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Forum Review

Endoplasmic Reticulum Stress and Oxidative Stress: A Vicious Cycle or a Double-Edged Sword?

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ABSTRACT

The endoplasmic reticulum (ER) is a well-orchestrated protein-folding machine composed of protein chaperones, proteins that catalyze protein folding, and sensors that detect the presence of misfolded or unfolded proteins. A sensitive surveillance mechanism exists to prevent misfolded proteins from transiting the secretory pathway and ensures that persistently misfolded proteins are directed toward a degradative pathway. The unfolded protein response (UPR) is an intracellular signaling pathway that coordinates ER protein-folding demand with protein-folding capacity and is essential to adapt to homeostatic alterations that cause protein misfolding. These include changes in intraluminal calcium, altered glycosylation, nutrient deprivation, pathogen infection, expression of folding-defective proteins, and changes in redox status. The ER provides a unique oxidizing folding-environment that favors the formation of the disulfide bonds. Accumulating evidence suggests that protein folding and generation of reactive oxygen species (ROS) as a byproduct of protein oxidation in the ER are closely linked events. It has also become apparent that activation of the UPR on exposure to oxidative stress is an adaptive mechanism to preserve cell function and survival. Persistent oxidative stress and protein misfolding initiate apoptotic cascades and are now known to play predominant roles in the pathogenesis of multiple human diseases including diabetes, atherosclerosis, and neurodegenerative diseases. *Antioxid. Redox Signal.* 9, 2277–2293.

INTRODUCTION

As PROTEIN FOLDING is an essential process for protein function in all organisms, all cells have evolved a plethora of sophisticated mechanisms to ensure that proper protein folding occurs and to prevent protein misfolding. It is now recognized that the efficiency of protein-folding reactions depends on appropriate environmental, genetic, and metabolic conditions. Conditions that disrupt protein folding present a threat to cell viability. All proteins that transit the secretory pathway in eukaryotic cells first enter the endoplasmic reticulum (ER), where they fold and assemble into multisubunit complexes before transit to the Golgi compartment (63). "Quality control" is a surveillance mechanism that permits only properly folded proteins to exit the ER *en route* to other intracellular organelles and the cell surface. Misfolded proteins are either retained within the ER lumen in complex with molecular chaperones or are directed toward degradation through the 26S proteasome in a process called ER-associated degradation (ERAD) or through autophagy.

The ER provides a unique environment that poses many challenges for correct protein folding as nascent polypeptide chains enter the ER lumen. The high concentration of partially folded and unfolded proteins predisposes protein-fold-

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ing intermediates to aggregation. Polypeptide-binding proteins, such as BiP and GRP94, act to slow protein-folding reactions and prevent aberrant interactions and aggregation. The ER lumen is an oxidizing environment, so disulfide bond formation occurs. As a consequence, cells have evolved sophisticated machinery composed of many protein disulfide isomerases (PDIs) that are required to ensure proper disulfide-bond formation and prevent formation of illegitimate disulfide bonds. The ER is also the primary Ca^{2+}-storage organelle in the cell. Both protein-folding reactions and protein chaperone functions require high levels of ER intraluminal calcium. Protein folding in the ER requires extensive amounts of energy, and depletion of energy stores prevents proper protein folding. ATP is required for chaperone function, to maintain Ca^{2+} stores and redox homeostasis, and for ERAD. Finally, proteins that enter the ER lumen are subject to numerous posttranslational modifications including N-linked glycosylation, amino acid modifications such as proline and aspartic acid hydroxylation and γ-carboxylation of glutamic acid residues, and addition of glycosylphosphatidylinositol anchors. N-linked glycosylation is a highly regulated process and is intimately coupled with protein folding and chaperone interactions to ensure that only properly folded proteins exit the ER compartment (Fig. 1). All these processes are highly sensitive to alterations in the ER luminal environment. As a consequence, innumerable environmental insults alter protein-folding reactions in the ER through mechanisms that include depletion of ER calcium, alteration in the redox status, and energy (sugar/glucose) deprivation. In addition, gene mutations, elevated protein traffic through the ER compartment, and altered posttranslational modification all contribute the accumulation of unfolded proteins in the ER lumen. Accumulation of unfolded protein initiates activation of an adaptive signaling cascade known as the unfolded protein response (UPR). Appropriate adaptation to misfolded protein accumulation in the ER lumen requires regulation at all levels of gene expression, including transcription, translation, translocation into the ER lumen, and

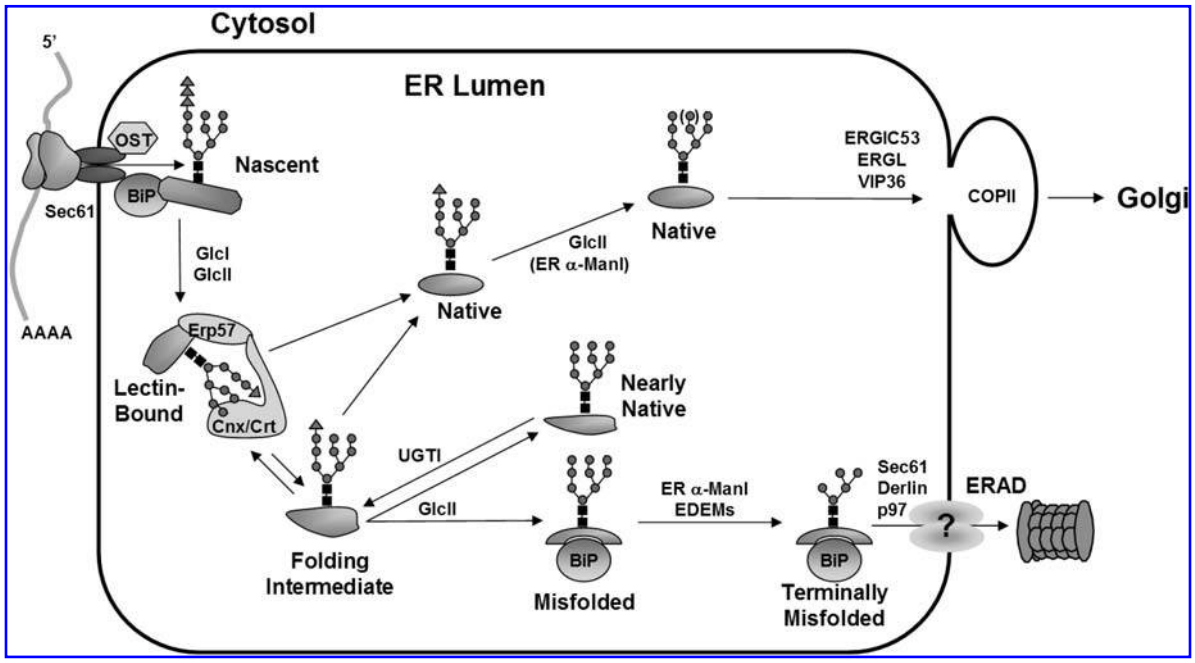

FIG. 1. Protein trafficking from the ER. On translocation of polypeptides through the Sec61 proteinaceous channel, asparagine residues are frequently modified by covalent addition of a preassembled oligosaccharide core (*N*-acetylglucosamine$_2$-mannose$_9$-glucose$_3$). This reaction is catalyzed by the oligosaccharyltransferase (OST), a multisubunit complex associated with translocon. To facilitate unidirectional transport through the translocon, nascent polypeptide chains in the ER lumen interact with BiP, a molecular chaperone that binds to exposed hydrophobic residues. Subsequently, rapid deglucosylation of the two outermost glucose residues on the oligosaccharide core structures, mediated by glucosidase I and II (GlcI and GlcII), prepares glycoproteins for association with the ER lectins calnexin and calreticulin. The calnexin/calreticulin-associated oxidoreductase ERp57 facilitates protein folding by catalyzing formation of intra- and intermolecular disulfide bonds, a rate-limiting step in the protein-folding process. Release from calnexin/calreticulin, followed by glucosidase II cleavage of the innermost glucose residue, prevents further interaction with calnexin and calreticulin. At this point, natively folded polypeptides transit the ER to the Golgi compartment, in a process possibly assisted by mannose-binding lectins, such as ERGIC-53, VIPL, and ERGL. As an essential component of protein-folding quality control, nonnative polypeptides are tagged for reassociation with calnexin/calreticulin by the UDP-glucose:glycoprotein glucosyltransferase (UGT1) to facilitate their ER retention and prevent anterograde transport. Polypeptides that are folding incompetent are targeted for degradation by retrotranslocation, possibly mediated by EDEM and Derlins, into the cytosol and delivery to the 26S proteosome. *Triangles,* glucose residues; *squares*, *N*-acetylglucosamine residues; *circles*, mannose residues.

ERAD. Coordinate regulation of all these processes is required to restore proper protein folding and ER homeostasis (40, 63, 86, 107, 122, 150). Conversely, if the protein-folding defect is not resolved, chronic activation of UPR signaling occurs, which eventually induces an apoptotic (programmed cell death) response.

Recent studies indicate that maintenance of ER homeostasis is intimately intertwined with the cellular redox potential. However, the mechanisms that link ER stress and oxidative stress are very poorly characterized. In this review, we attempt to summarize the signaling pathways that mediate the UPR, the role of oxidative stress in this adaptive response, the mechanisms underlying oxidative protein folding, and finally the clinical implications of these ER-associated processes in health and disease.

UPR SIGNALING

The molecular components of the UPR signaling pathway have been successfully dissected over the past couple of decades. It is now well established that in response to ER stress, three ER-localized transmembrane signal transducers are activated to initiate adaptive responses. These transducers are two protein kinases IRE1 (inositol-requiring kinase 1) (129, 159), and PERK (double-stranded RNA-activated protein kinase-like ER kinase) (42), and the transcription factor ATF6 (activating transcription factor 6) (159, 160). These three UPR transducers are constitutively expressed in all known metazoan cells (Fig. 2).

IRE1 signaling: selective mRNA splicing

The first component in the UPR pathway was identified in the budding yeast *Saccharomyces cerevisiae* in the early 1990s using a genetic screen to identify mutants in UPR signaling. Two independent groups identified Ire1p/Ern1p as an ER transmembrane protein kinase that acts as a proximal sensor in the yeast UPR (19, 86). Subsequently, it was discovered that Ire1p is a bifunctional protein that also has a site-specific endoribonuclease (RNase) activity (19, 86). When cells are not stressed, Ire1p protein kinase is maintained in an inactive monomeric form through interactions with the protein chaperone Kar2p/BiP. Under conditions of ER stress, Ire1p is released from Kar2p/BiP and undergoes homodimerization and trans-autophosphorylation to activate its RNase activity. The RNase activity of Ire1p cleaves a 252-base intron from mRNA encoding the basic leucine zipper (bZIP)-containing transcription factor Hac1p. The protein encoded by spliced *HAC1* mRNA binds and activates transcription from the UPR element [UPRE, minimal motif TGACGTG(C/A)] upstream of many UPR target genes (87, 107). In *S. cerevisiae*, the UPR activates transcription of ~381 genes (141), >50% of which provide functions in the secretory pathway. Two mammalian homologues of yeast IRE1 have been identified; IRE1α (139) and IRE1β (148). IRE1α is expressed in most cells and tissues, with highest levels of expression in the pancreas and placenta (139). IRE1β expression is prominent only in intestinal epithelial cells (148). The cleavage specificities of IRE1α and IRE1β are quite similar, thereby suggesting that they do not recognize distinct substrates but rather confer temporal- and tissue-specific expression (97).

Analysis of promoter regions of UPR-inducible genes in

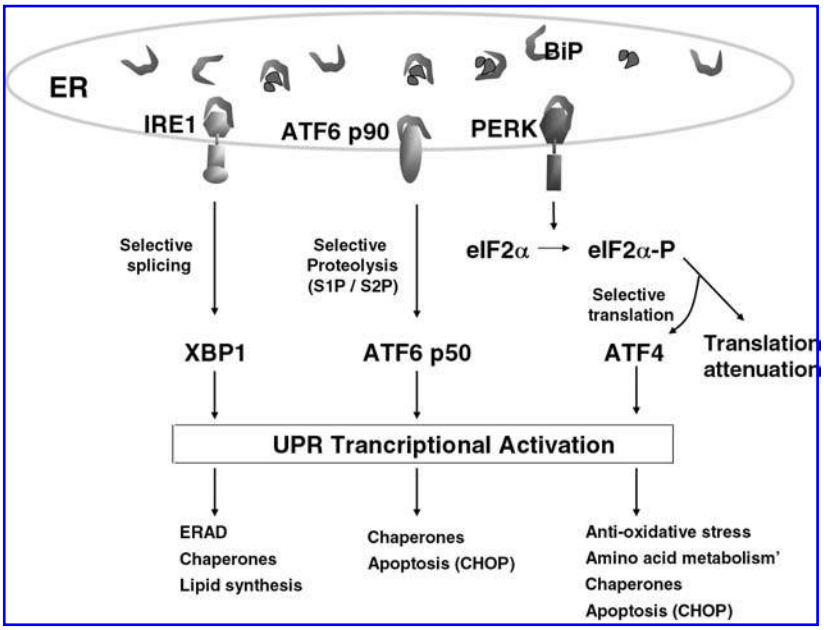

FIG. 2. Signaling the unfolded protein response. Three proximal sensors (IRE1, PERK, and ATF6) act in concert to regulate the UPR through their respective signaling cascades. The protein chaperone BiP is the master regulator and negatively regulates these pathways. Under nonstressed conditions, BiP binds to the luminal domains of IRE1 and PERK to prevent their dimerization. With the accumulation of the unfolded proteins, BiP is released from IRE1 and permits dimerization to activate its kinase and RNase activities to initiate XBP1 mRNA splicing thereby creating a potent transcriptional activator. Primary targets that require IRE1/XBP1 pathway for induction are genes encoding functions in ERAD. Similarly, BiP release from ATF6 permits transport to the Golgi compartment. where ATF6 is cleaved by S1P and S2P proteases to yield a cytosolic fragment that migrates to the nucleus to activate further the transcription of UPR-responsive genes. Finally, BiP release permits PERK dimerization and activation to phosphorylate eIF2α on Ser 51 that leads to general attenuation of translational initiation. Paradoxically, eIF2α phosphorylation induces translation of ATF4 mRNA. The PERK/eIF2α/ATF4 regulatory axis also induces expression of antioxidative stress-response genes and expression of genes encoding proteins with proapoptotic functions, such as CHOP.

mammals, such as BiP, Grp94, and calreticulin, identified a mammalian ER stress-response element (ERSE, CCAAT-(N_9)CCACG) that is necessary and sufficient for UPR gene activation (157). Subsequently, Yoshida *et al.* (157) used a yeast one-hybrid screen to identify the bZIP-containing transcription factor XBP1 (X-box binding protein) as an ERSE-binding protein (157). Several groups demonstrated that *XBP1* mRNA is a substrate for the endoribonuclease activity of metazoan IRE1 (13, 70, 126, 159). On activation of the UPR, IRE1 RNase cleaves *XBP1* mRNA to remove a 26-nucleotide intron. This splicing reaction creates a translational frameshift to produce a larger form of XBP1 that contains a novel transcriptional activation domain in its C-terminus. Spliced XBP1 is a transcriptional activator that plays a key role activation of wide variety of UPR target genes. Some of the genes identified that require the IRE1/XBP1 pathway are those that encode functions involved in ERAD, such as EDEM. Consistent with this observation, cells that are deficient in either IRE1 or XBP1 are defective in ERAD (158) (see Fig. 2).

Deletion of *Ire1α* or *Xbp1* in mice creates an embryonic lethality at E11.5-E14 (70, 111). Although deletion of *Ire1β* had no developmental phenotype, *Ire1β*$^{-/-}$ mice were susceptible to experimentally induced intestinal colitis (7). Mice with heterozygous *Xbp1* deletion appear normal but develop insulin resistance when fed a high-fat diet (104). Thus, it was proposed that the UPR might be important in insulin signaling (see later). In addition, both IRE1 and XBP1 have critical roles in B-cell differentiation. Antigenic stimulation of mature B lymphocytes activates the UPR, and signaling through IRE1-mediated *XBP1* mRNA splicing is required to drive B-lymphocyte differentiation into plasma cells (13, 56, 112, 165). These studies suggest that the IRE1/XBP1 subpathway of the UPR might be required for differentiation of cell types that secrete high levels of protein (69).

PERK signaling: mRNA translation attenuation

The essential and unique properties of the UPR present in yeast have been conserved in all eukaryotic cells, but higher eukaryotes also possess additional sensors that promote stress adaptation or cell death in a more complex, but coordinated manner. In response to ER stress in metazoan cells, an immediate transient attenuation of mRNA translation occurs, thereby preventing continued influx of newly synthesized polypeptides into the stressed ER lumen (64). This translational attenuation is signaled through PERK-mediated phosphorylation of the eukaryotic translation initiation factor 2 on the α subunit (eIF2α) at Ser51. eIF2α phosphorylation inhibits the guanine nucleotide exchange factor eIF2B, which recycles the eIF2 complex to its active GTP-bound form. The formation of the ternary translation initiation complex eIF2-GTP-tRNA^{Met} is required for AUG initiation codon recognition and joining of the 60S ribosomal subunit that occurs during initiation phase of polypeptide chain synthesis. Lower levels of active ternary complex result in lower levels of translation initiation (42–44, 121) (see Fig. 2).

PERK is an ER-associated transmembrane serine/threonine protein kinase. On accumulation of unfolded proteins in the ER lumen, PERK dimerization and trans-autophosphorylation leads to activation of its eIF2α kinase function (41, 42). In addition to translational attenuation, activation of PERK also induces transcription of approximately one third of the UPR-dependent genes (43, 44, 114, 121). Although phosphorylation of eIF2α inhibits general translation initiation, it is required for the selective translation of several mRNAs. One fundamental transcription factor for which translation is activated on PERK-mediated phosphorylation of eIF2α is the activating transcription factor 4 (ATF4) (43, 44, 114, 121). Expression profiling found that genes encoding amino acid biosynthesis and transport functions, antioxidative stress responses, and apoptosis, such as growth arrest and DNA damage 34 (GADD34) and CAAT/enhancer-binding protein (C/EBP) homologous protein (CHOP) (41, 80), require PERK, eIF2α phosphorylation, and ATF4 (43, 44, 114, 121).

Although the majority of PERK signaling is mediated through phosphorylation of eIF2α, studies suggest that the bZIP Cap 'n' Collar transcription factor nuclear respiratory factor 2 (NRF2) may also be a substrate for the PERK kinase activity. NRF1 and NRF2 are transcription factors that integrate a variety of responses to oxidative stress. NRF2 is distributed in the cytoplasm through its association with the microtubule-associated protein Keap1 (Kelch-like Ech-associated protein 1). On ER stress, PERK phosphorylates NRF2 to promote its dissociation from Keap1, leading to the nuclear accumulation of NRF2. *Nrf2*$^{-/-}$ cells are sensitive to ER stress-induced apoptosis. NRF2 is a direct PERK substrate and effector of PERK-dependent cell survival (21). NRF2 binds to the antioxidant response element (ARE) to activate transcription of genes encoding detoxifying enzymes, including A1 and A2 subunits of glutathione *S*-transferase, NAD(P)H:quinone oxidoreductase, γ-glutamylcysteine synthetase, HO-1, and UDP-glucoronosyl transferase (95). Possibly in a similar manner, NRF1 is localized to the ER membrane and translocates to the nucleus on ER stress (147). These data support the notion that PERK phosphorylates multiple substrates to protect cells from oxidative stress. Consistent with this idea, *Perk*$^{-/-}$ cells accumulate ROS when exposed to ER stress (44).

ATF6 signaling: regulated intramembrane proteolysis

The bZIP-containing activating transcription factor 6 (ATF6) was identified as another regulatory protein that, like XBP1, binds to the ERSE1 element in the promoters of UPR-responsive genes (157). The two alleles of ATF6, ATF6α (90kDa) and ATF6β (110 kDa) are both synthesized in all cell types as ER transmembrane proteins. In the unstressed state, ATF6 is localized at the ER membrane and bound to BiP. In response to ER stress, BiP dissociation leads to transport of ATF6 to the Golgi complex, where ATF6 is sequentially cleaved by two proteases (45, 74, 161). The serine protease site-1 protease S1P cleaves ATF6 in the luminal domain. The N-terminal portion is subsequently cleaved by the metalloprotease site-2 protease S2P (155). The processed forms of ATF6α and ATF6β translocate to the nucleus and bind to the ATF/cAMP response element (CRE) and to the ER stress-response element (ERSE-1) to activate target genes (161). ATF6α and ATF6β both require the presence of the transcription factor CBF (CAAT binding factor also called NF-Y) to bind ERSEI (45, 74, 161). The proteases S1P and S2P were originally identified for their essential role in processing of the sterol response element binding

protein (SREBP) transcription factor, that is activated on cholesterol deprivation (37) (see Fig. 2).

Recently, additional bZIP-containing transcription factors that are localized to the ER and regulated by RIP were identified. CREBH was identified as a liver-specific bZIP transcription factor of the CREB/ATF family, with a transmembrane domain that directs localization to the ER (164). Pro-inflammatory cytokines IL-6, 1L-1β, and TNFα increase transcription of CREBH to produce an inert protein that is localized to the ER. On ER stress, CREBH transits to the Golgi compartment, where it is cleaved by S1P and S2P processing enzymes. However, cleaved CREBH does not activate transcription of UPR genes, but rather, induces transcription of many acute-phase response genes, such as C-reactive protein and murine serum amyloid P component (SAP) in hepatocytes. These studies identified CREBH as a novel ER-localized transcription factor that has an essential role in induction of innate immune response genes and links for the first time ER stress to inflammatory responses (164).

In addition to ATF6 and CREBH, additional similarly related factors are regulated through ER stress-induced proteolytic processing, although their physiologic significance remains unknown. OASIS (old astrocyte specifically induced substance) and BBF2H7 (BBF2 human homologue on chromosome 7) are cleaved by S1P and S2P in response to ER stress in astrocytes and neurons, respectively (67, 68). Tisp40 (transcript induced in spermiogenesis 40) is cleaved by S1p and S2P to activate transcription of EDEM (91). These tissue-specific ATF6-like molecules may contribute to the ER stress response. Finally, Luman/LZIP/CREB3 and CREB4 are also two ATF6-like molecules that are cleaved by S1P and S2P to activate UPR transcription, although their cleavage appears not to be activated by ER stress (76, 110, 134). These transcription factors might be activated under conditions other than ER stress to activate transcription of ER chaperones.

Activation of the UPR: autoregulation through BiP

Biochemical studies have demonstrated that the luminal domains of IRE1, PERK, and ATF6 are bound to the protein chaperone BiP in unstressed cells. In response to stress, unfolded proteins accumulate and bind BiP, thereby sequestering BiP and promoting BiP release from the UPR sensors. When these sensors are bound to BiP, they are maintained in an inactive state (7). This BiP-mediated negative-regulation model for UPR activation is also supported by the observation that BiP overexpression prevented activation of the UPR on ER stress (90). In addition, sufficiently high levels of expression of any protein that binds BiP can activate UPR. In contrast, the accumulation of unfolded proteins that do not bind BiP does not activate the UPR. Analysis of the interaction between BiP and ATF6 suggested that this dissociation is not merely a consequence of competition between ATF6 and unfolded protein for binding to BiP, but rather may involve an active ER stress-dependent release of BiP from ATF6 (125). Recently, based on the x-ray crystal structure of the yeast Ire1p luminal domain, Credle *et al*. (20) identified a deep, long MHC1-type groove that exists in an Ire1p dimer and proposed that unfolded polypeptides directly bind Ire1p to mediate its dimerization. However, although the x-ray crystal analysis of the human IRE1 luminal domain indicated a similar structure as yeast Ire1p, the MHC1-type groove was not solvent accessible (167). In addition, the luminal domain was shown to form dimers *in vitro* in the absence of added polypeptide (167). These observations bring into question the requirement for peptide binding to the MHC1-type cleft to promote dimerization. It is possible that a combination of BiP binding and peptide binding regulates IRE1 dimerization. Future studies should resolve this issue.

ER STRESS-INDUCED APOPTOSIS

If the UPR-mediated efforts to correct the protein-folding defect fail, apoptosis is activated. Both mitochondria-dependent and -independent cell death pathways trigger apoptosis in response to ER stress (Fig. 3). The ER might actually serve as a site where apoptotic signals are generated and integrated to elicit the death response. Several mechanisms by which apoptotic signals are generated at the ER include PERK/eIF2α-dependent induction of the proapoptotic transcription factor CHOP; Bak/Bax-regulated Ca^{2+} release from the ER; IRE1-mediated activation of ASK1 (apoptosis signal-regulating kinase 1)/JNK (c-Jun amino terminal kinase); and cleavage and activation of procaspase 12 (see Fig. 3).

CHOP-mediated ER stress-induced cell death

Probably the most significant ER stress-induced apoptotic pathway is mediated through CHOP. CHOP/GADD153 (growth arrest and DNA damage 153) is a bZiP transcription factor that is induced through the ATF6 and PERK UPR pathways (80, 115). *Chop*$^{-/-}$ cells are protected from ER stress-induced apoptosis (168), indicating the significance of this pathway. Although the precise mechanism by which CHOP mediates apoptosis is unknown, CHOP activates the transcription of several genes that may potentiate apoptosis. These include *Gadd34*, *Ero1*, *Dr5* (death receptor 5), *Trb3* (Tribbles homolog 3), and carbonic anhydrase VI. *Gadd34* encodes a subunit of protein phosphatase 2C that enhances dephosphorylation of eIF2α and promotes protein synthesis (99). Persistent protein synthesis during periods of ER stress would chronically activate the UPR and initiate cell death pathways. *Ero1* encodes an ER oxidase that increases the oxidizing potential of the ER (82). *Dr5* encodes a cell-surface death receptor that may activate caspase cascades (153). *Trb3* encodes a human orthologue of *Drosophila* tribble, and *Trb3*-knockdown cells are resistant to ER stress-induced apoptosis (100). Carbonic anhydrase VI may decrease the intracellular pH during ER stress (131). CHOP has also been implicated in repressing transcription of the antiapoptotic BCL2 protein, which leads to enhanced oxidant injury and leads to apoptosis (85). However, the ability of CHOP to induce ER stress-associated apoptosis has recently been demonstrated to be dependent on the duration of the stress state. Long-term exposure to a mild stress can lead to adaptation by selective attenuation of CHOP expression mediated by degradation of CHOP mRNA and CHOP protein, whereas expression of downstream targets encoding adaptive functions, such as ER chaperones BiP and GRP94, is persistent because of long-lived mRNAs and proteins (117).

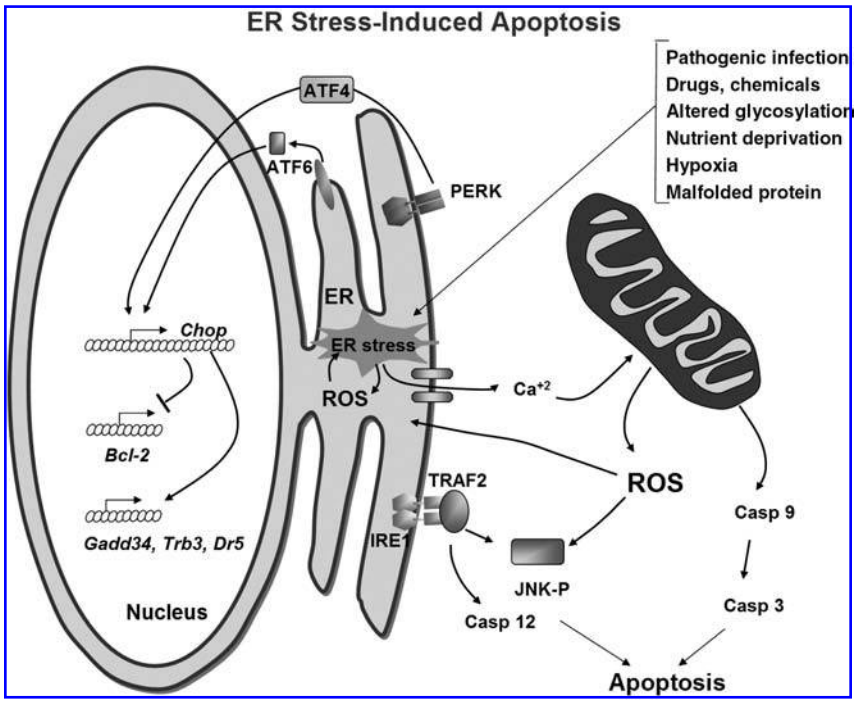

FIG. 3. ER stress–induced programmed cell death. ER stress leads to several redundant pathways for caspase activation that involve mitochondria-dependent and -independent pathways. Activated IRE1 recruits TRAF2 to elicit JNK phosphorylation and activation. Caspase 12 is a murine ER-associated proximal effector in the caspase activation cascade that activates procaspase 9 to cleave procaspase 3, the primary executioner of cell death. A second cell death–signaling pathway activated by ER stress is mediated by transcriptional induction of genes encoding proapoptotic functions. Activation of PERK, ATF6, and possibly IRE1 lead to transcriptional activation of CHOP that induces apoptosis, possibly through regulation of the genes *Gadd34*, *Dr5,* and *Trb3* or by inhibiting expression of the antiapoptotic gene *Bcl2*. ER stress can also lead to ROS production, and this also can occur subsequent to accumulation of unfolded protein in the ER. Mitochondrial ROS can also be generated as a result of ER stress–induced Ca^{2+} release and depolarization of the inner mitochondrial membrane. Thus, oxidative stress in association of unresolved ER stress contributes to multiple pathways of cell death.

BCL2-regulated ER stress-induced cell death

BCL2 family proteins are also fundamentally involved in ER stress-induced apoptosis. During ER stress, proapoptotic members of the BCL2 family are recruited to the ER surface and activate caspase-12. In contrast, the antiapoptotic members prevent this recruitment, although the exact relation between these factors is still unclear. Overexpression of BCL2 family members can prevent ER stress-induced apoptosis. BIM (BCL2-interacting mediator of cell death) translocates from the dynein-rich compartment to the ER membrane and activates caspase-12 in response to ER stress, whereas an antiapoptotic factor, BCL-xL (BCL2-like 1), binds to BIM and inhibits its translocation (89). Consistent with this notion, BIM knockdown cells are resistant to ER stress-induced death.

BH3 domain (Bcl2-homology domain 3)-only containing proapoptotic factors, such as BAX (Bcl2-associated X protein) and BAK (Bcl-2 homologous antagonist/killer), are present at the mitochondrial and ER membranes (123, 169). During ER stress, BAX and BAK oligomerize possibly to permit Ca^{2+} efflux into the cytoplasm. Increased cytosolic Ca^{2+} can activate both mitochondria-dependent and -independent caspase cascades (123, 169). *In vitro* experiments support the idea that the increase in the cytosolic Ca^{2+} concentration (from micromolar to millimolar) activates the calcium-dependent protease m-calpain, which subsequently cleaves and activates the ER-resident procaspase-12 to initiate caspase-dependent apoptosis (92). The Ca^{2+} released from the ER also enters mitochondria to depolarize the inner membrane, promoting cytochrome *c* release and activating APAF-1 (apoptosis protease-activating factor 1)/procaspase-9–regulated apoptosis. Thus, BCL2 family members regulate ER stress-induced apoptotic responses through Ca^{2+} signaling.

The regulation of BH3-only members of the BCL2 family during ER stress is quite complex. BAX and BAK are required for most forms of apoptosis (170). Additional BH3 domain–only family members, PUMA (p53 upregulated modulator of apoptosis) and NOXA (neutrophil NADPH oxidase factor), are upregulated by p53 during ER stress. In addition, $Puma^{-/-}$ cells and $Noxa^{-/-}$ cells are resistant to ER stress-induced apoptosis (73). BAX activation during ER stress is inhibited by the ER-localized antiapoptotic factor BI-1(Bax inhibitor (1). $Bi\text{-}1^{-/-}$ mice are sensitive to ER stress, whereas mice overexpressing BI-1 are resistant (15). BIK (BCL2-interacting killer) is an ER-localized proapoptotic component that enhances the recruitment of BAX and BAK to the ER membrane (83). Finally, BAX and BAK associate with IRE1α and potentiate its signaling during ER stress (46).

IRE-mediated ER stress-induced cell death

In addition to initiating splicing of *XBP1* mRNA, activation of IRE1 signals into the MAP kinase cascade. The IRE1 cytoplasmic domain interacts with the adaptor protein, TRAF2 (tumor necrosis factor receptor–associated factor 2). TRAF2 couples the activation of death receptors at the plasma membrane to activation of Jun kinase (JNK) and stress-activated protein kinase (SAPK) (144). IRE1 and TRAF2 interact with the mitogen-activated protein kinase kinase kinase, ASK1 (apoptosis signal-regulating kinase 1), which subsequently phosphorylates and activates JNK (96). Therefore, ER stress-induced JNK activation and apoptosis are reduced in $Ire1^{-/-}$ and $Ask1^{-/-}$ cells. However, this mechanism cannot account for the observation that $Traf2^{-/-}$ cells are more susceptible to ER stress-induced apoptosis (84). TRAF2 also associates with caspase-12 and reg-

ulates its activation (156). IRE1-TRAF2 activates the transcriptional repressor ATF3 as well, leading to apoptosis (163). Evidence suggests that UPR activation of IRE1 may initiate the extrinsic apoptotic pathway. IRE1 interacts with TNFR1 (tumor necrosis factor receptor 1) to form a complex with TRAF2 and ASK1 to mediate JNK activation. The activation of JNK by ER stress is impaired in *Tnfr1*$^{-/-}$ cells. In addition, the expression of TNF-α is upregulated by the IRE1 pathway during ER stress (51, 154.). ROS can directly activate ASK1 by disrupting an ASK1-thioredoxin (TDX) complex through oxidation of TDX, and thereby lead to activation of JNK, p38 MAP kinase, and cell death (140). The Jun activation domain-binding protein (JAB1) may be a feedback regulator because it can interact with IRE1 and inhibit *XBP1* mRNA splicing and BiP transcription (101). Thus, oxidative stress and ER stress may induce cell death using the same molecular complex consisting of IRE1/TRAF2/ASK1/TDX. Finally, TNF-α can activate the UPR in a ROS-dependent manner (152). These finding indicate that an intricate relation exists between death-receptor signaling, oxidative stress, and activation of the UPR.

Caspase-mediated ER stress-induced cell death

Caspases are well-known proapoptotic components, and caspases 2, 3, 4, 7, 9, and 12 are reported to be involved in ER stress-induced cell death (17, 23, 25, 47). Caspase-12 is associated with the ER membrane and activated by ER stress, possibly by calpain (137). In addition, proapoptotic BCL2 family members BAX and BAK also colocalize to the ER membrane and function to activate apoptosis through caspase-12 (17, 23, 25, 47). Caspase-12 activates caspase-9, which in turn activates caspase-3 (88), leading to cell death. *Caspase-12*$^{-/-}$ mice are resistant to ER stress-induced apoptosis but sensitive to other death stimuli, suggesting that caspase-12 is a regulator specific to ER stress-induced apoptosis (93). However, the involvement of caspase-12 in apoptosis of human cells is still open to question, as the human caspase-12 gene contains several inactivating mutations (32). It is possible that caspase 4 mediates ER stress-induced apoptosis in human cells (47, 66).

OXIDATIVE STRESS

ROS can be produced in all cellular compartments and ultimately results in protein damage (9). Furthermore, the exposure of biologic systems to various conditions of oxidative stress leads to age-dependent increases in the cellular levels of oxidatively modified proteins, lipids, and nucleic acids, and subsequently predisposes to the development of well-recognized, age-related disorders that cause impaired cognitive function and metabolic integrity (133). Accumulating evidence suggests that protein folding and production of ROS are closely linked events; however, this area of ER stress is not well explored. Because oxidative protein folding occurs in the ER and perturbations in protein folding can cause deleterious consequences, alterations in redox status or generation of ROS could directly or indirectly (or both) affect ER homeostasis and protein folding. Elucidating the relation between oxidative stress and oxidative protein folding represents a major area for future research.

PRODUCTION OF REACTIVE OXYGEN SPECIES (ROS)

ROS can be produced both as a result of exposure to toxic agents such as irradiation and environmental pollutants, and also as byproducts of oxygen(using enzymatic reactions, such as the mitochondrial respiratory chain, the arachidonic acid pathway, the cytochrome P450 family, glucose oxidase, amino acid oxidases, xanthine oxidase, NADPH/NADPH oxidases, or NO synthases (11, 31) (Fig. 4). The electron-transport chain produces membrane-impermeable superoxide anion, and the rate is dependent on the mitochondrial inner-membrane potential. In the presence of mitochondrial SOD, superoxide is converted to hydrogen peroxide (H_2O_2) that can diffuse out of mitochondria into the cytoplasm. In the presence of iron, hydrogen peroxide forms the highly reactive hydroxyl radical (OH·) *via* the Fenton reaction. The superoxide anion radical

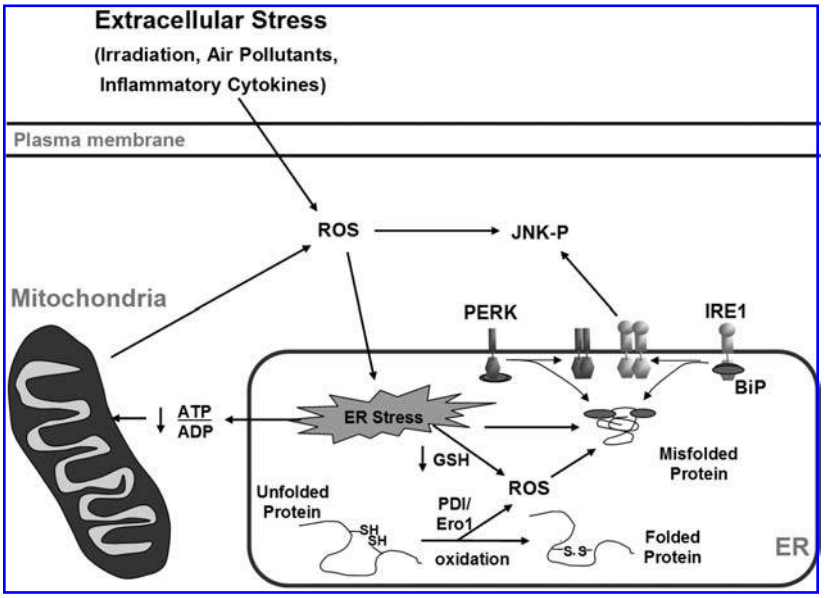

FIG. 4. Pathways of ROS production in the cell. ROS are generated by exposure to multiple stresses such as irradiation and environmental pollutants and also as natural byproducts of mitochondrial respiration. Alterations in redox status or generation of ROS directly or indirectly affect ER homeostasis and protein folding. Oxidative stress can cause accumulation of activated phosphorylated JNK. In addition, ER stress, through IRE1 activation, can activate the protein kinase JNK. Within the ER, disulfide bond formation is dependent on the redox state. The formation of disulfide bonds is driven by PDI that is recycled by ERO1. Oxidized PDI can subsequently further oxidize substrate polypeptides, thereby leading to ROS production.

($O_2^{-\cdot}$). also generates other toxic metabolites such as peroxynitrile ($ONOO^-$), hypochlorous acid (HOCl), and singlet oxygen ($^1O_2$). Under physiologic conditions, ROS accumulation is guarded by numerous endogenous antioxidant defense systems that include both enzymatic and nonenzymatic antioxidant mechanisms that can either scavenge ROS or prevent their formation. The enzymatic antioxidant defense mechanisms are mediated through superoxide dismutase (SOD), glutathione peroxidase (GPX), catalase, and thioredoxin reductase. Vitamins provide a nonenzymatic antioxidant defense (8). Finally, redox homeostasis is contributed by several redox systems, including NAD^+/NADH, $NADP^+$/NADPH, and oxidized glutathione/reduced glutathione (GSSG/GSH).

Both ER stress and oxidative stress, through ROS generation, may increase leak of Ca^{2+} from the ER lumen (6, 38, 79). Increases in cytosolic Ca^{2+} can stimulate mitochondrial ROS production through multiple mechanisms. The mitochondrial electron-transport chain generates ROS as a consequence of increased mitochondrial Ca^{2+} loading. The amount of mitochondrial ROS production primarily reflects the quantity of the ubisemiquinone radical intermediate (QH·), an intermediate in the Q cycle at complex III (27, 132). QH· is increased when complex III is inhibited. Ca^{2+} opens the permeability transition pore to release cytochrome *c* from the inner mitochondrial membrane, thereby blocking the respiratory chain at complex III. In addition, the generation of QH· is increased when the respiratory chain turns over more quickly. Ca^{2+} leak stimulates the TCA cycle, thereby increasing O_2 consumption and ROS generation. Ca^{2+} also stimulates nitric oxide synthase, which generates NO· that inhibits complex IV and can thereby enhance ROS production. Finally, Ca^{2+}-induced permeability transition pore opening may cause leak of GSH from the matrix and, as a consequence, deplete reducing equivalents.

High levels of ROS generation within the mitochondria further increase Ca^{2+} release from the ER. The very close proximity of ER and mitochondria leads to accumulation of Ca^{2+} near mitochondria, thereby increasing mitochondrial ROS production and leading to opening of the permeability transition pore (57). Furthermore, ROS can also feedback to sensitize the Ca^{2+}-release channels at the ER membrane (5, 146). For example, this may occur through ROS or reactive nitrogen species that can oxidize a critical thiol in the ryanodine receptor and cause its inactivation, thereby enhancing Ca^{2+} release from the sarcoplasmic reticulum (28, 151). As the antioxidation potential of the cell diminishes, the vicious cycle of Ca^{2+} release and ROS production becomes more threatening to cell survival.

Oxidative protein folding in the ER

The ER is an organelle in which proper protein folding and disulfide formation of proteins is dependent on the redox status within the lumen of the ER. In contrast to the cytosol, which has a reducing environment, the lumen of the ER is oxidizing with a high ratio of oxidized to reduced glutathione (GSSG/GSH) (145). Glutathione is a tripeptide (L-γ-glutamyl-L-cysteinyl-glycine) that is synthesized in the cytosol. The cell contains up to 10 m*M* GSH that is maintained in a reduced form through a cytosolic NADPH-dependent reaction catalyzed by glutathione reductase. Cellular redox homeostasis is maintained by a dynamic interaction between reduced glutathione (GSH) and protein thiols with ROS. Reduced glutathione GSH serves as a major thio-disulfide redox buffer in cells and the ratio of GSH to GSSG is used as an index of the redox state. Whereas the ratio of reduced glutathione to oxidized glutathione is (>50:1) in the cytoplasm, this ratio is (1:1 to 3:1) in the ER lumen (53). The oxidizing environment of the ER lumen promotes disulfide bond formation. In addition, the greater oxidizing environment of the ER was suggested to contribute to the preferred oxidation and inactivation of ER-resident proteins, such as protein disulfide isomerases, thereby contributing to unfolded protein accumulation (145).

Proteins that transit the secretory pathway frequently require disulfide bond formation for their maturation, stability, and/or function. Mispairing of cysteine residues and formation of inappropriate disulfide bonds prevents proteins from attaining their native conformation and leads to misfolding. Although it is likely that GSH reduces non-native disulfide bonds in misfolded proteins, this is likely not the major pathway used in cells. The ER lumen maintains redox conditions that enable a distinct set of folding catalysts to facilitate the formation and isomerization of disulfide bonds (53). The process of disulfide bond-dependent protein folding is slow because of its dependence on a redox reaction, which requires an electron acceptor. During this folding process, a protein may be oxidized to form disulfide bonds, isomerized to allow polypeptide rearrangement, or reduced to allow unfolding and subsequent degradation (16). The idea that disulfide bond formation is an assisted process *in vivo* is supported by the discovery of DsbA mutants in *Escherichia coli* that display compromised disulfide bond formation (3).

In eukaryotes, oxidative protein folding is catalyzed by a family of ER oxidoreductases, including PDI (protein disulfide isomerase), ERp57, ERp72, PDIR, PDIp, and P5. PDI is a multifunctional protein capable of catalyzing the formation, isomerization, and reduction of disulfide bonds *in vitro* as well as being an essential subunit for the enzymes prolyl 4-hydroxylase and microsomal triacylglycerol transfer protein (30). When chaperone-assisted disulfide bond formation occurs, cysteine residues within the PDI active site [-C-X-X-C-] accept two electrons from the polypeptide chain substrate. This electron transfer results in the oxidation of the substrate and the reduction of the PDI active site. Despite the ability of PDI to enhance the rate of disulfide-linked folding, the mechanisms by which the ER disposes of electrons as a result of the oxidative disulfide bond formation has remained an enigma. A number of different factors have been proposed to maintain the oxidizing environment of the ER, including the preferential secretion of reduced thiols and uptake of oxidized thiols, and a variety of different redox enzymes and small-molecule oxidants. However, no genetic evidence demonstrates that these factors are physiologically important (14, 34, 35). It was believed for many years that the low-molecular-mass thiol glutathione is responsible for oxidizing the PDI active sites. This was contrary to observations in yeast, in which depletion of glutathione did not interfere with disulfide bond formation (22, 58).

Extensive genetic and biochemical studies using the yeast *Saccharomyces cerevisiae* have provided detailed insights into

the mechanisms underlying oxidative protein folding. A genetic screen in yeast identified a conserved ER-membrane–associated protein Ero1p (ER oxidoreductin 1) (35, 109) that plays a role similar to that of the bacterial periplasmic protein DsbB in oxidative folding. The proteins Ero1p and DsbB specifically oxidize a thioredoxin-like protein (PDI in eukaryotes, DsbA in bacteria) that further serves as an intermediate in electron transfer. In both prokaryotes and eukaryotes, molecular oxygen serves as the terminal electron acceptor for disulfide bond formation. Ero1p uses a flavin-dependent reaction to pass electrons directly to molecular oxygen. This reaction has the potential to generate ROS that would contribute to cellular oxidative stress. The role of Ero1p in electron transfer suggests that the activity of Ero1p is tightly coupled with the protein-folding load in the ER (142). In mammals, two ERO1 genes, hERO1-Lα and hERO1-Lβ (10, 105), differ in their tissue distribution and transcriptional regulation. Only ERO1-Lβ is induced by the UPR (105), whereas ERO1-Lα is induced during hypoxia (36). Further studies in yeast, and later in metazoan cells, identified a critical role for flavin adenine dinucleotide (FAD) in oxidative protein folding. As Ero1p is a novel FAD-binding protein (142), the FAD requirement in oxidative folding may reflect its function in Ero1p. These studies suggest that the versatile redox molecule FAD functions in disulfide bond formation in the ER lumen.

One fundamental unanswered question is whether the presence of an unfolded protein in the ER lumen is sufficient to activate oxidative stress (see Fig. 4). It has been estimated that ~25% of the ROS generated in a cell may result from formation of disulfide bonds in the ER during oxidative protein folding (see Fig. 4) (142). Two mechanisms have been proposed for how disulfide bond formation generates ROS. During formation of disulfide bonds, ROS are a byproduct formed as ERO1 and PDI act in concert to transfer electrons from thiol groups in proteins to molecular oxygen. Alternatively, protein misfolding may be associated with inappropriate pairing and bonding of cysteine residues. In this case, ROS may be formed as a consequence of the glutathione depletion that occurs as glutathione reduces unstable and improper disulfide bonds. The consumption of GSH would return thiols involved in non-native disulfide bonds to their reduced form so they may again interact with ERO1/PDI1 to be reoxidized. This would generate a futile cycle of disulfide bond formation and breakage, in which each cycle would generate ROS and consume GSH (Fig. 5). As a consequence, it is expected that proteins that have multiple disulfide bonds may be more prone to generating oxidative stress. In addition, it will be important to determine whether misfolding of a protein that has no disulfide bonds can generate ROS.

Potential mechanisms exist by which unfolded protein may generate ROS, independent of disulfide bond formation. First, unfolded protein accumulation in the ER may elicit Ca^{2+} leak into the cytosol to increase ROS production in mitochondria. Alternatively, because both protein folding and refolding in the ER lumen are highly energy-dependent processes, ATP depletion as a consequence of protein misfolding could stimulate mitochondrial oxidative phosphorylation to increase ATP production, and consequently to increase ROS production.

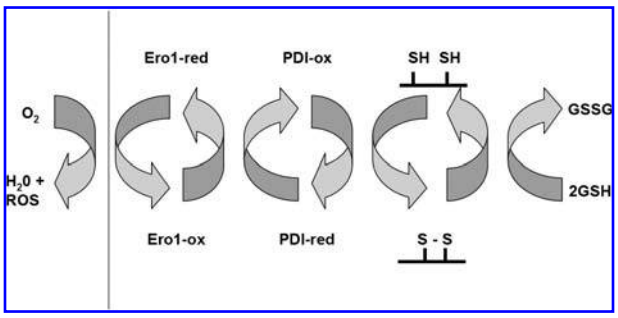

FIG. 5. Oxidative protein folding in ER. The trafficking of reducing equivalents within the lumen of the ER is depicted. The formation of disulfide bonds is catalyzed by PDI-mediated oxidation of substrate polypeptides. ERO1 subsequently reduces PDI so it can recycle to catalyze protein folding. Reduced ERO1 transfers electrons to molecular O_2, thereby leading to ROS production. Reduced glutathione (GSH) may also assist in reducing nonnative disulfide bonds in misfolded proteins, resulting in the production of oxidized glutathione (GSSG).

ER STRESS AND OXIDATIVE STRESS IN DISEASE

The UPR has evolved as a series of signaling pathways to ensure that the rate of protein synthesis, the capacity for chaperone-assisted protein folding, and the ERAD potential are coupled with environmental, genetic, and nutritional influences to prevent the accumulation of unfolded protein in the ER lumen. Increasing evidence suggests that protein misfolding in the ER lumen and alterations in UPR signaling play important roles in the etiology of numerous disease states, including metabolic disease, atherosclerosis, and neurodegenerative disease.

ER stress and oxidative stress in metabolic disease

The development of type 2 diabetes is associated with a combination of insulin resistance in fat, muscle, and liver and a failure of pancreatic β cells to compensate adequately to increase insulin production (119, 128). Evidence indicates that oxidative damage is associated with development of insulin resistance and the diabetic state (50, 60, 113). Is it possible that both oxidative stress and ER stress contribute to the progression from insulin resistance to diabetes?

Insulin signaling is very sensitive to alterations in ER homeostasis and redox status. ER stress and oxidative stress, as well as inflammatory cytokines and free fatty acids, inhibit insulin signaling through activation of the protein kinase JNK. JNK phosphorylation of IRS-1 on Ser307 reduces insulin receptor–stimulated Tyr phosphorylation and insulin signaling (60). Induction of ER stress may suppress insulin-receptor signaling *via* IRE1α-dependent activation of the JNK pathway. Indeed, suppressing the JNK pathway can ameliorate insulin resistance (62), possibly by counterbalancing the deleterious effects of ER stress, oxidative stress, free fatty acids, and proinflammatory cytokines. The role of ER stress in insulin signaling was also suggested by the finding that ectopic expression

of the molecular chaperone ORP150/GRP170 in hepatocytes improved insulin sensitivity (94). It is possible that elevated levels of ORP150 expression improve the protein-folding capacity of the ER and reduce UPR signaling. The ability of ER stress signaling to cause insulin resistance was also suggested by recent observations showing that treatment of mice with chemical chaperones that can improve protein folding in the ER, reduce ER stress, and reduce UPR signaling can increase insulin sensitivity (104). Alternatively, some observations suggest that ER stress and UPR signaling through IRE1 can actually improve insulin sensitivity. Heterozygous *Xbp1+/−* mice developed insulin resistance compared with control mice when fed a high-fat diet (104). It is possible that reduced XBP1 signaling impairs the ER protein-folding capacity, thereby activating the UPR, which may lead to JNK activation. Therefore, ER stress signaling through IRE1-mediated XBP1 mRNA splicing may increase the ER protein-folding capacity to improve insulin signaling, whereas IRE1-mediated JNK activation could cause insulin resistance. The sum of these observations indicates that a link exists between insulin resistance and ER stress, although the precise relation and mechanism(s) remain to be elucidated.

The requirement for the UPR in β-cell function was first suggested by the identification of *PERK* as the gene defective in the human disease, Wolcott–Rallison syndrome (WRS) (24). Individuals with WRS and *Perk*$^{-/-}$ mice develop β-cell apoptosis with early-onset insulin-dependent diabetes (42). In addition, mice with homozygous Ser51Ala mutation at the PERK phosphorylation site in eIF2α display even greater β-cell loss that appears *in utero* (121). Finally, although mice with heterozygous Ser51Ala mutation in eIF2α do not display a detectable phenotype, on feeding a high-fat diet, they develop insulin resistance and a failure in the β cells to produce insulin, typical of type 2 diabetes. The insulin secretion defect in the high-fat–fed heterozygous Ser51Ala eIF2α mutant mice was due to an increased rate of glucose-stimulated proinsulin translation, which overwhelmed the protein-folding machinery of the ER and led to (a) a distended ER compartment, (b) prolonged association of proinsulin with the ER chaperone BiP, (c) reduced processing of proinsulin to insulin, and (d) reduced insulin granule biogenesis (120). Thus, regulation of translation initiation through eIF2α phosphorylation is required for ER stress signaling to prevent β-cell dysfunction when the demand for insulin is increased because of an HF diet and insulin resistance. These findings indicate that β cells display a unique requirement for PERK/eIF2α-regulated translation.

Several mechanisms may explain why β cells uniquely require the PERK/eIF2α pathway. First, β cells may require PERK/eIF2α signaling because they are sensitive to physiologic fluctuations in blood glucose. In β cells, the generation of ATP fluctuates with blood glucose concentrations because glycolysis is controlled by glucokinase, which has a low affinity for glucose. Periodic decreases in blood glucose levels reduce the ATP/ADP ratio and would compromise protein folding in the ER so that UPR may be frequently activated. Through this mechanism, PERK/eIF2α signaling would be required in β cells to couple protein synthesis with energy available for protein-folding reactions in the ER lumen. Alternatively, glucose stimulates insulin transcription, translation, and secretion. PERK phosphorylation of eIF2α may be required for β cells to attenuate protein synthesis so that insulin production does not exceed the protein-folding capacity of the ER. Results from the high-fat–fed heterozygous Ser51Ala eIF2α mutant mice would support this hypothesis (120). Finally, as the PERK/eIF2α pathway is known to reduce oxidative stress, it is possible that β cells require PERK/eIF2α to minimize oxidative stress (81). Two mechanisms have been proposed to account for the role of the PERK/eIF2α in limiting oxidative stress. First, the PERK/eIF2α pathway can prevent oxidative stress through inhibition of translation initiation when protein folding in the ER lumen is disturbed (82). Alternatively, the PERK/eIF2α/ATF4 pathway induces expression of antioxidative stress-response genes (42, 82). It is likely that both mechanisms contribute to the protective role for PERK/eIF2α in limiting ROS accumulation. Increasing evidence suggests that oxidative stress contributes to the β-cell failure in diabetes (60, 113). β cells express low levels of catalase and glutathione peroxidase, two enzymes that protect from ROS (130). Therefore, oxidative stress would preferentially perturb β-cell function because of their reduced capacity to neutralize ROS. Further studies are required to elucidate why the PERK/eIF2α pathway is essential for β-cell function and survival.

Numerous reports indicate that antioxidants can ameliorate the diabetic state (61, 138). Antioxidants can preserve glucose-stimulated insulin secretion, prevent apoptosis, and expand β-cell mass, without significantly affecting cell proliferation. For example, treatment of Zucker diabetic fatty (ZDF) rats with the antioxidants *N*-acetyl-L-cysteine or aminoguanidine prevented hyperglycemia, improved insulin secretion, and increased PDX1 binding to the insulin promoter (138). Although the mechanism by which antioxidants improve β-cell function is not known, evidence supports the idea that oxidative stress activates JNK. An oxidizing environment causes oxidation and inhibition of JNK-inactivating phosphatases by converting their catalytic cysteine to sulfenic acid (59). As a consequence, activated JNK accumulates and can phosphorylate PDX1 to suppress PDX1 binding to specific promoters by preventing its translocation to the nucleus (65). Significantly, JNK inhibition protects β cells from oxidative stress, prevents apoptosis, improves islet graft function (98), and also improves systemic insulin responsiveness. The sum of these findings support the notion that oxidative stress and ER stress play central roles in the pathogenesis of type 2 diabetes and that targeted therapy to intervene to prevent JNK activation may reduce progression of insulin resistance to diabetes.

ER stress and oxidative stress in neurodegenerative disease

Neurodegenerative diseases, such as Alzheimer disease (AD) and Parkinson disease (PD), represent a large class of conformational diseases associated with accumulation of abnormal protein aggregates in and around affected neurons. Oxidative stress and protein misfolding play critical roles in the pathogenesis of these neurodegenerative diseases (33) that are characterized by fibrillar aggregates composed of misfolded proteins (124). At the cellular level, neuronal death or apoptosis may be mediated by oxidative stress and ER stress or both. Upregulation of ER stress markers has been demonstrated in postmortem brain tissues and cell-culture models of many neu-

rodegenerative disorders, including PD, AD, amyotropic lateral sclerosis (ALS), and expanded polyglutamine diseases such as Huntington disease and spinocerebellar ataxias (77). Recent studies indicate that oligomeric forms of polypeptides predisposed to β-sheet polymerization and fibril formation may be the toxic forms that cause neuronal death. The impact of these oligomeric, potentially toxic species on ER function and generation of ROS is presently not understood.

In vitro studies suggest that β-sheet polymerized aggregates can inhibit the proteasome and ERAD. For example, in the disease Machado-Joseph syndrome, the polyglutamine repeats present in spinocerebrocellular atrophy protein (SCA3) form cytosolic aggregates that can inhibit the proteasome. Proteasome inhibition in the cytosol can interfere with ERAD to elicit UPR activation, caspase 12 activation, and apoptosis (4, 96). Deletion of the ER stress-induced proapoptotic transcription factor CHOP preserved neuronal function, suggesting the importance of UPR signaling in this model.

PD is the second most common neurodegenerative disease and is characterized by a loss of dopaminergic neurons. Analyses of familial PD revealed involvement of three genes encoding α-synuclein, Parkin, and ubiquitin C-terminal esterase L1 (UCH-L1). α-Synuclein is a cytoplasmic protein that forms aggregates, called Lewy bodies, which are characteristic of PD. Although the link between α-synuclein and ER stress is unclear, Parkin is a ubiquitin-protein ligase (E3) involved in ERAD (127). One of the substrates of ERAD ubiquitinated by Parkin is the Pael receptor, a homologue of endothelin receptor type B (54). Interestingly, expression of Parkin is induced by ER stress, and neuronal cells overexpressing Parkin are resistant to ER stress (55). UCH-L1 is an abundant protein in neurons, stabilizes a monomeric ubiquitin to ubiquitinate unfolded proteins, and might be involved in ERAD (78, 102, 118). These findings strongly suggest the involvement of ER stress in PD. In addition, several additional reports support the link between ER stress and PD. First, PD mimetics, such as 6-hydroxydopamine, specifically induce ER stress in neuronal cells (49). Second, expression of ER chaperones such as PDI is upregulated in the brain of PD patients, and PDI is accumulated in Lewy bodies (18). The identification of PDI family member PDIp in experimental PD and Lewy bodies suggests that oxidative protein folding in the ER may be perturbed in PD.

In humans, mutations in SIL1, which encodes an adenine nucleotide exchange factor for BiP, cause Marinesco–Sjögren syndrome, a rare disease associated with cerebellar ataxia, progressive myopathy, and cataracts (1). In mice homozygous for a spontaneously occurring mutation in the *Sil1* transcript, cerebellar Purkinje cell degeneration and subsequent ataxia occur (166). Analysis of *Sil1* mutant mice demonstrated that affected Purkinje cells have ubiquitinated nuclear- and ER-associated protein aggregates and also display upregulation of several ER stress markers (BiP, CHOP, and ORP150) (166). It seems likely that the protein chaperone BiP uses an ATP/ADP exchange that is essential to preserve ER function and to prevent activation of the UPR. A reduced efficiency of ATP-dependent BiP-mediated chaperone function may predispose to unfolded protein accumulation in the ER, activate the UPR, and contribute to Purkinje cell degeneration.

Oxidative stress is implicated in the pathogenesis of neurodegenerative diseases. A group of neurodegenerative diseases including AD is characterized pathologically by the deposition of intracellular aggregates containing abnormally phosphorylated forms of the microtubule-binding protein Tau (71). Using a *Drosophila* model relevant to human neurodegenerative diseases, including AD, it was demonstrated that oxidative stress plays a casual role in neurotoxicity and promotes Tau-phosphorylation. In this model, activation of the JNK pathway correlated with the degree of tau-induced neurodegeneration (26). Although oxidative stress and ER stress have been linked to neurodegenerative diseases, at this point, it is not possible to conclude that these processes are the primary cause of neuron death. However, it is possible that these stresses modify the progression and severity of these complex diseases.

Nitric oxide (NO) is a second messenger for signaling pathways that regulate a variety of physiologic processes. In the brain, NO is implicated in neurotransmission, neuromodulation, and synaptic plasticity. However, excessive generation of NO and NO-derived reactive nitrogen species is implicated in the pathogenesis of neurodegenerative disorders, including AD and PD (12). Studies now indicate that ER stress and apoptosis are critical features underlying these disorders (106). Uehara and co-workers (143) elegantly demonstrated that NO-mediated *S*-nitrosylation of protein disulfide isomerase (PDI) inhibits PDI function, leads to dysregulated protein folding within the ER, elicits ER stress, and initiates neuronal cell death. A causal role for this sequence of events in neurodegenerative disease was supported by the demonstration that PDI is S-nitrosylated in the brains of patients with PD or AD, but not in normal brains. Thus, these findings provide additional evidence of a role for dysregulated protein S-nitrosylation (oxidative stress) in neurodegenerative disease and indicate that ER dysfunction may serve as a critical common factor that couples NO-induced cellular stress to neurodegeneration.

ER stress and oxidative stress in hyperhomocysteinemia and atherosclerosis

Elevated plasma levels of homocysteine (Hcy), a sulfur-containing amino acid, are linked to the development of ischemic heart disease, stroke, and peripheral vascular disease. However, it is not known whether Hcy is a primary cause of atherosclerosis and thrombosis. Hcy may mediate vascular toxicity through dysregulation of cholesterol and triglyceride biosynthesis. Hyperhomocysteinemia activates lipogenic signaling *via* the sterol-regulated element-binding proteins (SREBPs), leading to intracellular accumulation of cholesterol (149). Surprisingly, ER stress appears to contribute to the activation of SREBP by homocysteine. Livers of homocysteine-fed mice contain elevated levels of ER chaperones. In addition, overexpression of BiP prevented SREBP induction in response to homocysteine (149).

Under normal circumstances, Hcy is converted to cysteine and partly remethylated to methionine by vitamin B_{12} and folate. When normal metabolism is disturbed because of deficiency of cystathionine-β synthase (CBS), which requires vitamin B_6 for activation, Hcy accumulates in blood and results in severe hyperhomocysteinemia. CBS condenses homocysteine and serine to form cystathionine. The harmful effects of hyperhomocysteinemia may be mediated through several processes. First, a decrease in cysteine may cause disease, because

of reduced synthesis of glutathione (antioxidant). Thrombotic and cardiovascular diseases may also be encountered. Second, ROS generated during oxidation of Hcy to homocystine and disulfides may oxidize membrane lipids and proteins. Third, Hcy can react with thiols within proteins and form disulfides (thiolation) to interfere with protein folding, structure, and function. Finally, Hcy can be converted to highly reactive thiolactone that can react with proteins forming —NH—CO— adducts, thus affecting protein structure and function. In cultured vascular endothelial cells, Hcy induces protein misfolding in the ER by interfering with disulfide bond formation (72) and activates the UPR to induce expression of several ER stress-response proteins, such as BiP, GRP94, CHOP, and HERP (2, 52, 103, 162). Hcy can also trigger apoptosis by a signaling pathway that requires intact IRE1 (162). These studies support the notion that Hcy can disrupt ER homoeostasis to cause UPR induction (52, 103, 162). This is consistent with the observed activation of UPR markers in livers of normal or $Cbs^{+/-}$ mice in response to hyperhomocysteinemia (48).

Atherosclerosis is caused by the abnormal deposition of cholesterol in the coronary arteries. Cholesterol accumulation in macrophages plays a critical role in the progression of atherosclerosis. Macrophages have multiple mechanisms to prevent excess cholesterol accumulation, including an increase in cholesterol esterification, induction of cellular cholesterol efflux, and the repression of lipoprotein receptor and cholesterol biosynthetic enzymes (135, 136). On formation of an initial atherosclerotic lesion, these mechanisms are dysregulated, thereby leading to the characteristic appearance of foam cells within the vessel intima. The macrophage-derived foam cells take up oxidized lipoprotein particles and become laden with cholesterol. The cholesterol is stored as esters within large lipid vesicles, producing a foamy appearance, and hence their name. Overload of cholesterol in macrophages elicits apoptosis. Excess cholesterol must accumulate in specific pools within the cell to elicit cytotoxicity. Intracellular cholesterol is known to traffic to the plasma membrane, mitochondria, and the ER. Although the ER membrane has low levels of free cholesterol, it is particularly sensitive to cholesterol loading. Recent findings suggest that free cholesterol requires trafficking to the ER to produce its toxic effects (29). This trafficking results in activation of UPR signaling and caspase activation, and ultimately in macrophage cell death/apoptosis. Macrophages from $Perk^{-/-}$ mice are hypersensitive to cholesterol-induced cell death, whereas macrophages from $Chop^{-/-}$ mice are highly protected. Recent findings also suggest that defective insulin signaling and reduced Akt activity impair the ability of macrophages to deal with ER stress-induced apoptosis within atherosclerotic plaques (39). This mechanism may contribute to the association between insulin resistance in metabolic syndrome and atherogenesis (108). These findings suggest that the UPR plays an important role in the progression of the atherogenic disease process (29). In addition, free cholesterol loading of macrophages increases levels of cell-surface Fas ligand and activated proapoptotic Bax protein, and increases mitochondrial-dependent apoptosis. Although both the Fas death pathway and the mitochondrial cell-death pathway may contribute to macrophage apoptosis, accumulating evidence suggests that depletion of calcium stores in the ER and subsequent activation of the UPR is the dominant driving force in cholesterol-induced macrophage death (135, 136). Finally, ER stress caused by free cholesterol loading in macrophages promotes chemokine secretion, and this may contribute to the formation of vulnerable atherosclerotic lesions. These lesions lead to an inflammatory condition, with further infiltration of macrophages and lymphocytes from the blood and subsequent release of hydrolytic enzymes, cytokines, chemokines, and growth factors that can inflict more damage and eventually lead to focal necrosis (75, 116).

CONCLUDING REMARKS

Over the past few decades, tremendous progress has been made in understanding the mechanisms underlying the cause of ER stress and oxidative stress. Although it is known that both stress processes are intimately interrelated, the mechanisms linking ER stress to oxidative stress are not understood. Not only are future studies required to understand how these stresses affect protein folding, misfolding, and secretion *in vivo,* but studies also are required to elucidate how protein misfolding may cause oxidative stress to cause apoptosis. Further studies in this important area will aid in comprehending how interactions between ER stress and oxidative stress are integrated into other cellular signaling pathways. A greater understanding of the complex interrelation between protein misfolding and oxidative stress may lead to the development of general pharmacologic agents, such as chemical chaperones to improve protein folding and/or antioxidants to reduce oxidative stress, for the treatment of human disease. A coherent mechanistic understanding of the mechanisms and pathways that signal ER stress and oxidative stress responses should contribute to the development of more selective and specific-acting therapeutic agents targeted for diseases associated with ER/oxidative stress pathologies.

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ABBREVIATIONS

ER, endoplasmic reticulum; ERAD, endoplasmic reticulum–associated degradation; GSH, reduced glutathione; GSSG, oxidized glutathione; Hcy, homocysteine; PDI, protein disulfide isomerase; ROS, reactive oxygen species; SAP, serum amyloid P component; SOD, superoxide dismutase; UPR, unfolded protein response.

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