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Review

Coupling endoplasmic reticulum stress to the cell death program

RV Rao[1], HM Ellerby[1] and DE Bredesen*[,1,2]

[1] Buck Institute for Age Research, 8001 Redwood Boulevard, Novato, CA 94945, USA
[2] University of California, San Francisco, San Francisco, CA, 94143, USA
* Corresponding author: DE Bredesen, Buck Institute for Age Research, 8001 Redwood Boulevard, Novato, CA 94945-1400, USA;
Tel: +415-209-2090; Fax: +415-209-2230;
E-mail: dbredesen@buckinstitute.org

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Abstract

The endoplasmic reticulum (ER) regulates protein synthesis, protein folding and trafficking, cellular responses to stress and intracellular calcium (Ca^{2+}) levels. Alterations in Ca^{2+} homeostasis and accumulation of misfolded proteins in the ER cause ER stress that ultimately leads to apoptosis. Prolonged ER stress is linked to the pathogenesis of several different neurodegenerative disorders. Apoptosis is a form of cell death that involves the concerted action of a number of intracellular signaling pathways including members of the caspase family of cysteine proteases. The two main apoptotic pathways, the death receptor ('extrinsic') and mitochondrial ('intrinsic') pathways, are activated by caspase-8 and -9, respectively, both of which are found in the cytoplasm. Recent studies point to the ER as a third subcellular compartment implicated in apoptotic execution. Here, we review evidence for the contribution of various cellular molecules that contribute to ER stress and subsequent cellular death. It is hoped that dissection of the molecular components and pathways that alter ER structure and function and ultimately promote cellular death will provide a framework for understanding degenerative disorders that feature misfolded proteins.

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Abbreviations: ER, endoplasmic reticulum; UPR, unfolded protein response; EOR, ER-overload response; ERAD, ER-associated degradation; PKR, RNA-activated protein kinase; PERK, PKR-like ER kinase; eiF-2 alpha, eukaryotic translation initiation factor 2; GRP78/Bip, glucose-regulated protein of 78 kDa; PDI, protein disulfide isomerase; XBP1, X-box-binding protein-1; ATF-6, activating transcription factor 6; RIP, regulated intramembrane proteolysis; S1P, site 1 protease; S2P, site-2 protease; VCP, valosin-containing protein

Introduction

The endoplasmic reticulum (ER) is a principal site for protein synthesis and folding, calcium storage and calcium signaling. It also serves as a site of biosynthesis for steroids, cholesterol and other lipids. The physiological roles of the ER include regulation of protein synthesis, folding and targeting and maintenance of cellular calcium homeostasis. The ER relies on numerous resident chaperone proteins, a high level of calcium and an oxidative environment to carry out these functions efficiently. Proteins that are translocated into the ER lumen undergo post-translational modification and the folding required for optimal function. Properly folded proteins exit from the ER and progress down the secretory pathway, whereas unfolded and misfolded proteins are exported or dislocated from the ER and degraded by cytoplasmic proteasomes.[1–5]

The ER is highly sensitive to alterations in calcium homeostasis and perturbations in its environment. Thus, Ca^{2+} ionophores that deplete calcium levels from the ER lumen, inhibitors of glycosylation, chemical toxicants, oxidative stress and/or accumulation of misfolded proteins in the ER can all disrupt ER function, resulting in what has been referred to as 'ER stress.' The ER responds by triggering specific signaling pathways including the unfolded protein response (UPR), the ER-overload response (EOR) and the ER-associated degradation (ERAD), to survive the ER stress. The overall activation of all three pathways leads to: (a) a reduction in the amount of newly synthesized protein translocated into the ER lumen, in order to reduce the load of client proteins the ER must process; (b) increased translocation and degradation of ER-localized misfolded proteins; and (c) augmentation of the protein folding capacity of the ER.

The UPR is characterized by the coordinated activation of multiple proteins, including double-stranded RNA-activated protein kinase (PKR), the PKR-like ER kinase (PERK) and eucaryotic translation initiation factor 2 (eiF-2 alpha) kinase, all of which suppress the initiation step of protein synthesis; and by the activation of Ire1p, which triggers the expression of genes encoding ER chaperones, enzymes and structural components of the ER. The activation of the UPR may lead either to cell survival (by triggering the synthesis of ER chaperone proteins such as glucose-regulated protein of 78 kDa (GRP78, also referred to as Bip) and protein disulfide isomerase (PDI)) or to cell demise, the latter through the activation of programmed cell death signals. The ER chaperone proteins use the energy from ATP hydrolysis to prevent protein aggregation, and maintain their associating proteins in a folding-competent state. All of these 'quality

control mechanisms' operate to ensure that only properly folded proteins are exported from the ER lumen to the secretory pathway through the Golgi compartment.[1,2,5–9]

Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS (amyotrophic lateral sclerosis, or Lou Gehrig's disease) and prion protein diseases all feature misfolded proteins and the aggregation of misfolded proteins.[10–15] When misfolded proteins accumulate in excessive amounts, they may overwhelm the 'quality control' system designed to promote correct folding and eliminate faulty proteins, ultimately triggering cell death.[12] Neurons in particular are highly susceptible to the toxic effects of misfolded proteins.[11,12,15] The accumulation of misfolded proteins resulting in alterations in organelle structure, including the ER, has been observed in transgenic models of Huntington's disease, Alzheimer's disease and Lou Gehrig's disease, as well as in huntingtin-null mice.[13,14,16–30] Since these same diseases may be caused by specific mutant proteins that display altered folding and degradation, it is likely that ER stress plays an important pathogenetic role in these diseases, rather than simply being a nonspecific late event in dysfunctional cells. It has been suggested that the neurotoxic species of beta-amyloid peptide in Alzheimer's disease consists of oligomers of the A-beta peptide.[15,31] Similarly, Parkinson's disease is characterized by Lewy body formation; these cytoplasmic inclusions stain for alpha-synuclein, ubiquitin, proteasomal subunits[12,15,32] and other components including mutant forms of Parkin and unfolded Pael receptor protein.[33,34] Recent studies have shown that expanded polyglutamine tracts trigger ER stress-induced cell death.[35–37] Murine models of mutant CuZnSOD-mediated motor neuron degeneration feature prominent intracellular inclusions in degenerating neurons and glia that stain for CuZnSOD.[13,38] Misfolded proteins form insoluble aggregates and are deposited as inclusion bodies whose hydrophobic residues may permit interaction with a wide range of cellular targets to elicit cellular toxicity.[12,14,39] It is believed that toxicity may arise either due to organelle dysfunction, sequestration of critical factors by the misfolded proteins, inhibition of the ubiquitin–proteasome system, energy depletion, inhibition of critical neuronal functions and/or induction of proteases such as caspases, leading to apoptosis.

Apoptosis is a form of cell death that involves the concerted action of a number of intracellular signaling pathways including members of the caspase family of cysteine proteases, which exist as (relatively) latent zymogens or procaspases.[40] Oligomerization of procaspases is an important step leading to caspase activation, which in turn is amplified by the cleavage and activation of other downstream caspases.[41,42] The two main apoptotic pathways, the death receptor ('extrinsic') and mitochondrial ('intrinsic') pathways (Figure 1, inset), are activated by caspase-8 (or caspase-10) and caspase-9, respectively, both of which are found in the cytoplasm.[41] Caspase-8 is recruited to a death-inducing signaling complex only when death receptors such as Fas or the tumor necrosis factor receptor bind to specific multimeric (typically trimeric) ligands (Figure 1). In contrast, caspase-9 is activated when cytochrome *c* is released into the cytoplasm from the mitochondrial intermembranous space (Figure 1). Activated caspase-8 and -9 activate executioner

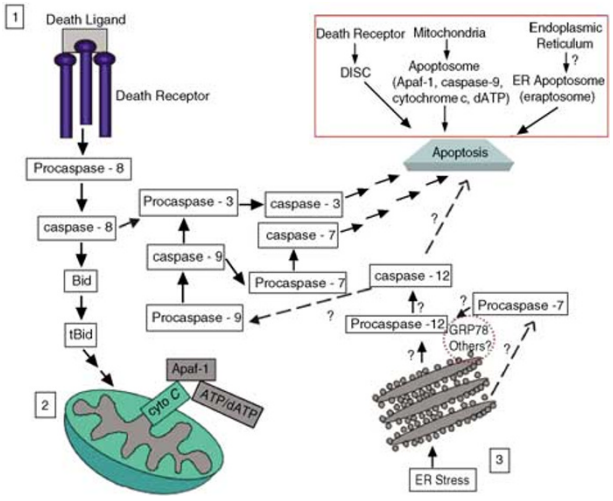

Figure 1 Three signaling pathways that trigger apoptosis (inset). (**1**) Binding of death receptors (Fas or the tumor necrosis factor receptors) to specific multimeric (typically trimeric) ligands results in the recruitment of adaptor molecules involved in the activation of caspase-8. (**2**) When the mitochondrion receives appropriate apoptotic signals, cytochrome *c* and other molecules are released into the cytosol. Cytochrome *c* forms a complex with Apaf-1 and (d)ATP, and activates procaspase-9. (**3**) Alterations in Ca^{2+} homeostasis and accumulation of misfolded proteins in the ER cause ER stress. Prolonged ER stress can result in the activation of caspase-12 that may feed back into a caspase-9-dependent loop and execute apoptosis. The solid arrows indicate known pathways. The dashed arrows and question marks denote possible but unconfirmed interactions and pathways. The dashed closed circle indicates possible interaction

caspases, including caspase-3. Once active, executioner caspases cleave a number of cellular proteins that include nuclear proteins, structural proteins, signaling molecules, cytoskeletal proteins and other proteins implicated in neurodegenerative disease.[41,43] Proteolysis of these proteins disrupts cellular homeostasis and terminates survival signals, among other effects.

Studies from multiple laboratories including ours point to the ER as a third subcellular compartment implicated in apoptotic execution (Figure 1, inset). Like the mitochondria, the ER is a repository for both proapoptotic and antiapoptotic molecules (Figure 1). The known proapoptotic molecules include caspase-12,[44–46] p28Bap31[47] and GADD153[1], while the antiapoptotic molecules identified to date include the ER chaperone proteins GRP78, calreticulin,[48] PDI and ORP-150,[1,49,50] as well as DAD1.[51,52] In addition, a significant fraction of endogenous Bcl-2 family members including Bcl-2, Bcl-x_L, Bax, Bak and Bik have been shown to be associated with the ER, suggesting that Bcl-2 family proteins operate at the ER (at least in part) to regulate calcium homeostasis and apoptotic cell death.[47,53,54–57] Here, we review evidence for the molecular components involved in cell death signaling induced by ER stress. Based on their actions in response to ER stress, these molecular components may be classified as sensors, modulators or effectors (Figure 2).

ER stress-induced cell death: sensors

Although the UPR-signaling pathway was first described in the budding yeast *Saccharomyces cerevisiae*, eucaryotic cells

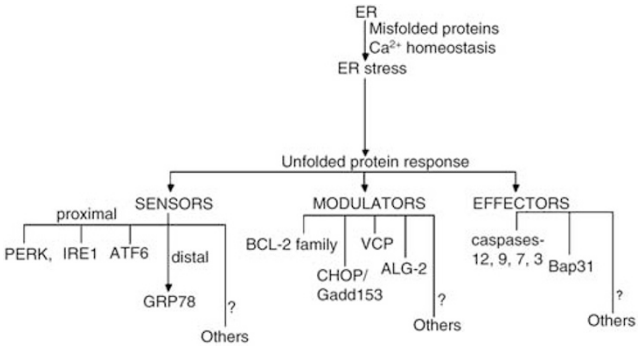

Figure 2 Alterations in calcium homeostasis and/or accumulation of misfolded proteins in the ER can all disrupt ER function resulting in 'ER stress'. The ER responds by triggering specific signaling pathways including the UPR. Prolonged ER stress leads to organelle damage and dysfunction and ultimately leads to cell death. The molecular components involved in the UPR leading to cell survival or cell death signaling can be classified as sensors, modulators or effectors. The balance between various modulators determines ER stress-induced cell survival *versus* death

also appear to have maintained the essential and unique properties of the UPR. In addition, higher eucaryotes also possess additional sensors that coordinate and regulate stress adaptation or cell death responses. PERK, IRE1 and activating transcription factor (ATF-6) serve as proximal sensors that regulate components that act to upregulate the capacity of the ER to fold newly synthesized proteins and degrade misfolded/unfolded proteins.[1,5,7,8,58]

Changes in the ER environment due to the accumulation of misfolded proteins or due to disruption of calcium homeostasis trigger the UPR. In turn, the UPR triggers two downstream signal transduction events: the induction of genes coding for ER-resident stress proteins and the suppression of initiation of protein synthesis.[4,5,7] The ER-resident protein kinase PERK has been implicated in the latter process. In normal unstressed cells, the binding of the ER chaperone protein GRP78 to the lumenal domain of PERK keeps it (PERK) in an inactive conformation. As misfolded proteins accumulate, the GRP78-PERK complex is disrupted, and PERK undergoes oligomerization and transautophosphorylation.[59] The kinase domain of the activated phosphorylated PERK phosphorylates the alpha subunit of eucaryotic translation initiation factor-2 alpha (eIF2α), thereby attenuating translation initiation and protein synthesis. Cells that lack PERK cannot induce the UPR, and are therefore extremely sensitive to ER stress-inducing agents, probably due to the accumulation of misfolded proteins and an overall failure in responding to ER stress. PERK activation and eIF2α phosphorylation lead to: (a) a decrease in protein folding load in the ER; (b) induction of the expression of eIF2α phosphorylation-dependent ER stress genes; and (c) promotion of cell survival.[7,60–64]

IRE1 was first identified as an ER membrane-spanning receptor protein kinase required for inositol phototrophy.[65–67] Later studies identified it as a sensor of misfolded/unfolded proteins in the ER lumen. The IRE1 gene encodes an 1115 amino-acid, type 1 transmembrane Ser/Thr receptor protein kinase that also possesses site-specific endoribonuclease (RNase) activity. The receptor protein has an amino-terminal signal peptide, an amino-terminal domain that localizes it to the ER lumen, a short transmembrane domain and a carboxy-terminal cytoplasmic domain with kinase activity. The lumenal domain of IRE1 has a significant similarity to the PERK protein, and is negatively regulated by GRP78.[59] The presence of misfolded/unfolded proteins in the ER lumen promotes dissociation of the GRP78-IRE1 complex, dimerization and *trans*-autophosphorylation of IRE1, rendering IRE1 active as an RNase, and allowing it to cleave a preformed substrate mRNA at two sites, resulting in the removal of a 252-base intron from the target mRNA.[68–70] The two ends of the cleaved mRNA are ligated together by tRNA ligase and the newly formed mRNA encodes a transcription factor, HAC1p, that can bind and activate the promoters of several ER stress-inducible target genes.[71,72] Two Ire1 isoforms, *IRE1*α and *IRE1*β, have been identified in the mammalian genome. Sequence comparisons show that the C-terminal kinase and endoribonuclease domains are more conserved among all known Ire1 homologs, while the ER-lumenal domains are more divergent.[73–75] *IRE1*α is expressed in most cells and tissues, with high-level expression in the pancreas and placenta. The expression of IRE1β is prominent only in intestinal epithelial cells.[73,74] The overexpression of either isoform induces the UPR that is blocked by the overexpression of its dominant-negative forms. Both IRE1 molecules respond to the accumulation of unfolded proteins in the ER, undergo kinase activation and, thereby, trigger their RNase activities. X-box-binding protein-1 (XBP1) mRNA is a substrate for mammalian IRE1, is processed similarly to yeast Hac1p, and the resulting processed mRNA encodes a novel and potent transcriptional activator.[76,77]

Yet another proximal ER stress sensor, activating transcription factor 6 (ATF6),[76] is activated by regulated intramembrane proteolysis (RIP).[78] In unstressed cells, ATF6 is present as an inactive protein associated with the ER membrane, and it is negatively regulated by GRP78. As misfolded proteins accumulate, GRP78 is released from ATF6, permitting the transport of ATF6 to the Golgi, where it is cleaved by site-1 protease (S1P) and site-2 protease (S2P). Proteolysis by S1P and S2P liberates the amino-terminal portion of ATF6 that migrates to the nucleus, binds ER stress elements in the promoter of UPR-responsive genes and triggers the expression of ER stress-inducible target genes.[79–84] There are two forms of ATF6: ATF6α (90 kDa) and ATF6β (110 kDa). Both forms are under RIP control and on activation of the UPR are processed to generate 50- to 60-kDa cytosolic protein fragments that migrate to the nucleus and activate target genes.

The glucose-regulated proteins or GRPs were initially identified as a family of Ca^{2+}-binding chaperone proteins whose transcription was induced during viral transformation or glucose deprivation. Subsequently, based on several reports, it became clear that the expression of GRPs is induced in response to several stimuli including oxidative stress, chemical toxicity, treatment with Ca^{2+} ionophores and exposure to inhibitors of glycosylation that disrupt ER structure and function.[1,85] GRP78 (Bip) is one the best-characterized ER chaperone proteins, and it has served as a classical marker for UPR activation. The induction of GRP78

is required to alleviate ER stress, maintain ER function, facilitate protein folding and protect cells from the aforementioned toxic insults.[1] GRP78 functions as a master regulator of the UPR by binding to, and preventing the activation of, all three proximal stress sensors (under nonstressed conditions): IRE1, PERK and ATF6. When misfolded proteins accumulate in the cell, they bind to GRP78 and disrupt its interaction with the stress sensors, resulting in their activation. GRP78 also binds transiently to the exposed hydrophobic residues of nascent folded proteins, ensures proper protein folding and prevents protein aggregation. In addition, studies from several laboratories suggest that GRP78 may also protect the host cell against cell death by suppressing oxyradical accumulation and stabilizing mitochondrial function.[86–89]

While GRP78 exists as an ER lumen protein,[1,85] several reports have suggested that GRP78 (and several mutants derived therefrom) may also redistribute to the cytosol, nucleus and cell surface, as well as establishing a microsomal subpopulation that is partially protease sensitive.[90–96] This latter effect suggests that, under stress conditions, GRP78 may also exist as an ER transmembrane protein (although how transient this effect is, is not clear). The potential explanations for the presence of GRP78 outside the ER are: (a) saturation of KDEL receptors in the ER, resulting in targeting overflow; (b) interactions with other proteins or lipids that consequently hinder binding to the KDEL receptor, allowing GRP78 egress from the ER; or (c) an active release from intact cells during cellular stress.[94,97,98] This phenomenon was also observed with calreticulin, an ER-lumenal protein that redistributes from the ER and appears in the cytosol during heat stress.[99,100] Similarly, a subpopulation of GRP94 associates with the ER membrane during an apoptotic insult, where it becomes a target of calpain activity.[101] Recent studies have also suggested that either a cytosolic pool of GRP78 or a subpopulation of GRP78 existing as an ER transmembrane protein may form a complex with caspase-7 and -12 at the ER surface, and prevent their activation and release.[95,96] These studies highlight the importance of GRP78 as an antiapoptotic protein, and shed new light on the mechanisms underlying the relationship between ER stress, the UPR and the cell death program.

Despite the efficient 'ER quality control mechanisms' that exist to respond to any disturbances that affect ER structure, function and integrity, prolonged ER stress ultimately leads to cell death. While the mechanisms underlying ER stress-induced cell death are not clear, recent studies have identified genes that trigger cell death pathways during prolonged ER stress. Coupling ER stress to the cell death program(s) may be advantageous to the organism not only by destroying damaged, dysfunctional cells but also as part of a recycling mechanism to allow recovery of organ function.[3,4,7]

ER stress-induced cell death: modulators

The roles of several ER stress-induced cell death modulators and effectors have been revealed by biochemical, pharmacological and genetic tools. The ER stress-induced cell death modulators include (but are not limited to) members of the Bcl-2 family (Bcl-2, Bcl-x_L, Bax, Bak and Bik), CHOP/Gadd153, valosin-containing protein (VCP) and apoptosis linked gene-2 (ALG-2).

One of the first genes to be identified as a modulator of cell death was *bcl-2*.[102–108] Bcl-2 proteins and their apparent roles in cell death have been evolutionarily conserved, and these proteins play key roles in regulating the integrity of the ER and mitochondrial membranes.[109–112] The Bcl-2 family can be either proapoptotic (e.g., Bax, Bak) or antiapoptotic (e.g., Bcl-2, Bcl-x_L), and based on their protein structures the proapoptotic proteins are classified into multidomain proteins (e.g., Bax, Bak) and BH3-only proteins (e.g., Bad, Bid, Bim, Bik).[112,113] On activation, the proapoptotic Bax and Bak proteins form protein-conducting channels in the mitochondrial outer membrane, causing release of proapoptotic proteins such as cytochrome *c*; the latter then binds to the adaptor protein Apaf-1 and the initiator caspase-9, resulting in a downstream proteolytic cascade. This cascade leads to the cleavage of specific cellular proteins as well as DNA, and is attended by the demise of the cell. Antiapoptotic Bcl-2 members inhibit apoptosis by: (a) binding and sequestering activated Bak and Bax, thus preventing pore formation; and/or (b) sequestering the BH3-only members that would otherwise displace the antiapoptotic Bcl-2 family proteins from the proapoptotic ones such as Bax and Bak, which would in that case become active.[57,111,114] A significant fraction of endogenous Bcl-2 family member proteins including Bcl-2, Bcl-x_L, Bax, Bak and Bik has been shown to be associated with the ER,[55–57,111,114] where, among other potential effects, these proteins function in the maintenance of Ca^{2+} homeostasis. The overexpression of Bax or Bak leads to Ca^{2+} efflux from the ER, Ca^{2+} influx into the mitochondria and increased cytochrome *c* release-induced ER Ca^{2+} efflux, leading to cell death that is inhibitable by Bcl-2.[115,116] Bax/Bak doubly deficient mouse embryonic fibroblasts are resistant to both mitochondrial-mediated apoptosis and ER stress stimuli, suggesting a possible crosstalk between ER and mitochondrial cell death pathways.[56,112] The ER–mitochondria crosstalk may be utilized for mitochondrial amplification of ER-initiated apoptotic pathways, or for other pathways. In any case, the balance between these various Bcl-2 family members determines an 'apoptotic rheostat' or 'apostat' that modulates ER—mitochondrial-dependent cell survival *versus* death.[42,117–119]

Another ER stress-induced cell death modulator is CHOP/Gadd153, a transcription factor induced during ER stress and subsequently activated by p38 mitogen-associated protein kinase.[1,7,63,120] Several reports suggest that CHOP negatively regulates cell growth and promotes ER stress-induced apoptosis.[1,121,122] Gadd153 overexpression promotes cell death, but the overexpression of GRP78 blocks Gadd153-mediated cell cycle arrest and apoptosis.[120,123] The deletion of the *CHOP* gene leads to an attenuation in cell death induced by ER stress.[124,125] While the identification of the downstream target genes that respond to CHOP/Gadd153 is still unclear, it has been suggested that Gadd153 may promote ER stress-induced cell death by downregulating Bcl-2 expression.[125]

Recent data have implicated two additional proteins[126] that, together with caspase-12, caspase-9, caspase-7, ATP and Ca^{2+}, appear to function as mediators of ER stress-induced

cell death. One of these, VCP, is a member of the AAA (ATPases associated with diverse cellular activities) family of ATP-binding, homo-oligomeric ATPase proteins, and participates in multiple cellular activities by binding to several target-specific adaptors. These cellular activities include vesicle transport and fusion, 26S proteasome function, assembly of peroxisomes, membrane transport processes and ubiquitin–proteasome degradation.[127–129] VCP also functions as a sensor of abnormally folded proteins (and therefore may also be appropriately included in the group of sensors above) and has been reported to act as a cell death effector in polyglutamine-induced cell death.[130,131]

ALG-2 is a low molecular weight (22 kDa) Ca^{2+}-binding protein that possesses strong apoptosis-inducing activity and is involved in T-cell receptor-, Fas- and glucocorticoid-induced cell death. ALG-2 translocates from the membrane compartment to the cytosol during Fas-mediated apoptosis and ALG-2 depletion blocks programmed cell death induced by several stimuli, such as synthetic glucocorticoids, T-cell receptor ligation and Fas ligand.[132–135]

Coimmunoprecipitation studies have suggested that both VCP and ALG-2 may function as part of an ER stress-induced caspase-activating complex, that is, an ER-based apoptosome or 'eraptosome'[126], (Figure 1); this would be compatible with previous reports that caspase-12 zymogen may be identified as part of a complex with a relative molecular mass greater than 600 kD.[136,137]

However, additional studies will be required to determine whether this putative complex does indeed include VCP and/or ALG-2, and, if so, what role these modulators play in caspase activation induced by ER stress.

ER stress-induced cell death: effectors

Several molecules either present on the ER surface or in the soluble compartment have been implicated as effectors that cause cell death in response to prolonged ER stress. Caspase-12 (a murine caspase not yet unequivocally identified in human tissue), which is associated with the ER, is specifically involved in apoptosis that results from ER stress.[44–46,95,138] The activation of caspase-12 may occur through ER stress-induced calpain or caspase-7 cleavage of procaspase-12.[46,138] ER stress-activated IRE1 may also aggregate procaspase-12 at the ER membrane surface through the cytosolic adaptor TRAF2 proteins, resulting in the cleavage and activation of caspase-12,[139] presumably via an induced proximity mechanism. Caspase-12, together with caspase-9, serves as a mediator of a novel intrinsic apoptosis pathway that is independent of Apaf-1, cytochrome *c* and mitochondria (this is not to say that mitochondria may not be involved in the amplification of this pathway, simply that they are not required for its activation).[138,140,141] It is worth noting that caspase-12 was identified in the murine system, and its presence in human tissues is controversial; however, antibodies directed against mouse caspase-12 crossreact with a human cellular protein that is of similar relative molecular mass to that of mouse caspase-12, and is cleaved similarly to murine caspase-12.[44–46,142] This human caspase-12 candidate has been shown not to be one of the previously described human caspases (Rao *et al*., unpublished data). Although the human genome has not revealed a clear caspase-12 candidate, one group has reported a human caspase-12 sequence;[143] however, this putative caspase-12 sequence is predicted to encode a protein that has a significant deletion, so that it would be highly unlikely to demonstrate a molecular mass similar to the murine caspase-12.

BAP31 is an ER transmembrane protein that binds to nascent membrane proteins in transit between ER and *cis*-Golgi, and exists in a complex with procaspase-8 and the antiapoptotic regulator Bcl-2 or Bcl-x_L. ER stress and other apoptotic signals lead to the cleavage of BAP31, giving rise to a p20 fragment that causes the following: (a) early release of Ca^{2+} from the ER; (b) uptake of Ca^{2+} into mitochondria; and (c) induction of cytochrome *c* release, caspase activation and apoptosis. Furthermore, caspase-8 cleavage of BAP31 at the ER stimulates Ca^{2+}-dependent mitochondrial fission, enhancing the release of cytochrome *c* in response to this initiator caspase. Thus the caspase-derived fragment of Bap31 may be a coordinator of cell death signals between the ER and mitochondria.[53,114,144–147]

Conclusions

The ER is very sensitive to changes in its environment leading to disruption of its normal homeostasis. A variety of environmental insults (leading, for example, to changes in Ca^{2+} homeostasis), as well as genetic diseases associated with the accumulation of misfolded proteins, can all affect the ER structure, function and integrity, leading to ER stress and contributing to the pathogenesis of different disease states. Prolonged stress leads to organelle damage and dysfunction, and ultimately to cell death. The accumulation of misfolded proteins seen in various neurodegenerative diseases leads to an ER stress response, irrespective of whether the misfolded proteins build up within the ER or outside the ER. It is thus important to define the biochemical pathways by which ER stress induces programmed cell death, since an understanding of the relationship between the accumulation of misfolded proteins, cellular stress responses and cell death programs should facilitate the development of new therapeutic strategies for degenerative disorders that feature misfolded proteins.

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