gene in the control of apoptosis. *Oncogene* **19:** 2877–2886.

Chami M, Oules B, Szabadkai G, Tacine R, Rizzuto R, Paterlini-Brechot P. 2008. Role of SERCA1 truncated isoform in the proapoptotic calcium transfer from ER to mitochondria during ER stress. *Mol Cell* **32:** 641–651.

Charlier C, Coppieters W, Rollin F, Desmecht D, Agerholm JS, Cambisano N, Carta E, Dardano S, Dive M, Fasquelle C, et al. 2008. Highly effective SNP-based association mapping and management of recessive defects in livestock. *Nat Genet* **40:** 449–454.

Chen Y, Liu CP, Xu KF, Mao XD, Lu YB, Fang L, Yang JW, Liu C. 2008. Effect of taurine-conjugated ursodeoxycholic acid on endoplasmic reticulum stress and apoptosis induced by advanced glycation end products in cultured mouse podocytes. *Am J Nephrol* **28:** 1014–1022.

Chen YJ, Wu CL, Liu JF, Fong YC, Hsu SF, Li TM, Su YC, Liu SH, Tang CH. 2010. Honokiol induces cell apoptosis in human chondrosarcoma cells through mitochondrial dysfunction and endoplasmic reticulum stress. *Cancer Lett* **291:** 20–30.

Cheshenko N, Del Rosario B, Woda C, Marcellino D, Satlin LM, Herold BC. 2003. Herpes simplex virus triggers activation of calcium-signaling pathways. *J Cell Biol* **163:** 283–293.

Chien CM, Yang SH, Chang LS, Lin SR. 2008. Involvement of both endoplasmic reticulum- and mitochondria-dependent pathways in cardiotoxin III-induced apoptosis in HL-60 cells. *Clin Exp Pharmacol Physiol* **35:** 1059–1064.

Chipuk JE, Green DR. 2008. How do BCL-2 proteins induce mitochondrial outer membrane permeabilization? *Trends Cell Biol* **18:** 157–164.

Choi KM, Zhong Y, Hoit BD, Grupp IL, Hahn H, Dilly KW, Guatimosim S, Lederer WJ, Matlib MA. 2002. Defective intracellular Ca^{2+} signaling contributes to cardiomyopathy in type 1 diabetic rats. *Am J Physiol* **283:** H1398–H1408.

Clark RJ, McDonough PM, Swanson E, Trost SU, Suzuki M, Fukuda M, Dillmann WH. 2003. Diabetes and the accompanying hyperglycemia impairs cardiomyocyte calcium cycling through increased nuclear O-GlcNAcylation. *J Biol Chem* **278:** 44230–44237.

Cooper ME, Bonnet F, Oldfield M, Jandeleit-Dahm K. 2001. Mechanisms of diabetic vasculopathy: an overview. *Am J Hypert* **14:** 475–486.

Cunha DA, Hekerman P, Ladriere L, Bazarra-Castro A, Ortis F, Wakeham MC, Moore F, Rasschaert J, Cardozo AK, Bellomo E, et al. 2008. Initiation and execution of lipotoxic ER stress in pancreatic β-cells. *J Cell Sci* **121:** 2308–2318.

Dahl C, Haug LS, Spilsberg B, Johansen J, Ostvold AC, Diemer NH. 2000. Reduced [^{3}H]IP_3 binding but unchanged IP_3 receptor levels in the rat hippocampus CA1 region following transient global ischemia and tolerance induction. *Neurochem Int* **36:** 379–388.

Dally S, Monceau V, Corvazier E, Bredoux R, Raies A, Bobe R, del Monte F, Enouf J. 2009. Compartmentalized expression of three novel sarco/endoplasmic reticulum Ca^{2+}ATPase 3 isoforms including the switch to ER stress, SERCA3f, in non-failing and failing human heart. *Cell Calcium* **45:** 144–154.

Dayanithi G, Yahi N, Baghdiguian S, Fantini J. 1995. Intracellular calcium release induced by human immunodeficiency virus type 1 (HIV-1) surface envelope glycoprotein in human intestinal epithelial cells: a putative mechanism for HIV-1 enteropathy. *Cell Calcium* **18:** 9–18.

DeGracia DJ, Kumar R, Owen CR, Krause GS, White BC. 2002. Molecular pathways of protein synthesis inhibition during brain reperfusion: implications for neuronal survival or death. *J Cereb Blood Flow Metab* **22:** 127–141.

de Jong AS, de Mattia F, Van Dommelen MM, Lanke K, Melchers WJ, Willems PH, van Kuppeveld FJ. 2008. Functional analysis of picornavirus 2B proteins: effects on calcium homeostasis and intracellular protein trafficking. *J Virol* **82:** 3782–3790.

de Jong AS, Visch HJ, de Mattia F, van Dommelen MM, Swarts HG, Luyten T, Callewaert G, Melchers WJ, Willems PH, van Kuppeveld FJ. 2006. The coxsackievirus 2B protein increases efflux of ions from the endoplasmic reticulum and Golgi, thereby inhibiting protein trafficking through the Golgi. *J Biol Chem* **281:** 14144–14150.

Dellis O, Arbabian A, Brouland JP, Kovacs T, Rowe M, Chomienne C, Joab I, Papp B. 2009. Modulation of B-cell endoplasmic reticulum calcium homeostasis by Epstein-Barr virus latent membrane protein-1. *Mol Cancer* **8:** 59. doi:101186/1476-4598-8-59.

del Monte F, Hajjar RJ. 2008. Intracellular devastation in heart failure. *Heart Fail Rev* **13:** 151–162.

Deng X, Wang Y, Zhou Y, Soboloff J, Gill DL. 2009. STIM and Orai: dynamic intermembrane coupling to control cellular calcium signals. *J Biol Chem* **284:** 22501–22505.

Denmeade SR, Jakobsen CM, Janssen S, Khan SR, Garrett ES, Lilja H, Christensen SB, Isaacs JT. 2003. Prostate-specific antigen-activated thapsigargin prodrug as targeted therapy for prostate cancer. *J Natl Cancer Inst* **95:** 990–1000.

Dickhout JG, Sood SK, Austin RC. 2007. Role of endoplasmic reticulum calcium disequilibria in the mechanism of homocysteine-induced ER stress. *Antioxid Redox Signal* **9:** 1863–1873.

Dickhout JG, Hossain GS, Pozza LM, Zhou J, Lhotak S, Austin RC. 2005. Peroxynitrite causes endoplasmic reticulum stress and apoptosis in human vascular endothelium: implications in atherogenesis. *Arterioscler Thromb Vasc Biol* **25:** 2623–2629.

Dieterle T, Meyer M, Gu Y, Belke DD, Swanson E, Iwatate M, Hollander J, Peterson KL, Ross J Jr, Dillmann WH. 2005. Gene transfer of a phospholamban-targeted antibody improves calcium handling and cardiac function in heart failure. *Cardiovasc Res* **67:** 678–688.

Ding W, Albrecht B, Kelley RE, Muthusamy N, Kim SJ, Altschuld RA, Lairmore MD. 2002. Human T-cell lymphotropic virus type 1 p12^{I} expression increases cytoplasmic calcium to enhance the activation of nuclear factor of activated T cells. *J Virol* **76:** 10374–10382.

Doi M, Yano M, Kobayashi S, Kohno M, Tokuhisa T, Okuda S, Suetsugu M, Hisamatsu Y, Ohkusa T, Kohno M, et al. 2002. Propranolol prevents the development of heart failure by restoring FKBP12.6-mediated stabilization of ryanodine receptor. *Circulation* **105:** 1374–1379.

Dong Y, Zeng CQ, Ball JM, Estes MK, Morris AP. 1997. The rotavirus enterotoxin NSP4 mobilizes intracellular calcium in human intestinal cells by stimulating phospholipase C-mediated inositol 1,4,5-trisphosphate production. *Proc Natl Acad Sci* **94:** 3960–3965.

Doutheil J, Althausen S, Treiman M, Paschen W. 2000. Effect of nitric oxide on endoplasmic reticulum calcium homeostasis, protein synthesis and energy metabolism. *Cell Calcium* **27:** 107–115.

Drogemuller C, Drogemuller M, Leeb T, Mascarello F, Testoni S, Rossi M, Gentile A, Damiani E, Sacchetto R. 2008. Identification of a missense mutation in the bovine ATP2A1 gene in congenital pseudomyotonia of Chianina cattle: an animal model of human Brody disease. *Genomics* **92:** 474–477.

Durham WJ, Wehrens XH, Sood S, Hamilton SL. 2007. Diseases associated with altered ryanodine receptor activity. *Subcell Biochem* **45:** 273–321.

Dutta K, Carmody MW, Cala SE, Davidoff AJ. 2002. Depressed PKA activity contributes to impaired SERCA function and is linked to the pathogenesis of glucose-induced cardiomyopathy. *J Mol Cell Cardiol* **34:** 985–996.

Egger L, Schneider J, Rheme C, Tapernoux M, Hacki J, Borner C. 2003. Serine proteases mediate apoptosis-like cell death and phagocytosis under caspase-inhibiting conditions. *Cell Death Differ* **10:** 1188–1203.

Eizirik DL, Cardozo AK, Cnop M. 2008. The role for endoplasmic reticulum stress in diabetes mellitus. *Endocr Rev* **29:** 42–61.

Endo M. 2009. Calcium-induced calcium release in skeletal muscle. *Physiol Rev* **89:** 1153–1176.

Endo Y, Uzawa K, Mochida Y, Shiiba M, Bukawa H, Yokoe H, Tanzawa H. 2004. Sarcoendoplasmic reticulum Ca^{2+} ATPase type 2 downregulated in human oral squamous cell carcinoma. *Int J Cancer* **110:** 225–231.

Ermakova SP, Kang BS, Choi BY, Choi HS, Schuster TF, Ma WY, Bode AM, Dong Z. 2006. (-)-Epigallocatechin gallate overcomes resistance to etoposide-induced cell death by targeting the molecular chaperone glucose-regulated protein 78. *Cancer Res* **66:** 9260–9269.

Evans-Molina C, Robbins RD, Kono T, Tersey SA, Vestermark GL, Nunemaker CS, Garmey JC, Deering TG, Keller SR, Maier B, et al. 2009. Peroxisome proliferator-activated receptor γ activation restores islet function in diabetic mice through reduction of endoplasmic reticulum stress and maintenance of euchromatin structure. *Mol Cell Biol* **29:** 2053–2067.

Fan J, Watanabe T. 2003. Inflammatory reactions in the pathogenesis of atherosclerosis. *J Atheroscler Thromb* **10:** 63–71.

Farfel-Becker T, Vitner E, Dekel H, Leshem N, Enquist IB, Karlsson S, Futerman AH. 2009. No evidence for activation of the unfolded protein response in neuronopathic models of Gaucher disease. *Hum Mol Genet* **18:** 1482–1488.

Fedirko NV, Kruglikov IA, Kopach OV, Vats JA, Kostyuk PG, Voitenko NV. 2006. Changes in functioning of rat submandibular salivary gland under streptozotocin-induced diabetes are associated with alterations of Ca^{2+} signaling and Ca^{2+} transporting pumps. *Biochim Biophys Acta* **1762:** 294–303.

Feng B, Yao PM, Li Y, Devlin CM, Zhang D, Harding HP, Sweeney M, Rong JX, Kuriakose G, Fisher EA, et al. 2003. The endoplasmic reticulum is the site of cholesterol-induced cytotoxicity in macrophages. *Nat Cell Biol* **5:** 781–792.

Fernyhough P, Calcutt NA. 2010. Abnormal calcium homeostasis in peripheral neuropathies. *Cell Calcium* **47:** 130–139.

Ferreiro E, Resende R, Costa R, Oliveira CR, Pereira CM. 2006. An endoplasmic-reticulum-specific apoptotic pathway is involved in prion and amyloid-β peptides neurotoxicity. *Neurobiol Dis* **23:** 669–678.

Ferreiro E, Costa R, Marques S, Cardoso SM, Oliveira CR, Pereira CM. 2008. Involvement of mitochondria in endoplasmic reticulum stress-induced apoptotic cell death pathway triggered by the prion peptide PrP(106-126). *J Neurochem* **104:** 766–776.

Foggia L, Hovnanian A. 2004. Calcium pump disorders of the skin. *Am J Med Genet C* **131C:** 20–31.

Foggia L, Aronchik I, Aberg K, Brown B, Hovnanian A, Mauro TM. 2006. Activity of the hSPCA1 Golgi Ca^{2+} pump is essential for Ca^{2+}-mediated Ca^{2+} response and cell viability in Darier disease. *J Cell Sci* **119:** 671–679.

Fonseca SG, Ishigaki S, Oslowski CM, Lu S, Lipson KL, Ghosh R, Hayashi E, Ishihara H, Oka Y, Permutt MA, et al. 2010. Wolfram syndrome 1 gene negatively regulates ER stress signaling in rodent and human cells. *J Clin Invest* **120:** 744–755.

Foskett JK, White C, Cheung KH, Mak DO. 2007. Inositol trisphosphate receptor Ca^{2+} release channels. *Physiol Rev* **87:** 593–658.

Foti M, Cartier L, Piguet V, Lew DP, Carpentier JL, Trono D, Krause KH. 1999. The HIV Nef protein alters Ca^{2+} signaling in myelomonocytic cells through SH3-mediated protein-protein interactions. *J Biol Chem* **274:** 34765–34772.

Frank KF, Bolck B, Brixius K, Kranias EG, Schwinger RH. 2002. Modulation of SERCA: implications for the failing human heart. *Basic Res Cardiol* **97:** I72–I78.

Franz WM, Muller OJ, Katus HA. 2001. Cardiomyopathies: from genetics to the prospect of treatment. *Lancet* **358:** 1627–1637.

French JP, Quindry JC, Falk DJ, Staib JL, Lee Y, Wang KK, Powers SK. 2006. Ischemia-reperfusion-induced calpain

activation and SERCA2a degradation are attenuated by exercise training and calpain inhibition. *Am J Physiol* **290:** H128–H136.

Gaut JR, Hendershot LM. 1993. The modification and assembly of proteins in the endoplasmic reticulum. *Curr Opin Cell Biol* **5:** 589–595.

Gelebart P, Kovacs T, Brouland JP, van Gorp R, Grossmann J, Rivard N, Panis Y, Martin V, Bredoux R, Enouf J, et al. 2002. Expression of endomembrane calcium pumps in colon and gastric cancer cells. Induction of SERCA3 expression during differentiation. *J Biol Chem* **277:** 26310–26320.

Gemes G, Rigaud M, Weyker PD, Abram SE, Weihrauch D, Poroli M, Zoga V, Hogan QH. 2009. Depletion of calcium stores in injured sensory neurons: anatomic and functional correlates. *Anesthesiology* **111:** 393–405.

Ginzburg L, Futerman AH. 2005. Defective calcium homeostasis in the cerebellum in a mouse model of Niemann-Pick A disease. *J Neurochem* **95:** 1619–1628.

Ginzburg L, Li SC, Li YT, Futerman AH. 2008. An exposed carboxyl group on sialic acid is essential for gangliosides to inhibit calcium uptake via the sarco/endoplasmic reticulum Ca^{2+}-ATPase: relevance to gangliosidoses. *J Neurochem* **104:** 140–146.

Giorgi C, De Stefani D, Bononi A, Rizzuto R, Pinton P. 2009. Structural and functional link between the mitochondrial network and the endoplasmic reticulum. *Int J Biochem Cell Biol* **41:** 1817–1827.

Giorgi C, Romagnoli A, Pinton P, Rizzuto R. 2008. Ca^{2+} signaling, mitochondria and cell death. *Curr Mol Med* **8:** 119–130.

Gotoh T, Mori M. 2006. Nitric oxide and endoplasmic reticulum stress. *Arterioscler Thromb Vasc Biol* **26:** 1439–1446.

Griffin SD, Beales LP, Clarke DS, Worsfold O, Evans SD, Jaeger J, Harris MP, Rowlands DJ. 2003. The p7 protein of hepatitis C virus forms an ion channel that is blocked by the antiviral drug, Amantadine. *FEBS Lett* **535:** 34–38.

Grover AK, Kwan CY, Samson SE. 2003. Effects of peroxynitrite on sarco/endoplasmic reticulum Ca^{2+} pump isoforms SERCA2b and SERCA3a. *Am J Physiol* **285:** C1537–C1543.

Guest PC, Bailyes EM, Hutton JC. 1997. Endoplasmic reticulum Ca^{2+} is important for the proteolytic processing and intracellular transport of proinsulin in the pancreatic β-cell. *Biochem J* **323:** 445–450.

Guinea R, Lopez-Rivas A, Carrasco L. 1989. Modification of phospholipase C and phospholipase A2 activities during poliovirus infection. *J Biol Chem* **264:** 21923–21927.

Guner S, Arioglu E, Tay A, Tasdelen A, Aslamaci S, Bidasee KR, Dincer UD. 2004. Diabetes decreases mRNA levels of calcium-release channels in human atrial appendage. *Mol Cell Biochem* **263:** 143–150.

Gurzov EN, Ortis F, Cunha DA, Gosset G, Li M, Cardozo AK, Eizirik DL. 2009. Signaling by IL-1β+IFN-γ and ER stress converge on DP5/Hrk activation: a novel mechanism for pancreatic β-cell apoptosis. *Cell Death Differ* **16:** 1539–1550.

Gwiazda KS, Yang TL, Lin Y, Johnson JD. 2009. Effects of palmitate on ER and cytosolic Ca^{2+} homeostasis in β-cells. *Am J Physiol* **296:** E690–E701.

Gyorke S. 2009. Molecular basis of catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm* **6:** 123–129.

Gyorke S, Terentyev D. 2008. Modulation of ryanodine receptor by luminal calcium and accessory proteins in health and cardiac disease. *Cardiovasc Res* **77:** 245–255.

Haghighi K, Kolokathis F, Gramolini AO, Waggoner JR, Pater L, Lynch RA, Fan GC, Tsiapras D, Parekh RR, Dorn GW II, et al. 2006. A mutation in the human phospholamban gene, deleting arginine 14, results in lethal, hereditary cardiomyopathy. *Proc Natl Acad Sci* **103:** 1388–1393.

Han I, Kudlow JE. 1997. Reduced O glycosylation of Sp1 is associated with increased proteasome susceptibility. *Mol Cell Biol* **17:** 2550–2558.

Harding HP, Zhang Y, Ron D. 1999. Protein translation and folding are coupled by an endoplasmic-reticulum-resident kinase. *Nature* **397:** 271–274.

Harding HP, Zhang Y, Bertolotti A, Zeng H, Ron D. 2000. Perk is essential for translational regulation and cell survival during the unfolded protein response. *Mol Cell* **5:** 897–904.

Harding HP, Zhang Y, Zeng H, Novoa I, Lu PD, Calfon M, Sadri N, Yun C, Popko B, Paules R, et al. 2003. An integrated stress response regulates amino acid metabolism and resistance to oxidative stress. *Mol Cell* **11:** 619–633.

Hartshorn KL, Collamer M, Auerbach M, Myers JB, Pavlotsky N, Tauber AI. 1988. Effects of influenza A virus on human neutrophil calcium metabolism. *J Immunol* **141:** 1295–1301.

Hasenfuss G, Pieske B. 2002. Calcium cycling in congestive heart failure. *J Mol Cell Cardiol* **34:** 951–969.

Haughey NJ, Mattson MP. 2002. Calcium dysregulation and neuronal apoptosis by the HIV-1 proteins Tat and gp120. *J Acquir Immune Defic Syndr* **31 Suppl 2:** S55–S61.

Heighway J, Betticher DC, Hoban PR, Altermatt HJ, Cowen R. 1996. Coamplification in tumors of KRAS2, type 2 inositol 1,4,5 triphosphate receptor gene, and a novel human gene, KRAG. *Genomics* **35:** 207–214.

Hermanson D, Addo SN, Bajer AA, Marchant JS, Das SG, Srinivasan B, Al-Mousa F, Michelangeli F, Thomas DD, Lebien TW, et al. 2009. Dual mechanisms of sHA 14-1 in inducing cell death through endoplasmic reticulum and mitochondria. *Mol Pharmacol* **76:** 667–678.

Hetz C, Russelakis-Carneiro M, Maundrell K, Castilla J, Soto C. 2003. Caspase-12 and endoplasmic reticulum stress mediate neurotoxicity of pathological prion protein. *EMBO J* **22:** 5435–5445.

Hjelmqvist L, Tuson M, Marfany G, Herrero E, Balcells S, Gonzalez-Duarte R. 2002. ORMDL proteins are a conserved new family of endoplasmic reticulum membrane proteins. *Genome Biol* **3:** RESEARCH0027. doi:101186/gb-2002-3-6-research0027.

Hollien J, Weissman JS. 2006. Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. *Science* **313:** 104–107.

Hoshijima M, Ikeda Y, Iwanaga Y, Minamisawa S, Date MO, Gu Y, Iwatate M, Li M, Wang L, Wilson JM, et al. 2002. Chronic suppression of heart-failure progression by a pseudophosphorylated mutant of phospholamban via in vivo cardiac rAAV gene delivery. *Nat Med* **8:** 864–871.

Hoyer-Hansen M, Jaattela M. 2007. Connecting endoplasmic reticulum stress to autophagy by unfolded protein response and calcium. *Cell Death Differ* **14:** 1576–1582.

Hsu YL, Wu LY, Kuo PL. 2009. Dehydrocostuslactone, a medicinal plant-derived sesquiterpene lactone, induces apoptosis coupled to endoplasmic reticulum stress in liver cancer cells. *J Pharmacol Exp Ther* **329:** 808–819.

Hu Y, Belke D, Suarez J, Swanson E, Clark R, Hoshijima M, Dillmann WH. 2005. Adenovirus-mediated overexpression of *O*-GlcNAcase improves contractile function in the diabetic heart. *Circ Res* **96:** 1006–1013.

Huang TJ, Sayers NM, Fernyhough P, Verkhratsky A. 2002. Diabetes-induced alterations in calcium homeostasis in sensory neurones of streptozotocin-diabetic rats are restricted to lumbar ganglia and are prevented by neurotrophin-3. *Diabetologia* **45:** 560–570.

Huang F, Shan J, Reiken S, Wehrens XH, Marks AR. 2006. Analysis of calstabin2 (FKBP12.6)-ryanodine receptor interactions: rescue of heart failure by calstabin2 in mice. *Proc Natl Acad Sci* **103:** 3456–3461.

Hung JY, Hsu YL, Ni WC, Tsai YM, Yang CJ, Kuo PL, Huang MS. 2010. Oxidative and endoplasmic reticulum stress signaling are involved in dehydrocostuslactone-mediated apoptosis in human non-small cell lung cancer cells. *Lung Cancer* **68:** 355–365.

Inesi G, Prasad AM, Pilankatta R. 2008. The Ca^{2+} ATPase of cardiac sarcoplasmic reticulum: Physiological role and relevance to diseases. *Biochem Biophys Res Commun* **369:** 182–187.

Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, Bernal-Mizrachi E, Mueckler M, Marshall H, Donis-Keller H, Crock P, et al. 1998. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). *Nat Genet* **20:** 143–148.

Irvine RF. 1990. Quantal Ca^{2+} release and the control of Ca^{2+} entry by inositol phosphates–a possible mechanism. *FEBS Lett* **263:** 5–9.

Jakobsen CH, Storvold GL, Bremseth H, Follestad T, Sand K, Mack M, Olsen KS, Lundemo AG, Iversen JG, Krokan HE, et al. 2008. DHA induces ER stress and growth arrest in human colon cancer cells: associations with cholesterol and calcium homeostasis. *J Lipid Res* **49:** 2089–2100.

Janssen K, Horn S, Niemann MT, Daniel PT, Schulze-Osthoff K, Fischer U. 2009. Inhibition of the ER Ca^{2+} pump forces multidrug-resistant cells deficient in Bak and Bax into necrosis. *J Cell Sci* **122:** 4481–4491.

Jaski BE, Jessup ML, Mancini DM, Cappola TP, Pauly DF, Greenberg B, Borow K, Dittrich H, Zsebo KM, Hajjar RJ. 2009. Calcium upregulation by percutaneous administration of gene therapy in cardiac disease (CUPID Trial), a first-in-human phase 1/2 clinical trial. *J Card Fail* **15:** 171–181.

Jeschke MG, Gauglitz GG, Song J, Kulp GA, Finnerty CC, Cox RA, Barral JM, Herndon DN, Boehning D. 2010. Calcium and ER stress mediate hepatic apoptosis after burn injury. *J Cell Mol Med* **13:** 1857–1865.

Jie H, Donghua H, Xingkui X, Liang G, Wenjun W, Xiaoyan H, Zhen C. 2007. Homoharringtonine-induced apoptosis of MDS cell line MUTZ-1 cells is mediated by the endoplasmic reticulum stress pathway. *Leuk Lymphoma* **48:** 964–977.

Johnson AJ, Hsu AL, Lin HP, Song X, Chen CS. 2002. The cyclo-oxygenase-2 inhibitor celecoxib perturbs intracellular calcium by inhibiting endoplasmic reticulum Ca^{2+}-ATPases: a plausible link with its anti-tumour effect and cardiovascular risks. *Biochem J* **366:** 831–837.

Kanekura K, Suzuki H, Aiso S, Matsuoka M. 2009. ER stress and unfolded protein response in amyotrophic lateral sclerosis. *Mol Neurobiol* **39:** 81–89.

Kang S, Kang J, Kwon H, Frueh D, Yoo SH, Wagner G, Park S. 2008. Effects of redox potential and Ca^{2+} on the inositol 1,4,5-trisphosphate receptor L3-1 loop region: implications for receptor regulation. *J Biol Chem* **283:** 25567–25575.

Karakikes I, Kim M, Hadri L, Sakata S, Sun Y, Zhang W, Chemaly ER, Hajjar RJ, Lebeche D. 2009. Gene remodeling in type 2 diabetic cardiomyopathy and its phenotypic rescue with SERCA2a. *PLoS One* **4:** e6474. doi:101371/journalpone0006474.

Kawada H, Nishiyama C, Takagi A, Tokura T, Nakano N, Maeda K, Mayuzumi N, Ikeda S, Okumura K, Ogawa H. 2005. Transcriptional regulation of ATP2C1 gene by Sp1 and YY1 and reduced function of its promoter in Hailey-Hailey disease keratinocytes. *J Invest Dermatol* **124:** 1206–1214.

Kawase Y, Hajjar RJ. 2008. The cardiac sarcoplasmic/endoplasmic reticulum calcium ATPase: a potent target for cardiovascular diseases. *Nat Clin Pract Cardiovasc Med* **5:** 554–565.

Keay S, Baldwin BR, Smith MW, Wasserman SS, Goldman WF. 1995. Increases in $[Ca^{2+}]_i$ mediated by the 92.5-kDa putative cell membrane receptor for HCMV gp86. *Am J Physiol* **269:** C11–C21.

Kim I, Xu W, Reed JC. 2008. Cell death and endoplasmic reticulum stress: disease relevance and therapeutic opportunities. *Nat Rev Drug Discov* **7:** 1013–1030.

Kim HW, Ch YS, Lee HR, Park SY, Kim YH. 2001. Diabetic alterations in cardiac sarcoplasmic reticulum Ca^{2+}-ATPase and phospholamban protein expression. *Life Sci* **70:** 367–379.

Knobler H, Savion N, Shenkman B, Kotev-Emeth S, Varon D. 1998. Shear-induced platelet adhesion and aggregation on subendothelium are increased in diabetic patients. *Thromb Res* **90:** 181–190.

Kobayashi T, Taguchi K, Takenouchi Y, Matsumoto T, Kamata K. 2007. Insulin-induced impairment via peroxynitrite production of endothelium-dependent relaxation and sarco/endoplasmic reticulum Ca^{2+}-ATPase function in aortas from diabetic rats. *Free Radic Biol Med* **43:** 431–443.

Korkotian E, Schwarz A, Pelled D, Schwarzmann G, Segal M, Futerman AH. 1999. Elevation of intracellular glucosylceramide levels results in an increase in endoplasmic reticulum density and in functional calcium stores in cultured neurons. *J Biol Chem* **274:** 21673–21678.

Korosec B, Glavac D, Rott T, Ravnik-Glavac M. 2006. Alterations in the ATP2A2 gene in correlation with colon and lung cancer. *Cancer Genet Cytogenet* **171:** 105–111.

Korosec B, Glavac D, Volavsek M, Ravnik-Glavac M. 2008. Alterations in genes encoding sarcoplasmic-endoplasmic reticulum Ca^{2+} pumps in association with head and neck squamous cell carcinoma. *Cancer Genet Cytogenet* **181:** 112–118.

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Kouroku Y, Fujita E, Tanida I, Ueno T, Isoai A, Kumagai H, Ogawa S, Kaufman RJ, Kominami E, Momoi T. 2007. ER stress (PERK/eIF2α phosphorylation) mediates the polyglutamine-induced LC3 conversion, an essential step for autophagy formation. *Cell Death Differ* **14:** 230–239.

Kranias EG, Bers DM. 2007. Calcium and cardiomyopathies. *Subcell Biochem* **45:** 523–537.

Kroemer G, Galluzzi L, Brenner C. 2007. Mitochondrial membrane permeabilization in cell death. *Physiol Rev* **87:** 99–163.

Kruglikov I, Gryshchenko O, Shutov L, Kostyuk E, Kostyuk P, Voitenko N. 2004. Diabetes-induced abnormalities in ER calcium mobilization in primary and secondary nociceptive neurons. *Pflugers Arch* **448:** 395–401.

Kulkarni RN, Roper MG, Dahlgren G, Shih DQ, Kauri LM, Peters JL, Stoffel M, Kennedy RT. 2004. Islet secretory defect in insulin receptor substrate 1 null mice is linked with reduced calcium signaling and expression of sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA)-2b and -3. *Diabetes* **53:** 1517–1525.

Lai P, Michelangeli F. 2009. Changes in expression and activity of the secretory pathway Ca^{2+} ATPase 1 (SPCA1) in A7r5 vascular smooth muscle cells cultured at different glucose concentrations. *Biosci Rep* **29:** 397–404.

Lai WW, Yang JS, Lai KC, Kuo CL, Hsu CK, Wang CK, Chang CY, Lin JJ, Tang NY, Chen PY, et al. 2009. Rhein induced apoptosis through the endoplasmic reticulum stress, caspase- and mitochondria-dependent pathways in SCC-4 human tongue squamous cancer cells. *In Vivo* **23:** 309–316.

Lee B, Jonas JC, Weir GC, Laychock SG. 1999. Glucose regulates expression of inositol 1,4,5-trisphosphate receptor isoforms in isolated rat pancreatic islets. *Endocrinology* **140:** 2173–2182.

Lee SY, Lee MS, Cherla RP, Tesh VL. 2008. Shiga toxin 1 induces apoptosis through the endoplasmic reticulum stress response in human monocytic cells. *Cell Microbiol* **10:** 770–780.

Lehnart SE, Wehrens XH, Marks AR. 2005. Defective ryanodine receptor interdomain interactions may contribute to intracellular Ca^{2+} leak: a novel therapeutic target in heart failure. *Circulation* **111:** 3342–3346.

Lehnart SE, Mongillo M, Bellinger A, Lindegger N, Chen BX, Hsueh W, Reiken S, Wronska A, Drew LJ, Ward CW, et al. 2008. Leaky Ca^{2+} release channel/ryanodine receptor 2 causes seizures and sudden cardiac death in mice. *J Clin Invest* **118:** 2230–2245.

Lei K, Davis RJ. 2003. JNK phosphorylation of Bim-related members of the Bcl2 family induces Bax-dependent apoptosis. *Proc Natl Acad Sci* **100:** 2432–2437.

Leonardi O, Mints G, Hussain MA. 2003. β-cell apoptosis in the pathogenesis of human type 2 diabetes mellitus. *Eur J Endocrinol* **149:** 99–102.

Levine B, Kroemer G. 2008. Autophagy in the pathogenesis of disease. *Cell* **132:** 27–42.

Levy J. 1999. Abnormal cell calcium homeostasis in type 2 diabetes mellitus: a new look on old disease. *Endocrine* **10:** 1–6.

Li Y, Ge M, Ciani L, Kuriakose G, Westover EJ, Dura M, Covey DF, Freed JH, Maxfield FR, Lytton J, et al. 2004. Enrichment of endoplasmic reticulum with cholesterol inhibits sarcoplasmic-endoplasmic reticulum calcium ATPase-2b activity in parallel with increased order of membrane lipids: implications for depletion of endoplasmic reticulum calcium stores and apoptosis in cholesterol-loaded macrophages. *J Biol Chem* **279:** 37030–37039.

Li G, Mongillo M, Chin KT, Harding H, Ron D, Marks AR, Tabas I. 2009. Role of ERO1-α-mediated stimulation of inositol 1,4,5-triphosphate receptor activity in endoplasmic reticulum stress-induced apoptosis. *J Cell Biol* **186:** 783–792.

Liao PC, Tan SK, Lieu CH, Jung HK. 2008. Involvement of endoplasmic reticulum in paclitaxel-induced apoptosis. *J Cell Biochem* **104:** 1509–1523.

Lievremont JP, Rizzuto R, Hendershot L, Meldolesi J. 1997. BiP, a major chaperone protein of the endoplasmic reticulum lumen, plays a direct and important role in the storage of the rapidly exchanging pool of Ca^{2+}. *J Biol Chem* **272:** 30873–30879.

Lin JH, Li H, Yasumura D, Cohen HR, Zhang C, Panning B, Shokat KM, Lavail MM, Walter P. 2007a. IRE1 signaling affects cell fate during the unfolded protein response. *Science* **318:** 944–949.

Lin JH, Li H, Zhang Y, Ron D, Walter P. 2009. Divergent effects of PERK and IRE1 signaling on cell viability. *PLoS One* **4:** e4170. doi:101371/journalpone0004170.

Lin JP, Yang JS, Chang NW, Chiu TH, Su CC, Lu KW, Ho YT, Yeh CC, Yang MD, Lin HJ, et al. 2007b. GADD153 mediates berberine-induced apoptosis in human cervical cancer Ca ski cells. *Anticancer Res* **27:** 3379–3386.

Lindenmeyer MT, Rastaldi MP, Ikehata M, Neusser MA, Kretzler M, Cohen CD, Schlondorff D. 2008. Proteinuria and hyperglycemia induce endoplasmic reticulum stress. *J Am Soc Nephrol* **19:** 2225–2236.

Lindholm D, Wootz H, Korhonen L. 2006. ER stress and neurodegenerative diseases. *Cell Death Differ* **13:** 385–392.

Lipskaia L, Hulot JS, Lompre AM. 2009. Role of sarco/endoplasmic reticulum calcium content and calcium ATPase activity in the control of cell growth and proliferation. *Pflugers Arch* **457:** 673–685.

Liu LH, Boivin GP, Prasad V, Periasamy M, Shull GE. 2001. Squamous cell tumors in mice heterozygous for a null allele of Atp2a2, encoding the sarco(endo)plasmic reticulum Ca^{2+}-ATPase isoform 2 Ca^{2+} pump. *J Biol Chem* **276:** 26737–26740.

Liu G, Sun Y, Li Z, Song T, Wang H, Zhang Y, Ge Z. 2008. Apoptosis induced by endoplasmic reticulum stress involved in diabetic kidney disease. *Biochem Biophys Res Commun* **370:** 651–656.

Lloyd-Evans E, Pelled D, Riebeling C, Bodennec J, de-Morgan A, Waller H, Schiffmann R, Futerman AH. 2003. Glucosylceramide and glucosylsphingosine modulate calcium mobilization from brain microsomes via different mechanisms. *J Biol Chem* **278:** 23594–23599.

Lopez JJ, Jardin I, Bobe R, Pariente JA, Enouf J, Salido GM, Rosado JA. 2008. STIM1 regulates acidic Ca^{2+} store refilling by interaction with SERCA3 in human platelets. *Biochem Pharmacol* **75:** 2157–2164.

Lorenzon NM, Beam KG. 2008. Disease causing mutations of calcium channels. *Channels (Austin)* **2:** 163–179.

Lucero HA, Kaminer B. 1999. The role of calcium on the activity of ERcalcistorin/protein-disulfide isomerase and the significance of the C-terminal and its calcium binding. A comparison with mammalian protein-disulfide isomerase. *J Biol Chem* **274:** 3243–3251.

Luciani DS, Gwiazda KS, Yang TL, Kalynyak TB, Bychkivska Y, Frey MH, Jeffrey KD, Sampaio AV, Underhill TM, Johnson JD. 2009. Roles of IP_3R and RyR Ca^{2+} channels in endoplasmic reticulum stress and β-cell death. *Diabetes* **58:** 422–432.

Ma Y, Hendershot LM. 2004. ER chaperone functions during normal and stress conditions. *J Chem Neuroanat* **28:** 51–65.

Ma L, Zhu B, Chen X, Liu J, Guan Y, Ren J. 2008. Abnormalities of sarcoplasmic reticulum Ca^{2+} mobilization in aortic smooth muscle cells from streptozotocin-induced diabetic rats. *Clin Exp Pharmacol Physiol* **35:** 568–573.

Magyar JE, Gamberucci A, Konta L, Margittai E, Mandl J, Banhegyi G, Benedetti A, Csala M. 2009. Endoplasmic reticulum stress underlying the pro-apoptotic effect of epigallocatechin gallate in mouse hepatoma cells. *Int J Biochem Cell Biol* **41:** 694–700.

Mahabusarakam W, Iriyachitra P, Taylor WC. 1987. Chemical constituents of garcinia mangostana. *J Nat Prod* **50:** 474–478.

Mahn K, Hirst SJ, Ying S, Holt MR, Lavender P, Ojo OO, Siew L, Simcock DE, McVicker CG, Kanabar V, et al. 2009. Diminished sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA) expression contributes to airway remodelling in bronchial asthma. *Proc Natl Acad Sci* **106:** 10775–10780.

Malhotra JD, Kaufman RJ. 2007. The endoplasmic reticulum and the unfolded protein response. *Semin Cell Dev Biol* **18:** 716–731.

Manninen A, Saksela K. 2002. HIV-1 Nef interacts with inositol trisphosphate receptor to activate calcium signaling in T cells. *J Exp Med* **195:** 1023–1032.

Marciniak SJ, Yun CY, Oyadomari S, Novoa I, Zhang Y, Jungreis R, Nagata K, Harding HP, Ron D. 2004. CHOP induces death by promoting protein synthesis and oxidation in the stressed endoplasmic reticulum. *Genes Dev* **18:** 3066–3077.

Marx SO, Reiken S, Hisamatsu Y, Jayaraman T, Burkhoff D, Rosemblit N, Marks AR. 2000. PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell* **101:** 365–376.

Mattson MP. 2007. Calcium and neurodegeneration. *Aging Cell* **6:** 337–350.

Mayne M, Holden CP, Nath A, Geiger JD. 2000. Release of calcium from inositol 1,4,5-trisphosphate receptor-regulated stores by HIV-1 Tat regulates TNF-α production in human macrophages. *J Immunol* **164:** 6538–6542.

McCullough KD, Martindale JL, Klotz LO, Aw TY, Holbrook NJ. 2001. Gadd153 sensitizes cells to endoplasmic reticulum stress by down-regulating Bcl2 and perturbing the cellular redox state. *Mol Cell Biol* **21:** 1249–1259.

Michalak M, Robert Parker JM, Opas M. 2002. Ca^{2+} signaling and calcium binding chaperones of the endoplasmic reticulum. *Cell Calcium* **32:** 269–278.

Mikoshiba K. 2007. IP_3 receptor/Ca^{2+} channel: from discovery to new signaling concepts. *J Neurochem* **102:** 1426–1446.

Missiaen L, De Smedt H, Droogmans G, Casteels R. 1992. Ca^{2+} release induced by inositol 1,4,5-trisphosphate is a steady-state phenomenon controlled by luminal Ca^{2+} in permeabilized cells. *Nature* **357:** 599–602.

Missiaen L, Robberecht W, Van Den Bosch L, Callewaert G, Parys JB, Wuytack F, Raeymaekers L, Nilius B, Eggermont J, De Smedt H. 2000. Abnormal intracellular Ca^{2+} homeostasis and disease. *Cell Calcium* **28:** 1–21.

Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S, Depner M, von Berg A, Bufe A, Rietschel E, et al. 2007. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* **448:** 470–473.

Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, et al. 1998. Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet* **351:** 857–861.

Moncada S, Erusalimsky JD. 2002. Does nitric oxide modulate mitochondrial energy generation and apoptosis? *Nat Rev Mol Cell Biol* **3:** 214–220.

Monteith GR, McAndrew D, Faddy HM, Roberts-Thomson SJ. 2007. Calcium and cancer: targeting Ca^{2+} transport. *Nat Rev Cancer* **7:** 519–530.

Nagata E, Tanaka K, Gomi S, Mihara B, Shirai T, Nogawa S, Nozaki H, Mikoshiba K, Fukuuchi Y. 1994. Alteration of inositol 1,4,5-trisphosphate receptor after six-hour hemispheric ischemia in the gerbil brain. *Neuroscience* **61:** 983–990.

Nakano K, Isegawa Y, Zou P, Tadagaki K, Inagi R, Yamanishi K. 2003. Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded vMIP-I and vMIP-II induce signal transduction and chemotaxis in monocytic cells. *Arch Virol* **148:** 871–890.

Nakano T, Watanabe H, Ozeki M, Asai M, Katoh H, Satoh H, Hayashi H. 2006. Endoplasmic reticulum Ca^{2+} depletion induces endothelial cell apoptosis independently of caspase-12. *Cardiovasc Res* **69:** 908–915.

Nawrocki ST, Carew JS, Pino MS, Highshaw RA, Dunner K Jr, Huang P, Abbruzzese JL, McConkey DJ. 2005. Bortezomib sensitizes pancreatic cancer cells to endoplasmic reticulum stress-mediated apoptosis. *Cancer Res* **65:** 11658–11666.

Nelson TE, Nelson KE. 1990. Intra- and extraluminal sarcoplasmic reticulum membrane regulatory sites for Ca^{2+}-induced Ca^{2+} release. *FEBS Lett* **263:** 292–294.

Nicolau J, De Souza DN, Simoes A. 2009. Alteration of Ca^{2+}-ATPase activity in the homogenate, plasma membrane and microsomes of the salivary glands of streptozotocin-induced diabetic rats. *Cell Biochem Funct* **27:** 128–134.

Nieto-Miguel T, Fonteriz RI, Vay L, Gajate C, Lopez-Hernandez S, Mollinedo F. 2007. Endoplasmic reticulum stress in the proapoptotic action of edelfosine in solid tumor cells. *Cancer Res* **67:** 10368–10378.

Norman JP, Perry SW, Reynolds HM, Kiebala M, De Mesy Bentley KL, Trejo M, Volsky DJ, Maggirwar SB, Dewhurst S, Masliah E, et al. 2008. HIV-1 Tat activates neuronal

ryanodine receptors with rapid induction of the unfolded protein response and mitochondrial hyperpolarization. *PLoS One* **3:** e3731. doi:101371/journalpone0003731.

Oakes SA, Scorrano L, Opferman JT, Bassik MC, Nishino M, Pozzan T, Korsmeyer SJ. 2005. Proapoptotic BAX and BAK regulate the type 1 inositol trisphosphate receptor and calcium leak from the endoplasmic reticulum. *Proc Natl Acad Sci* **102:** 105–110.

Odermatt A, Taschner PE, Khanna VK, Busch HF, Karpati G, Jablecki CK, Breuning MH, MacLennan DH. 1996. Mutations in the gene-encoding SERCA1, the fast-twitch skeletal muscle sarcoplasmic reticulum Ca^{2+} ATPase, are associated with Brody disease. *Nat Genet* **14:** 191–194.

Ogata M, Hino S, Saito A, Morikawa K, Kondo S, Kanemoto S, Murakami T, Taniguchi M, Tanii I, Yoshinaga K, et al. 2006. Autophagy is activated for cell survival after endoplasmic reticulum stress. *Mol Cell Biol* **26:** 9220–9231.

O'Neil BJ, McKeown TR, DeGracia DJ, Alousi SS, Rafols JA, White BC. 1999. Cell death, calcium mobilization, and immunostaining for phosphorylated eukaryotic initiation factor 2-α (eIF2α) in neuronally differentiated NB-104 cells: arachidonate and radical-mediated injury mechanisms. *Resuscitation* **41:** 71–83.

Ong DS, Mu TW, Palmer AE, Kelly JW. 2010. Endoplasmic reticulum Ca^{2+} increases enhance mutant glucocerebrosidase proteostasis. *Nat Chem Biol* **6:** 424–432.

Onozuka T, Sawamura D, Goto M, Yokota K, Shimizu H. 2006. Possible role of endoplasmic reticulum stress in the pathogenesis of Darier's disease. *J Dermatol Sci* **41:** 217–220.

O'Rourke B, Kass DA, Tomaselli GF, Kaab S, Tunin R, Marban E. 1999. Mechanisms of altered excitation-contraction coupling in canine tachycardia-induced heart failure, I: experimental studies. *Circ Res* **84:** 562–570.

Osman AA, Saito M, Makepeace C, Permutt MA, Schlesinger P, Mueckler M. 2003. Wolframin expression induces novel ion channel activity in endoplasmic reticulum membranes and increases intracellular calcium. *J Biol Chem* **278:** 52755–52762.

Oyadomari S, Mori M. 2004. Roles of CHOP/GADD153 in endoplasmic reticulum stress. *Cell Death Differ* **11:** 381–389.

Oyadomari S, Takeda K, Takiguchi M, Gotoh T, Matsumoto M, Wada I, Akira S, Araki E, Mori M. 2001. Nitric oxide-induced apoptosis in pancreatic β cells is mediated by the endoplasmic reticulum stress pathway. *Proc Natl Acad Sci* **98:** 10845–10850.

Ozcan U, Cao Q, Yilmaz E, Lee AH, Iwakoshi NN, Ozdelen E, Tuncman G, Gorgun C, Glimcher LH, Hotamisligil GS. 2004. Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. *Science* **306:** 457–461.

Pacifico F, Ulianich L, De Micheli S, Treglia S, Leonardi A, Vito P, Formisano S, Consiglio E, Di Jeso B. 2003. The expression of the sarco/endoplasmic reticulum Ca^{2+}-ATPases in thyroid and its down-regulation following neoplastic transformation. *J Mol Endocrinol* **30:** 399–409.

Papp S, Dziak E, Michalak M, Opas M. 2003. Is all of the endoplasmic reticulum created equal? The effects of the heterogeneous distribution of endoplasmic reticulum Ca^{2+}-handling proteins. *J Cell Biol* **160:** 475–479.

Park KS, Poburko D, Wollheim CB, Demaurex N. 2009. Amiloride derivatives induce apoptosis by depleting ER Ca^{2+} stores in vascular endothelial cells. *Br J Pharmacol* **156:** 1296–1304.

Parsons JT, Churn SB, DeLorenzo RJ. 1999. Global ischemia-induced inhibition of the coupling ratio of calcium uptake and ATP hydrolysis by rat whole brain microsomal Mg^{2+}/Ca^{2+} ATPase. *Brain Res* **834:** 32–41.

Paschen W, Mengesdorf T. 2005. Endoplasmic reticulum stress response and neurodegeneration. *Cell Calcium* **38:** 409–415.

Pattacini L, Mancini M, Mazzacurati L, Brusa G, Benvenuti M, Martinelli G, Baccarani M, Santucci MA. 2004. Endoplasmic reticulum stress initiates apoptotic death induced by STI571 inhibition of p210 bcr-abl tyrosine kinase. *Leuk Res* **28:** 191–202.

Pattni K, Millard TH, Banting G. 2003. Calpain cleavage of the B isoform of Ins(1,4,5)P_3 3-kinase separates the catalytic domain from the membrane anchoring domain. *Biochem J* **375:** 643–651.

Pelled D, Lloyd-Evans E, Riebeling C, Jeyakumar M, Platt FM, Futerman AH. 2003. Inhibition of calcium uptake via the sarco/endoplasmic reticulum Ca^{2+}-ATPase in a mouse model of Sandhoff disease and prevention by treatment with N-butyldeoxynojirimycin. *J Biol Chem* **278:** 29496–29501.

Pelled D, Trajkovic-Bodennec S, Lloyd-Evans E, Sidransky E, Schiffmann R, Futerman AH. 2005. Enhanced calcium release in the acute neuronopathic form of Gaucher disease. *Neurobiol Dis* **18:** 83–88.

Pereira L, Matthes J, Schuster I, Valdivia HH, Herzig S, Richard S, Gomez AM. 2006. Mechanisms of $[Ca^{2+}]_i$ transient decrease in cardiomyopathy of db/db type 2 diabetic mice. *Diabetes* **55:** 608–615.

Petersen OH, Tepikin A, Park MK. 2001. The endoplasmic reticulum: one continuous or several separate Ca^{2+} stores? *Trends Neurosci* **24:** 271–276.

Pirot P, Cardozo AK, Eizirik DL. 2008. Mediators and mechanisms of pancreatic β-cell death in type 1 diabetes. *Arq Bras Endocrinol Metabol* **52:** 156–165.

Pozzan T, Rizzuto R, Volpe P, Meldolesi J. 1994. Molecular and cellular physiology of intracellular calcium stores. *Physiol Rev* **74:** 595–636.

Prusiner SB. 1998. Prions. *Proc Natl Acad Sci* **95:** 13363–13383.

Putcha GV, Le S, Frank S, Besirli CG, Clark K, Chu B, Alix S, Youle RJ, LaMarche A, Maroney AC, et al. 2003. JNK-mediated BIM phosphorylation potentiates BAX-dependent apoptosis. *Neuron* **38:** 899–914.

Puthalakath H, O'Reilly LA, Gunn P, Lee L, Kelly PN, Huntington ND, Hughes PD, Michalak EM, McKimm-Breschkin J, Motoyama N, et al. 2007. ER stress triggers apoptosis by activating BH3-only protein Bim. *Cell* **129:** 1337–1349.

Putney JW Jr. 1986. A model for receptor-regulated calcium entry. *Cell Calcium* **7:** 1–12.

Pyrko P, Kardosh A, Liu YT, Soriano N, Xiong W, Chow RH, Uddin J, Petasis NA, Mircheff AK, Farley RA, et al. 2007. Calcium-activated endoplasmic reticulum stress as a major component of tumor cell death induced by

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2,5-dimethyl-celecoxib, a non-coxib analogue of celecoxib. *Mol Cancer Ther* **6:** 1262–1275.

Qi MY, Liu HR, Dai DZ, Li N, Dai Y. 2008. Total triterpene acids, active ingredients from Fructus Corni, attenuate diabetic cardiomyopathy by normalizing ET pathway and expression of FKBP12.6 and SERCA2a in streptozotocin-rats. *J Pharm Pharmacol* **60:** 1687–1694.

Rahmani M, Davis EM, Crabtree TR, Habibi JR, Nguyen TK, Dent P, Grant S. 2007. The kinase inhibitor sorafenib induces cell death through a process involving induction of endoplasmic reticulum stress. *Mol Cell Biol* **27:** 5499–5513.

Randriamboavonjy V, Pistrosch F, Bolck B, Schwinger RH, Dixit M, Badenhoop K, Cohen RA, Busse R, Fleming I. 2008. Platelet sarcoplasmic endoplasmic reticulum Ca^{2+}-ATPase and mu-calpain activity are altered in type 2 diabetes mellitus and restored by rosiglitazone. *Circulation* **117:** 52–60.

Rao RV, Bredesen DE. 2004. Misfolded proteins, endoplasmic reticulum stress and neurodegeneration. *Curr Opin Cell Biol* **16:** 653–662.

Rardon DP, Cefali DC, Mitchell RD, Seiler SM, Hathaway DR, Jones LR. 1990. Digestion of cardiac and skeletal muscle junctional sarcoplasmic reticulum vesicles with calpain II. Effects on the Ca^{2+} release channel. *Circ Res* **67:** 84–96.

Reiken S, Gaburjakova M, Gaburjakova J, He KL, Prieto A, Becker E, Yi GH, Wang J, Burkhoff D, Marks AR. 2001. ß-adrenergic receptor blockers restore cardiac calcium release channel (ryanodine receptor) structure and function in heart failure. *Circulation* **104:** 2843–2848.

Reiken S, Lacampagne A, Zhou H, Kherani A, Lehnart SE, Ward C, Huang F, Gaburjakova M, Gaburjakova J, Rosemblit N, et al. 2003. PKA phosphorylation activates the calcium release channel (ryanodine receptor) in skeletal muscle: defective regulation in heart failure. *J Cell Biol* **160:** 919–928.

Ren J, Gintant GA, Miller RE, Davidoff AJ. 1997. High extracellular glucose impairs cardiac E-C coupling in a glycosylation-dependent manner. *Am J Physiol* **273:** H2876–H2883.

Rengifo J, Gibson CJ, Winkler E, Collin T, Ehrlich BE. 2007. Regulation of the inositol 1,4,5-trisphosphate receptor type I by O-GlcNAc glycosylation. *J Neurosci* **27:** 13813–13821.

Reuter H, Gronke S, Adam C, Ribati M, Brabender J, Zobel C, Frank KF, Wippermann J, Schwinger RH, Brixius K, et al. 2008. Sarcoplasmic Ca^{2+} release is prolonged in nonfailing myocardium of diabetic patients. *Mol Cell Biochem* **308:** 141–149.

Rigaud M, Gemes G, Weyker PD, Cruikshank JM, Kawano T, Wu HE, Hogan QH. 2009. Axotomy depletes intracellular calcium stores in primary sensory neurons. *Anesthesiology* **111:** 381–392.

Rizzuto R, Marchi S, Bonora M, Aguiari P, Bononi A, De Stefani D, Giorgi C, Leo S, Rimessi A, Siviero R, et al. 2009. Ca^{2+} transfer from the ER to mitochondria: when, how and why. *Biochim Biophys Acta* **1787:** 1342–1351.

Roach JC, Deutsch K, Li S, Siegel AF, Bekris LM, Einhaus DC, Sheridan CM, Glusman G, Hood L, Lernmark A, et al. 2006. Genetic mapping at 3-kilobase resolution reveals inositol 1,4,5-triphosphate receptor 3 as a risk factor for type 1 diabetes in Sweden. *Am J Hum Genet* **79:** 614–627.

Robinson LC, Marchant JS. 2008. Enhanced Ca^{2+} leak from ER Ca^{2+} stores induced by hepatitis C NS5A protein. *Biochem Biophys Res Commun* **368:** 593–599.

Roe MW, Philipson LH, Frangakis CJ, Kuznetsov A, Mertz RJ, Lancaster ME, Spencer B, Worley JF III, Dukes ID. 1994. Defective glucose-dependent endoplasmic reticulum Ca^{2+} sequestration in diabetic mouse islets of Langerhans. *J Biol Chem* **269:** 18279–18282.

Ron D, Walter P. 2007. Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Rev Mol Cell Biol* **8:** 519–529.

Rong Y, Distelhorst CW. 2008. Bcl-2 protein family members: versatile regulators of calcium signaling in cell survival and apoptosis. *Annu Rev Physiol* **70:** 73–91.

Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. 1972. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* **30:** 595–602.

Ryu EJ, Harding HP, Angelastro JM, Vitolo OV, Ron D, Greene LA. 2002. Endoplasmic reticulum stress and the unfolded protein response in cellular models of Parkinson's disease. *J Neurosci* **22:** 10690–10698.

Saavedra FR, Redondo PC, Hernandez-Cruz JM, Salido GM, Pariente JA, Rosado JA. 2004. Store-operated Ca^{2+} entry and tyrosine kinase $pp60^{src}$ hyperactivity are modulated by hyperglycemia in platelets from patients with non insulin-dependent diabetes mellitus. *Arch Biochem Biophys* **432:** 261–268.

Sacchetto R, Testoni S, Gentile A, Damiani E, Rossi M, Liguori R, Drogemuller C, Mascarello F. 2009. A defective SERCA1 protein is responsible for congenital pseudomyotonia in Chianina cattle. *Am J Pathol* **174:** 565–573.

Sakakura C, Hagiwara A, Fukuda K, Shimomura K, Takagi T, Kin S, Nakase Y, Fujiyama J, Mikoshiba K, Okazaki Y, et al. 2003. Possible involvement of inositol 1,4,5-trisphosphate receptor type 3 (IP_3R3) in the peritoneal dissemination of gastric cancers. *Anticancer Res* **23:** 3691–3697.

Sakata S, Lebeche D, Sakata Y, Sakata N, Chemaly ER, Liang L, Nakajima-Takenaka C, Tsuji T, Konishi N, del Monte F, et al. 2007. Transcoronary gene transfer of SERCA2a increases coronary blood flow and decreases cardiomyocyte size in a type 2 diabetic rat model. *Am J Physiol* **292:** H1204–H1207.

Sakuntabhai A, Ruiz-Perez V, Carter S, Jacobsen N, Burge S, Monk S, Smith M, Munro CS, O'Donovan M, Craddock N, et al. 1999. Mutations in ATP2A2, encoding a Ca^{2+} pump, cause Darier disease. *Nat Genet* **21:** 271–277.

Sambrook JF. 1990. The involvement of calcium in transport of secretory proteins from the endoplasmic reticulum. *Cell* **61:** 197–199.

Sammels E, Parys JB, Missiaen L, De Smedt H, Bultynck G. 2010. Intracellular Ca^{2+} storage in health and disease: a dynamic equilibrium. *Cell Calcium* **47:** 297–314.

Sano R, Annunziata I, Patterson A, Moshiach S, Gomero E, Opferman J, Forte M, d'Azzo A. 2009. G_{M1}-ganglioside accumulation at the mitochondria-associated ER membranes links ER stress to Ca^{2+}-dependent mitochondrial apoptosis. *Mol Cell* **36:** 500–511.

Sathish V, Thompson MA, Bailey JP, Pabelick CM, Prakash YS, Sieck GC. 2009. Effect of proinflammatory cytokines on regulation of sarcoplasmic reticulum Ca^{2+} reuptake in human airway smooth muscle. *Am J Physiol* **297:** L26–L34.

Sato A, Fujiwara H, Oku H, Ishiguro K, Ohizumi Y. 2004. α-mangostin induces Ca^{2+}-ATPase-dependent apoptosis via mitochondrial pathway in PC12 cells. *J Pharmacol Sci* **95:** 33–40.

Savino JA III, Evans JF, Rabinowitz D, Auborn KJ, Carter TH. 2006. Multiple, disparate roles for calcium signaling in apoptosis of human prostate and cervical cancer cells exposed to diindolylmethane. *Mol Cancer Ther* **5:** 556–563.

Schindl R, Muik M, Fahrner M, Derler I, Fritsch R, Bergsmann J, Romanin C. 2009. Recent progress on STIM1 domains controlling Orai activation. *Cell Calcium* **46:** 227–232.

Schmidt AG, Haghighi K, Frank B, Pater L, Dorn GW, Walsh RA, Kranias EG. 2003a. Polymorphic SERCA2a variants do not account for inter-individual differences in phospholamban-SERCA2a interactions in human heart failure. *J Mol Cell Cardiol* **35:** 867–870.

Schmidt T, Zaib F, Samson SE, Kwan CY, Grover AK. 2003b. Peroxynitrite resistance of sarco/endoplasmic reticulum Ca^{2+} pump in pig coronary artery endothelium and smooth muscle. *Cell Calcium* **36:** 77–82.

Schmitt JP, Kamisago M, Asahi M, Li GH, Ahmad F, Mende U, Kranias EG, MacLennan DH, Seidman JG, Seidman CE. 2003. Dilated cardiomyopathy and heart failure caused by a mutation in phospholamban. *Science* **299:** 1410–1413.

Schroder M, Kaufman RJ. 2005. The mammalian unfolded protein response. *Annu Rev Biochem* **74:** 739–789.

Scorrano L, Oakes SA, Opferman JT, Cheng EH, Sorcinelli MD, Pozzan T, Korsmeyer SJ. 2003. BAX and BAK regulation of endoplasmic reticulum Ca^{2+}: a control point for apoptosis. *Science* **300:** 135–139.

Searls YM, Loganathan R, Smirnova IV, Stehno-Bittel L. 2010. Intracellular Ca^{2+} regulating proteins in vascular smooth muscle cells are altered with type 1 diabetes due to the direct effects of hyperglycemia. *Cardiovasc Diabetol* **9:** 8. 2010. doi: 101186/1475-2840-9-8.

Seidler T, Hasenfuss G, Maier LS. 2007. Targeting altered calcium physiology in the heart: translational approaches to excitation, contraction, and transcription. *Physiology* **22:** 328–334.

Seo NS, Zeng CQ, Hyser JM, Utama B, Crawford SE, Kim KJ, Hook M, Estes MK. 2008. Inaugural article: integrins α1β1 and α2β1 are receptors for the rotavirus enterotoxin. *Proc Natl Acad Sci* **105:** 8811–8818.

Shah RD, Gonzales F, Golez E, Augustin D, Caudillo S, Abbott A, Morello J, McDonough PM, Paolini PJ, Shubeita HE. 2005. The antidiabetic agent rosiglitazone upregulates SERCA2 and enhances TNF-α- and LPS-induced NF-kB-dependent transcription and TNF-α-induced IL-6 secretion in ventricular myocytes. *Cell Physiol Biochem* **15:** 41–50.

Shao CH, Rozanski GJ, Patel KP, Bidasee KR. 2007. Dyssynchronous (non-uniform) Ca^{2+} release in myocytes from streptozotocin-induced diabetic rats. *J Mol Cell Cardiol* **42:** 234–246.

Shao CH, Wehrens XH, Wyatt TA, Parbhu S, Rozanski GJ, Patel KP, Bidasee KR. 2009. Exercise training during diabetes attenuates cardiac ryanodine receptor dysregulation. *J Appl Physiol* **106:** 1280–1292.

Sharma K, Wang L, Zhu Y, DeGuzman A, Cao GY, Lynn RB, Joseph SK. 1999. Renal type I inositol 1,4,5-trisphosphate receptor is reduced in streptozotocin-induced diabetic rats and mice. *Am J Physiol* **276:** F54–F61.

Sharon-Friling R, Goodhouse J, Colberg-Poley AM, Shenk T. 2006. Human cytomegalovirus pUL37x1 induces the release of endoplasmic reticulum calcium stores. *Proc Natl Acad Sci* **103:** 19117–19122.

Shen J, Yu WM, Brotto M, Scherman JA, Guo C, Stoddard C, Nosek TM, Valdivia HH, Qu CK. 2009. Deficiency of MIP/MTMR14 phosphatase induces a muscle disorder by disrupting Ca^{2+} homeostasis. *Nat Cell Biol* **11:** 769–776.

Stathopulos PB, Zheng L, Li GY, Plevin MJ, Ikura M. 2008. Structural and mechanistic insights into STIM1-mediated initiation of store-operated calcium entry. *Cell* **135:** 110–122.

Stockwin LH, Han B, Yu SX, Hollingshead MG, ElSohly MA, Gul W, Slade D, Galal AM, Newton DL. 2009. Artemisinin dimer anticancer activity correlates with heme-catalyzed reactive oxygen species generation and endoplasmic reticulum stress induction. *Int J Cancer* **125:** 1266–1275.

Stolen TO, Hoydal MA, Kemi OJ, Catalucci D, Ceci M, Aasum E, Larsen T, Rolim N, Condorelli G, Smith GL, et al. 2009. Interval training normalizes cardiomyocyte function, diastolic Ca^{2+} control, and SR Ca^{2+} release synchronicity in a mouse model of diabetic cardiomyopathy. *Circ Res* **105:** 527–536.

Strom TM, Hortnagel K, Hofmann S, Gekeler F, Scharfe C, Rabl W, Gerbitz KD, Meitinger T. 1998. Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolframin) coding for a predicted transmembrane protein. *Hum Mol Genet* **7:** 2021–2028.

Suarez J, Scott B, Dillmann WH. 2008. Conditional increase in SERCA2a protein is able to reverse contractile dysfunction and abnormal calcium flux in established diabetic cardiomyopathy. *Am J Physiol* **295:** R1439–R1445.

Sulaiman M, Matta MJ, Sunderesan NR, Gupta MP, Periasamy M, Gupta M. 2010. Resveratrol, an activator of SIRT1, upregulates sarcoplasmic calcium ATPase and improves cardiac function in diabetic cardiomyopathy. *Am J Physiol* **298:** H833–H843.

Supnet C, Bezprozvanny I. 2010. The dysregulation of intracellular calcium in Alzheimer disease. *Cell Calcium* **47:** 183–189.

Szegezdi E, Fitzgerald U, Samali A. 2003. Caspase-12 and ER-stress-mediated apoptosis: the story so far. *Ann N Y Acad Sci* **1010:** 186–194.

Taiyab A, Sreedhar AS, Rao ChM. 2009. Hsp90 inhibitors, GA and 17AAG, lead to ER stress-induced apoptosis in rat histiocytoma. *Biochem Pharmacol* **78:** 142–152.

Takei D, Ishihara H, Yamaguchi S, Yamada T, Tamura A, Katagiri H, Maruyama Y, Oka Y. 2006. WFS1 protein modulates the free Ca^{2+} concentration in the endoplasmic reticulum. *FEBS Lett* **580:** 5635–5640.

Takenaka H, Adler PN, Katz AM. 1982. Calcium fluxes across the membrane of sarcoplasmic reticulum vesicles. *J Biol Chem* **257:** 12649–12656.

Teshima Y, Takahashi N, Saikawa T, Hara M, Yasunaga S, Hidaka S, Sakata T. 2000. Diminished expression of sarcoplasmic reticulum Ca^{2+}-ATPase and ryanodine sensitive Ca^{2+} channel mRNA in streptozotocin-induced diabetic rat heart. *J Mol Cell Cardiol* **32:** 655–664.

Tessitore A, del P Martin M, Sano R, Ma Y, Mann L, Ingrassia A, Laywell ED, Steindler DA, Hendershot LM, d'Azzo A. 2004. G_{M1}-ganglioside-mediated activation of the unfolded protein response causes neuronal death in a neurodegenerative gangliosidosis. *Mol Cell* **15:** 753–766.

Thompson S, Chen X, Hui L, Toschi A, Foster DA, Drain CM. 2008. Low concentrations of a non-hydrolysable tetra-S-glycosylated porphyrin and low light induces apoptosis in human breast cancer cells via stress of the endoplasmic reticulum. *Photochem Photobiol Sci* **7:** 1415–1421.

Tian P, Estes MK, Hu Y, Ball JM, Zeng CQ, Schilling WP. 1995. The rotavirus nonstructural glycoprotein NSP4 mobilizes Ca^{2+} from the endoplasmic reticulum. *J Virol* **69:** 5763–5772.

Tong X, Evangelista A, Cohen RA. 2009. Targeting the redox regulation of SERCA in vascular physiology and disease. *Curr Opin Pharmacol* **10:** 1–6.

Tong X, Ying J, Pimentel DR, Trucillo M, Adachi T, Cohen RA. 2008. High glucose oxidizes SERCA cysteine-674 and prevents inhibition by nitric oxide of smooth muscle cell migration. *J Mol Cell Cardiol* **44:** 361–369.

Tonnesen MF, Grunnet LG, Friberg J, Cardozo AK, Billestrup N, Eizirik DL, Storling J, Mandrup-Poulsen T. 2009. Inhibition of Nuclear Factor-kB or Bax prevents endoplasmic reticulum stress- but not nitric oxide-mediated apoptosis in INS-1E cells. *Endocrinology* **150:** 4094–4103.

Tosch V, Rohde HM, Tronchere H, Zanoteli E, Monroy N, Kretz C, Dondaine N, Payrastre B, Mandel JL, Laporte J. 2006. A novel PtdIns3P and PtdIns(3,5)P_2 phosphatase with an inactivating variant in centronuclear myopathy. *Hum Mol Genet* **15:** 3098–3106.

Trost SU, Belke DD, Bluhm WF, Meyer M, Swanson E, Dillmann WH. 2002. Overexpression of the sarcoplasmic reticulum Ca^{2+}-ATPase improves myocardial contractility in diabetic cardiomyopathy. *Diabetes* **51:** 1166–1171.

Tsuchiya S, Tsuji M, Morio Y, Oguchi K. 2006. Involvement of endoplasmic reticulum in glycochenodeoxycholic acid-induced apoptosis in rat hepatocytes. *Toxicol Lett* **166:** 140–149.

Tu H, Nelson O, Bezprozvanny A, Wang Z, Lee SF, Hao YH, Serneels L, De Strooper B, Yu G, Bezprozvanny I. 2006. Presenilins form ER Ca^{2+} leak channels, a function disrupted by familial Alzheimer's disease-linked mutations. *Cell* **126:** 981–993.

Van Baelen K, Dode L, Vanoevelen J, Callewaert G, De Smedt H, Missiaen L, Parys JB, Raeymaekers L, Wuytack F. 2004. The Ca^{2+}/Mn^{2+} pumps in the Golgi apparatus. *Biochim Biophys Acta* **1742:** 103–112.

Vanderheyden V, Devogelaere B, Missiaen L, De Smedt H, Bultynck G, Parys JB. 2009. Regulation of inositol 1,4,5-trisphosphate-induced Ca^{2+} release by reversible phosphorylation and dephosphorylation. *Biochim Biophys Acta* **1793:** 959–970.

van der Kallen CJ, van Greevenbroek MM, Stehouwer CD, Schalkwijk CG. 2009. Endoplasmic reticulum stress-induced apoptosis in the development of diabetes: is there a role for adipose tissue and liver? *Apoptosis* **14:** 1424–1434.

Vangheluwe P, Sepulveda MR, Missiaen L, Raeymaekers L, Wuytack F, Vanoevelen J. 2009. Intracellular Ca^{2+}- and Mn^{2+}-transport ATPases. *Chem Rev* **109:** 4733–4759.

van Kuppeveld FJ, de Jong AS, Melchers WJ, Willems PH. 2005. Enterovirus protein 2B po(u)res out the calcium: a viral strategy to survive? *Trends Microbiol* **13:** 41–44.

Vanoverberghe K, Vanden Abeele F, Mariot P, Lepage G, Roudbaraki M, Bonnal JL, Mauroy B, Shuba Y, Skryma R, Prevarskaya N. 2004. Ca^{2+} homeostasis and apoptotic resistance of neuroendocrine-differentiated prostate cancer cells. *Cell Death Differ* **11:** 321–330.

Varadi A, Lebel L, Hashim Y, Mehta Z, Ashcroft SJ, Turner R. 1999. Sequence variants of the sarco(endo)plasmic reticulum Ca^{2+}-transport ATPase 3 gene (SERCA3) in Caucasian type II diabetic patients (UK Prospective Diabetes Study 48). *Diabetologia* **42:** 1240–1243.

Vasanji Z, Cantor EJ, Juric D, Moyen M, Netticadan T. 2006. Alterations in cardiac contractile performance and sarcoplasmic reticulum function in sucrose-fed rats is associated with insulin resistance. *Am J Physiol* **291:** C772–C780.

Vasanji Z, Dhalla NS, Netticadan T. 2004. Increased inhibition of SERCA2 by phospholamban in the type I diabetic heart. *Mol Cell Biochem* **261:** 245–249.

Vericel E, Januel C, Carreras M, Moulin P, Lagarde M. 2004. Diabetic patients without vascular complications display enhanced basal platelet activation and decreased antioxidant status. *Diabetes* **53:** 1046–1051.

Verkhratsky A. 2005. Physiology and pathophysiology of the calcium store in the endoplasmic reticulum of neurons. *Physiol Rev* **85:** 201–279.

Verkhratsky A, Fernyhough P. 2008. Mitochondrial malfunction and Ca^{2+} dyshomeostasis drive neuronal pathology in diabetes. *Cell Calcium* **44:** 112–122.

Vermassen E, Parys JB, Mauger JP. 2004. Subcellular distribution of the inositol 1,4,5-trisphosphate receptors: functional relevance and molecular determinants. *Biol Cell* **96:** 3–17.

Vetter R, Rehfeld U, Reissfelder C, Weiss W, Wagner KD, Gunther J, Hammes A, Tschope C, Dillmann W, Paul M. 2002. Transgenic overexpression of the sarcoplasmic reticulum Ca^{2+}ATPase improves reticular Ca^{2+} handling in normal and diabetic rat hearts. *FASEB J* **16:** 1657–1659.

Viner RI, Ferrington DA, Williams TD, Bigelow DJ, Schoneich C. 1999. Protein modification during biological aging: selective tyrosine nitration of the SERCA2a isoform of the sarcoplasmic reticulum Ca^{2+}-ATPase in skeletal muscle. *Biochem J* **340:** 657–669.

Wang XZ, Ron D. 1996. Stress-induced phosphorylation and activation of the transcription factor CHOP (GADD153) by p38 MAP Kinase. *Science* **272:** 1347–1349.

Wang HG, Pathan N, Ethell IM, Krajewski S, Yamaguchi Y, Shibasaki F, McKeon F, Bobo T, Franke TF, Reed JC. 1999. Ca^{2+}-induced apoptosis through calcineurin dephosphorylation of BAD. *Science* **284:** 339–343.

Wang M, Zhang WB, Zhu JH, Fu GS, Zhou BQ. 2010. Breviscapine ameliorates cardiac dysfunction and regulates the myocardial Ca^{2+}-cycling proteins in streptozotocin-induced diabetic rats. *Acta Diabetol* doi:101007/s00592-009-0164-x.

Wehrens XH, Lehnart SE, Huang F, Vest JA, Reiken SR, Mohler PJ, Sun J, Guatimosim S, Song LS, Rosemblit N, et al. 2003. FKBP12.6 deficiency and defective calcium release channel (ryanodine receptor) function linked to exercise-induced sudden cardiac death. *Cell* **113:** 829–840.

Wehrens XH, Lehnart SE, Marks AR. 2005a. Intracellular calcium release and cardiac disease. *Annu Rev Physiol* **67:** 69–98.

Wehrens XH, Lehnart SE, Reiken S, van der Nagel R, Morales R, Sun J, Cheng Z, Deng SX, de Windt LJ, Landry DW, et al. 2005b. Enhancing calstabin binding to ryanodine receptors improves cardiac and skeletal muscle function in heart failure. *Proc Natl Acad Sci* **102:** 9607–9612.

Wehrens XH, Lehnart SE, Reiken S, Vest JA, Wronska A, Marks AR. 2006. Ryanodine receptor/calcium release channel PKA phosphorylation: a critical mediator of heart failure progression. *Proc Natl Acad Sci* **103:** 511–518.

Wei H, Perry DC. 1996. Dantrolene is cytoprotective in two models of neuronal cell death. *J Neurochem* **67:** 2390–2398.

Wei H, Kim SJ, Zhang Z, Tsai PC, Wisniewski KE, Mukherjee AB. 2008a. ER and oxidative stresses are common mediators of apoptosis in both neurodegenerative and non-neurodegenerative lysosomal storage disorders and are alleviated by chemical chaperones. *Hum Mol Genet* **17:** 469–477.

Wei H, Liang G, Yang H, Wang Q, Hawkins B, Madesh M, Wang S, Eckenhoff RG. 2008b. The common inhalational anesthetic isoflurane induces apoptosis via activation of inositol 1,4,5-trisphosphate receptors. *Anesthesiology* **108:** 251–260.

Wei Y, Wang D, Gentile CL, Pagliassotti MJ. 2009. Reduced endoplasmic reticulum luminal calcium links saturated fatty acid-mediated endoplasmic reticulum stress and cell death in liver cells. *Mol Cell Biochem* **331:** 31–40.

White C, Li C, Yang J, Petrenko NB, Madesh M, Thompson CB, Foskett JK. 2005. The endoplasmic reticulum gateway to apoptosis by Bcl-X_L modulation of the $InsP_3R$. *Nat Cell Biol* **7:** 1021–1028.

Williams BL, Lipkin WI. 2006. Endoplasmic reticulum stress and neurodegeneration in rats neonatally infected with borna disease virus. *J Virol* **80:** 8613–8626.

Wold LE, Dutta K, Mason MM, Ren J, Cala SE, Schwanke ML, Davidoff AJ. 2005. Impaired SERCA function contributes to cardiomyocyte dysfunction in insulin resistant rats. *J Mol Cell Cardiol* **39:** 297–307.

Wu X, Sun L, Zha W, Studer E, Gurley E, Chen L, Wang X, Hylemon PB, Pandak WM Jr, Sanyal AJ, et al. 2010. HIV protease inhibitors induce ER stress and disrupt barrier integrity in intestinal epithelial cells. *Gastroenterology* **138:** 197–209.

Xiong ZG, Chu XP, Simon RP. 2007. Acid sensing ion channels–novel therapeutic targets for ischemic brain injury. *Front Biosci* **12:** 1376–1386.

Xu C, Bailly-Maitre B, Reed JC. 2005. Endoplasmic reticulum stress: cell life and death decisions. *J Clin Invest* **115:** 2656–2664.

Xu L, Eu JP, Meissner G, Stamler JS. 1998. Activation of the cardiac calcium release channel (ryanodine receptor) by poly-S-nitrosylation. *Science* **279:** 234–237.

Yamada T, Ishihara H, Tamura A, Takahashi R, Yamaguchi S, Takei D, Tokita A, Satake C, Tashiro F, Katagiri H, et al. 2006. WFS1-deficiency increases endoplasmic reticulum stress, impairs cell cycle progression and triggers the apoptotic pathway specifically in pancreatic β-cells. *Hum Mol Genet* **15:** 1600–1609.

Yamamoto K, Ichijo H, Korsmeyer SJ. 1999. BCL-2 is phosphorylated and inactivated by an ASK1/Jun N-terminal protein kinase pathway normally activated at G_2/M. *Mol Cell Biol* **19:** 8469–8478.

Yang H, Liang G, Hawkins BJ, Madesh M, Pierwola A, Wei H. 2008. Inhalational anesthetics induce cell damage by disruption of intracellular calcium homeostasis with different potencies. *Anesthesiology* **109:** 243–250.

Yano M, Kobayashi S, Kohno M, Doi M, Tokuhisa T, Okuda S, Suetsugu M, Hisaoka T, Obayashi M, Ohkusa T, et al. 2003. FKBP12.6-mediated stabilization of calcium-release channel (ryanodine receptor) as a novel therapeutic strategy against heart failure. *Circulation* **107:** 477–484.

Yano M, Yamamoto T, Kobayashi S, Ikeda Y, Matsuzaki M. 2008. Defective Ca^{2+} cycling as a key pathogenic mechanism of heart failure. *Circ J* **72:** A22–A30.

Yaras N, Ugur M, Ozdemir S, Gurdal H, Purali N, Lacampagne A, Vassort G, Turan B. 2005. Effects of diabetes on ryanodine receptor Ca release channel (RyR2) and Ca^{2+} homeostasis in rat heart. *Diabetes* **54:** 3082–3088.

Ying J, Sharov V, Xu S, Jiang B, Gerrity R, Schoneich C, Cohen RA. 2008. Cysteine-674 oxidation and degradation of sarcoplasmic reticulum Ca^{2+} ATPase in diabetic pig aorta. *Free Radic Biol Med* **45:** 756–762.

Yoneda T, Imaizumi K, Oono K, Yui D, Gomi F, Katayama T, Tohyama M. 2001. Activation of caspase-12, an endoplastic reticulum (ER) resident caspase, through tumor necrosis factor receptor-associated factor 2-dependent mechanism in response to the ER stress. *J Biol Chem* **276:** 13935–13940.

Yoshida H, Matsui T, Hosokawa N, Kaufman RJ, Nagata K, Mori K. 2003. A time-dependent phase shift in the mammalian unfolded protein response. *Dev Cell* **4:** 265–271.

Yoshida H, Matsui T, Yamamoto A, Okada T, Mori K. 2001. XBP1 mRNA is induced by ATF6 and spliced by IRE1 in response to ER stress to produce a highly active transcription factor. *Cell* **107:** 881–891.

Yoshida I, Monji A, Tashiro K, Nakamura K, Inoue R, Kanba S. 2006. Depletion of intracellular Ca^{2+} store itself may be a major factor in thapsigargin-induced ER stress and apoptosis in PC12 cells. *Neurochem Int* **48:** 696–702.

Zalk R, Lehnart SE, Marks AR. 2007. Modulation of the ryanodine receptor and intracellular calcium. *Annu Rev Biochem* **76:** 367–385.

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Zbidi H, Redondo PC, Lopez JJ, Bartegi A, Salido GM, Rosado JA. 2010. Homocysteine induces caspase activation by endoplasmic reticulum stress in platelets from type 2 diabetics and healthy donors. *Thromb Haemost* **103:** 1022–1032.

Zhang S, Ong CN, Shen HM. 2004. Critical roles of intracellular thiols and calcium in parthenolide-induced apoptosis in human colorectal cancer cells. *Cancer Lett* **208:** 143–153.

Zhang L, Cannell MB, Phillips AR, Cooper GJ, Ward ML. 2008. Altered calcium homeostasis does not explain the contractile deficit of diabetic cardiomyopathy. *Diabetes* **57:** 2158–2166.

Zhang Y, Chen HS, Khanna VK, De Leon S, Phillips MS, Schappert K, Britt BA, Browell AK, MacLennan DH. 1993. A mutation in the human ryanodine receptor gene associated with central core disease. *Nat Genet* **5:** 46–50.

Zhang Z, Lee YC, Kim SJ, Choi MS, Tsai PC, Xu Y, Xiao YJ, Zhang P, Heffer A, Mukherjee AB. 2007. Palmitoyl-protein thioesterase-1 deficiency mediates the activation of the unfolded protein response and neuronal apoptosis in INCL. *Hum Mol Genet* **15:** 337–346.

Zhong Y, Ahmed S, Grupp IL, Matlib MA. 2001. Altered SR protein expression associated with contractile dysfunction in diabetic rat hearts. *Am J Physiol* **281:** H1137–H1147.

Zhou Y, Frey TK, Yang JJ. 2009. Viral calciomics: interplays between Ca^{2+} and virus. *Cell Calcium* **46:** 1–17.

Zhou BQ, Hu SJ, Wang GB. 2006. The analysis of ultrastructure and gene expression of sarco/endoplasmic reticulum calcium handling proteins in alloxan-induced diabetic rat myocardium. *Acta Cardiol* **61:** 21–27.

Zhou H, Pandak WM Jr, Lyall V, Natarajan R, Hylemon PB. 2005. HIV protease inhibitors activate the unfolded protein response in macrophages: implication for atherosclerosis and cardiovascular disease. *Mol Pharmacol* **68:** 690–700.

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