ANTIOXIDANTS & REDOX SIGNALING
Volume 21, Number 3, 2014

DOI: 10.1089/ars.2014.5851

Discoveries

FORUM REVIEW ARTICLE

Endoplasmic Reticulum Stress and Oxidative Stress in Cell Fate Decision and Human Disease

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Abstract

Significance: The endoplasmic reticulum (ER) is a specialized organelle for the folding and trafficking of proteins, which is highly sensitive to changes in intracellular homeostasis and extracellular stimuli. Alterations in the protein-folding environment cause accumulation of misfolded proteins in the ER that profoundly affect a variety of cellular signaling processes, including reduction–oxidation (redox) homeostasis, energy production, inflammation, differentiation, and apoptosis. The unfolded protein response (UPR) is a collection of adaptive signaling pathways that evolved to resolve protein misfolding and restore an efficient protein-folding environment. ***Recent Advances:*** Production of reactive oxygen species (ROS) has been linked to ER stress and the UPR. ROS play a critical role in many cellular processes and can be produced in the cytosol and several organelles, including the ER and mitochondria. Studies suggest that altered redox homeostasis in the ER is sufficient to cause ER stress, which could, in turn, induce the production of ROS in the ER and mitochondria. ***Critical Issues:*** Although ER stress and oxidative stress coexist in many pathologic states, whether and how these stresses interact is unknown. It is also unclear how changes in the protein-folding environment in the ER cause oxidative stress. In addition, how ROS production and protein misfolding commit the cell to an apoptotic death and contribute to various degenerative diseases is unknown. ***Future Directions:*** A greater fundamental understanding of the mechanisms that preserve protein folding homeostasis and redox status will provide new information toward the development of novel therapeutics for many human diseases. *Antioxid. Redox Signal.* 21, 396–413.

Introduction

LIFE CANNOT EXIST without proteins, the macromolecules that need to acquire specific three-dimensional structures for function. The most error-prone step in gene expression is protein folding. In eukaryotic cells, the endoplasmic reticulum (ER) is a membrane-bound organelle that is specialized for the folding and post-translational maturation of almost all membrane proteins and most secreted proteins. In addition, the ER plays important roles in lipid biosynthesis, detoxification, energy metabolism, as well as homeostasis of intracellular Ca^{2+} and reduction–oxidation (redox) balance. Protein folding and maturation in the ER are subject to ''quality control,'' an essential surveillance mechanism that ensures only properly folded and modified proteins exit the ER and traffic to other intracellular organelles/vesicles and the plasma membrane. Protein folding in the ER is highly sensitive to extracellular stimuli and changes in intracellular homeostasis, including ER Ca^{2+}, glycosylation, energy stores, redox state, metabolic and inflammatory challenges, increased ER-associated mRNA translation, and expression of proteins that are prone to misfolding. The accumulation of unfolded and misfolded proteins in the ER lumen, a condition called ER stress, activates the unfolded protein response (UPR) to resolve this protein-folding defect. The UPR enhances the ER capacity for protein folding and modification, attenuates global mRNA translation, and disposes terminally misfolded proteins by ER-associated protein degradation (ERAD) and autophagy. However, when ER stress is too severe or chronic, or the UPR is chemically or genetically impaired and unable to mitigate the protein-folding defects, pro-apoptotic signaling pathways are activated in the cell (20, 75, 161).

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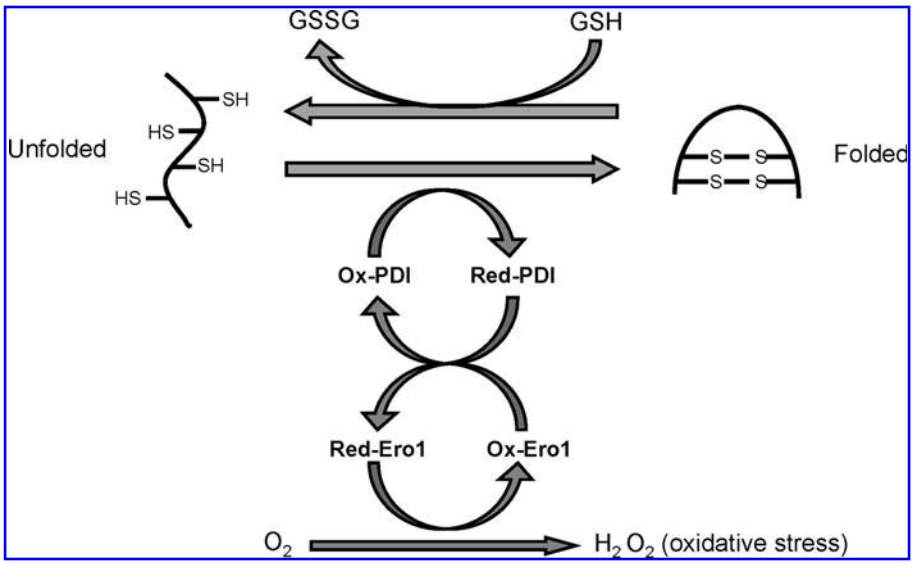

FIG. 1. Oxidative protein folding in the ER. Oxidative protein folding of eukaryotic cells occurs in the ER, which is mediated by ER protein PDI and ERO1. ROS are generated as a byproduct of oxidative protein folding. Improperly paired disulfide bonds formed during protein folding can be reduced at the expense of glutathione, an essential antioxidant in the ER. See Introduction section for details. ER, endoplasmic reticulum; ROS, reactive oxygen species.

The ER redox state is closely linked to ER protein-folding homeostasis. Disulfide bond formation in the ER lumen is highly sensitive to altered redox balance, where both reducing and oxidizing reagents disrupt protein folding and cause ER stress (104). During oxidative protein folding in the ER, the thiol groups on cysteines of substrate peptides are oxidized and form disulfide bonds with hydrogen peroxide (H_2O_2) generated as a byproduct (Fig. 1). In a stressed ER, dysregulated disulfide bond formation and breakage may result in reactive oxygen species (ROS) accumulation and cause oxidative stress. In addition, some UPR components such as the C/EBP homologous protein CHOP can contribute to oxidative stress. Meanwhile, ER stress can cause mitochondrial dysfunction and increase mitochondrial ROS production. In many ER stress-related *in vitro* and *in vivo* models, ER stress and oxidative stress accentuate each other in a positive feed-forward loop, which interferes with cell function and activates pro-apoptotic signaling (104). Basic and clinical studies in the last decade suggest that ROS crucially impacts the pathogenesis of many human diseases, including metabolic disease, neurodegenerative disease, inflammatory disease, neoplasms, as well as pathologies in the heart, kidney, and lung (6, 20, 178). In this review, we summarize our knowledge regarding the generation of ER stress and oxidative stress in the cell and the signaling pathways activated in response to these two cellular stresses. We also highlight how cross-talk between ER stress and oxidative stress causes multiple human pathologies, which suggest and encourage the development of novel therapeutic applications in the future.

ER Stress and the UPR

In metazoans, three protein sensors on the ER membrane initiate the UPR: inositol-requiring kinase 1 (IRE1), pancreatic ER eukaryotic translation initiation factor 2 (eIF2α) kinase (PERK), and activating transcription factor 6 (ATF6). Binding of the ER luminal protein chaperone BiP/GRP78 to the UPR sensors prevents their signaling (Fig. 2). Based on the competition-binding model of UPR initiation, unfolded/misfolded proteins in the ER lumen compete with the ER stress sensors for binding to the most abundant protein chaperone in the ER, BiP/GRP78. Accumulation of unfolded/misfolded proteins in the ER activates the three UPR transducers as a consequence of BiP from their luminal domains (20, 75).

IRE1, a type I transmembrane protein, is the most conserved ER stress sensor with both an Ser/Thr kinase domain and an endoribonuclease (RNase) domain in its cytosolic portion. On release from BiP, the luminal domain of IRE1α dimerizes in the plane of the ER membrane, leading to *trans*-autophosphorylation and activation of its kinase and RNase activities. Activated IRE1α cleaves and removes a 26-base intron from an mRNA and produces a translational frameshift that is translated to produce the active CREB/ATF basic leucine zipper-containing (bZIP) transcription factor X-box-binding protein 1 (XBP1). XBP1 is an essential transcriptional activator of many UPR genes that control ER protein folding, intracellular trafficking, ERAD, phospholipid biosynthesis, and ER membrane expansion. In addition to the cleavage of *Xbp1* mRNA, the RNase domain of IRE1 also degrades a subset of ER-localized mRNAs during ER stress, a process called regulated IRE1-dependent decay of mRNA (RIDD). Recently, IRE1 was shown to cleave several microRNAs, and this is linked to the activation of inflammatory and apoptotic signaling (96, 169). In addition, the kinase domain of IRE1α also integrates ER stress with pro-inflammatory responses through direct binding with adaptor protein tumor necrosis factor alpha (TNFα) receptor-associated factor 2 (TRAF2) and subsequent activation of the nuclear factor-kappaB (NF-κB) and c-Jun N-terminal kinase (JNK) pathways (20, 75, 176). In mammals, there are two IRE1 genes, *IRE1*α and *IRE1*β. Deletion studies demonstrated that the IRE1α-XBP1 pathway is necessary for murine embryonic development and critical for the differentiation, function, and survival of many cell types which secrete large amounts of protein. *IRE1*α is ubiquitously expressed, whereas *IRE1*β is selectively expressed in intestinal and respiratory epithelial cells (111). Mice deleted of *Ire1*β display increased sensitivity to experimentally induced colitis and disrupted mucin secretion in the colon and respiratory tract (9, 111, 166).

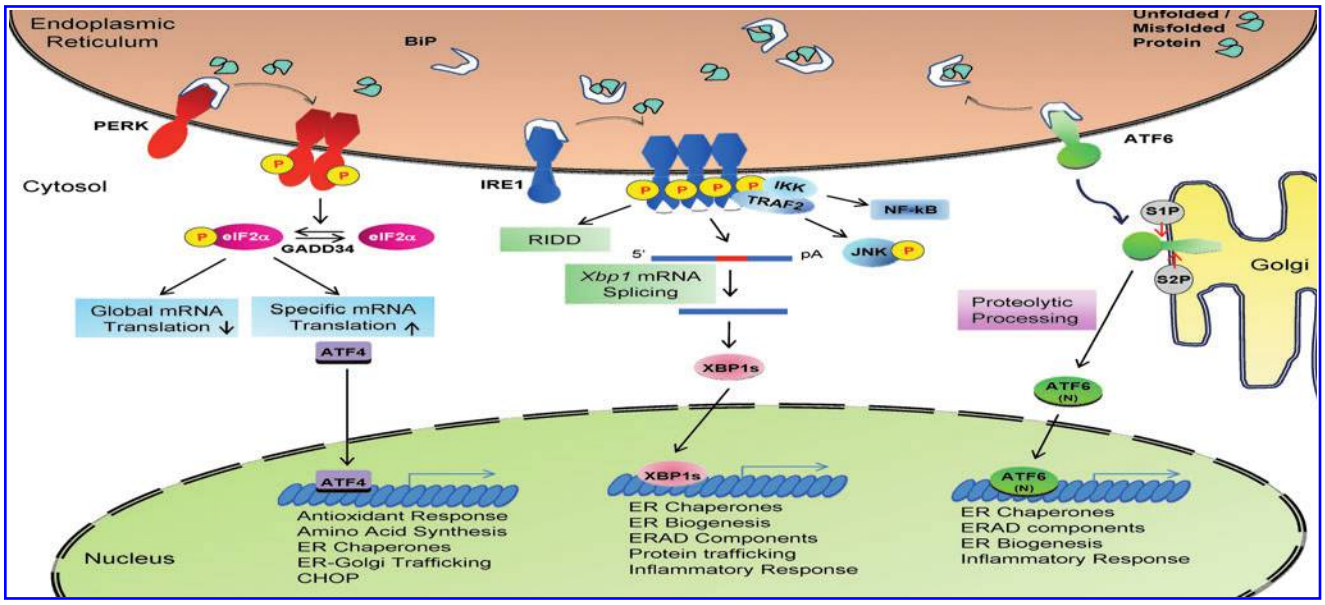

FIG. 2. The mammalian UPR. In most mammalian cells, three UPR branches were identified: the PERK-eIF2α-ATF4-CHOP pathway, the IRE1α-XBP1 pathway, and the ATF6 pathway. The functions of the three pathways overlap and are redundant in many cell types. However, complete ablation of any of the three branches causes embryonic/perinatal death in mice, suggesting their unique and essential role at the physiological level. See ''ER Stress and the UPR'' section for details. ATF6, activating transcription factor 6; PERK, pancreatic ER eIF2α kinase; UPR, unfolded protein response.

PERK is a type I transmembrane protein with a cytosolic Ser/Thr kinase domain. During ER stress, PERK is activated in a similar manner as IRE1. Activated PERK phosphorylates Ser51 on the α subunit of eIF2α, which attenuates global protein synthesis, thereby reducing the ER protein-folding burden. In mammalian cells, three cytosolic kinases also phosphorylate eIF2α at Ser51, which are activated by different stress conditions: general control nonrepressed 2 kinase (GCN2) activated by amino-acid deprivation, dsRNA-activated protein kinase (PKR) activated by dsRNA, and heme-regulated eIF2α kinase (HRI) activated by heme depletion and oxidative stress. The concerted action of these four eIF2α kinases, all of which are encoded by single genes, regulate mRNA translation initiation in a process termed the integrated stress response (142). eIF2α phosphorylation is conserved in all nucleated cells from protozoa to plants and humans. Therefore, it was surprising that mice with whole-body knock-in mutation of a Ser51Ala non-phosphorylatable eIF2α develop normally, although they die at 1 day after birth, due to hypoglycemia associated with defective gluconeogenesis in the liver (147). This observation was the first that linked stress response signaling and protein synthesis to metabolic control in metazoans. Typically, eIF2α phosphorylation-mediated translation attenuation is transient due to the activities of GADD34 and CReP, two regulatory targeting subunits of protein phosphatase PPP1, which directs eIF2α dephosphorylation to restore protein synthesis. In addition to global translational attenuation, phosphorylated eIF2α is required for selective translation of a subset of mRNAs, including the activating transcription factor 4 (ATF4), a potent bZIP transcription factor that activates genes encoding transcription factors, ER chaperones and trafficking machinery, amino-acid biosynthesis, antioxidative stress responses, and autophagy (68). Among the downstream targets of ATF4 is CHOP/GADD153, a bZIP transcription factor that plays a crucial role in ER stress-induced apoptosis (20, 142).

The ER stress sensor ATF6 is a type II transmembrane protein harboring a CREB/ATF bZIP domain at its N-terminus. During ER stress, release of the chaperone BiP from the luminal domain permits trafficking of ATF6 to the Golgi apparatus, where it is sequentially cleaved by site-1 protease (S1P) and S2P at the transmembrane site to release a cytosolic fragment that migrates to the nucleus to activate gene transcription. S1P and S2P are the same processing enzymes which are responsible for cleavage of sterol-regulatory element-binding proteins that control lipid and cholesterol biosynthesis (185). There are two ATF6 genes in mammals, *ATF6α* and *ATF6β*. Where mice without ATF6α or ATF6β survive under normal conditions, double deletion of *Atf6α* and *Atf6β* causes very early embryonic lethality although the mechanism is unknown. The released ATF6α cytosolic fragment migrates to the nucleus and transactivates numerous ER chaperone genes, including *BiP*, *Grp94*, and $P58^{IPK}$, as well as some ERAD components. ATF6α is required to optimize protein folding, maturation, and secretion in response ER stress, and, as a consequence, $Atf6\alpha^{-/-}$ cells cannot survive chronic ER stress. Genes that require ATF6β for transcription have yet to be defined. In addition to ATF6, several other transcription factors that are activated by regulated intramembrane proteolysis exist in mice, including CREBH, Luman, and OASIS, which serve diverse and important biological functions in different cell types (20, 176).

Production of ROS in the Cell

In eukaryotic cells, ROS can be generated in multiple organelles, including the ER and mitochondria as a byproduct of oxidative protein folding, mitochondrial respiration, and detoxification. As a highly regulated process, ROS

production profoundly affects cell function and homeostasis in all organisms.

Oxidative protein folding and production of ROS

In the lumen of the ER, correct folding of most membrane and secretory proteins requires the generation of disulfide bonds between cysteine residues to stabilize tertiary and quaternary structures. Disulfide bond formation is a reversible process that is achieved by a thiol-disulfide exchange reaction (31). In eukaryotic cells, oxidative protein folding is catalyzed by a number of ER oxidoreductases, including protein disulfide isomerases (PDI), ERp72, and ERp57. In addition, ER protein folding is kinetically and thermodynamically regulated by the redox state of the microenvironment, which is under the control of redox buffers, including thiol-disulfide pairs and reduced/oxidized pyridine nucleotides in the ER lumen (167). Glutathione (GSH), the most abundant non-protein thiol in eukaryotic cells, can be oxidized to glutathione disulfide (GSSG). A balance between GSH and GSSG maintains the redox homeostasis in the cell. The cytosol is a reducing environment with a GSH/GSSG ratio ranging from 30:1 to 100:1, while the GSH/GSSG ratio in ER lumen is as high as 1:1–3:1 (83). The highly oxidized environment in the ER is essential for oxidative protein folding.

PDI is a multifunctional oxidoreductase and chaperone that catalyzes the formation, isomerization, and reduction of disulfide bonds in the ER. During disulfide bond formation, cysteine residues in the active site of PDI accept two electrons from the cysteine residues in polypeptide substrates, leading to the reduction of PDI and oxidation of the substrate. Then, PDI transfers the electrons to an acceptor to start another cycle of disulfide bond formation. The ER oxidoreductase 1 (Ero1), a flavin adenine dinucleotide-binding protein, functions and accepts electrons from PDI both *in vitro* and *in vivo* (52, 132). While Ero1p is required for oxidative protein folding in yeast, mammalian cells lacking both *Ero1α* and *Ero1β*, two homologs of Ero1p, do not display dramatic defects in disulfide bond formation (194). So far, several ER enzymes can mediate ERO1-independent disulfide bond formation during oxidative protein folding, including vitamin K epoxide reductase, quiescin sulfhydryl oxidase (QSOX), and peroxiredoxin IV (Fig. 1) (64).

Evidence suggests that oxidative protein folding is an important resource of ROS production in the cell. After accepting electrons from PDI, ERO1 transfers the electrons to molecular oxygen (O_2) and produces H_2O_2, the major ROS produced in the ER lumen. The QSOX family enzymes generate H_2O_2 during oxidative protein folding *via* a similar mechanism (145). Based on the amount of H_2O_2 generated during ER oxidative protein folding, it was estimated that approximately 25% of all ROS produced in yeast results from Ero1p-mediated disulfide bond formation (167). Most eukaryotic cells have a variety of antioxidative stress responses. However, some evidence suggests that the ER has limited enzymatic antioxidant protection under basal conditions (145), which could predispose the ER to oxidative stress under conditions of an increased protein folding load.

Mitochondrial respiration and production of ROS

Mitochondrial respiration produces ATP that is coupled with ROS production, mostly in the form of superoxide ($O_2^{-\bullet}$) after one electron reduction of molecular oxygen. In mammalian mitochondria, there are seven known sites of superoxide production: pyruvate and 2-oxoglutarate dehydrogenases, glycerol 3-phosphate dehydrogenase, the flavin in complex I, ubiquinone-binding sites in complex I and complex III, and the electron transferring flavoprotein:Q oxidoreductase in fatty acid β-oxidation (16).

Mitochondrial ROS profoundly impact cellular physiology and pathogenesis, and it is under multilayer control. First, the proton motive force of the electron transport chain (ETC) produces ROS. Mitochondrial ROS can be eliminated by a number of mitochondrial and cytosolic enzymatic antioxidants, including superoxide dismutases (SODs), glutathione peroxidases, peroxiredoxins, and catalase. ROS production in mitochondria is under direct and indirect regulation by a number of signaling pathways, including Ca^{2+} influx, energy demand, cellular redox status, hypoxia, ER stress, inflammation, immune responses, autophagy, and mitochondrial biogenesis (13, 150). Other important ROS producers in the cell include NADPH oxidase (NOX), xanthine oxidase, 5-lipoxygenase, and cyclooxygenase (42).

ER Stress and Oxidative Stress in Cellular Homeostasis and Apoptosis

ER stress in apoptosis

UPR signaling is an important adaptive mechanism in response to protein misfolding in the ER. However, prolonged ER stress leads to activation of the pro-apoptotic UPR, which plays critical roles in certain physiological and many pathological conditions.

In response to ER stress, eIF2α phosphorylation attenuates global protein synthesis, which serves to reduce the ER protein-folding load and simultaneously selectively increases translation of adaptive response mRNAs, including that of ATF4, to restore ER homeostasis. Subsequently, ATF4 activates transcription of CHOP. *In vitro* and animals studies demonstrated that CHOP is a master regulator of ER stress-induced apoptosis (143). During ER stress, CHOP increases the level of pro-apoptotic BH3-only protein Bim through CHOP-C/EBPα-mediated transcriptional activation (135). In neuronal cells, CHOP may transactivate BIM and the p53 upregulated modulator of apoptosis (PUMA) on ER stress through cooperation with the transcription factor forkhead box, class O, 3a (59). CHOP can also inhibit pro-survival protein Bcl-2 through transcriptional suppression, which may require liver inhibitory protein, an isoform of C/EBPβ (26). In addition, CHOP can activate transcription of other pro-apoptotic genes, including telomere repeat binding factor 3 and death receptor 5, both of which are important mediators of ER stress-induced apoptosis in several cancer cells (161). Studies also implicate a role for CHOP in promoting protein synthesis to cause oxidative stress, leading to apoptosis (107). Recently, chromatin immunoprecipitation and mRNA deep sequencing analyses demonstrated that CHOP and ATF4 form a heterodimer to induce transcription of genes that encode protein synthetic machinery (65). Indeed, forced expression of ATF4 with CHOP increases protein synthesis and causes oxidative stress that is required for cell death. One component of the ATF4/CHOP-stimulated increase in protein synthesis is mediated through transcriptional activation of GADD34, the regulatory subunit of PPP1 that directs

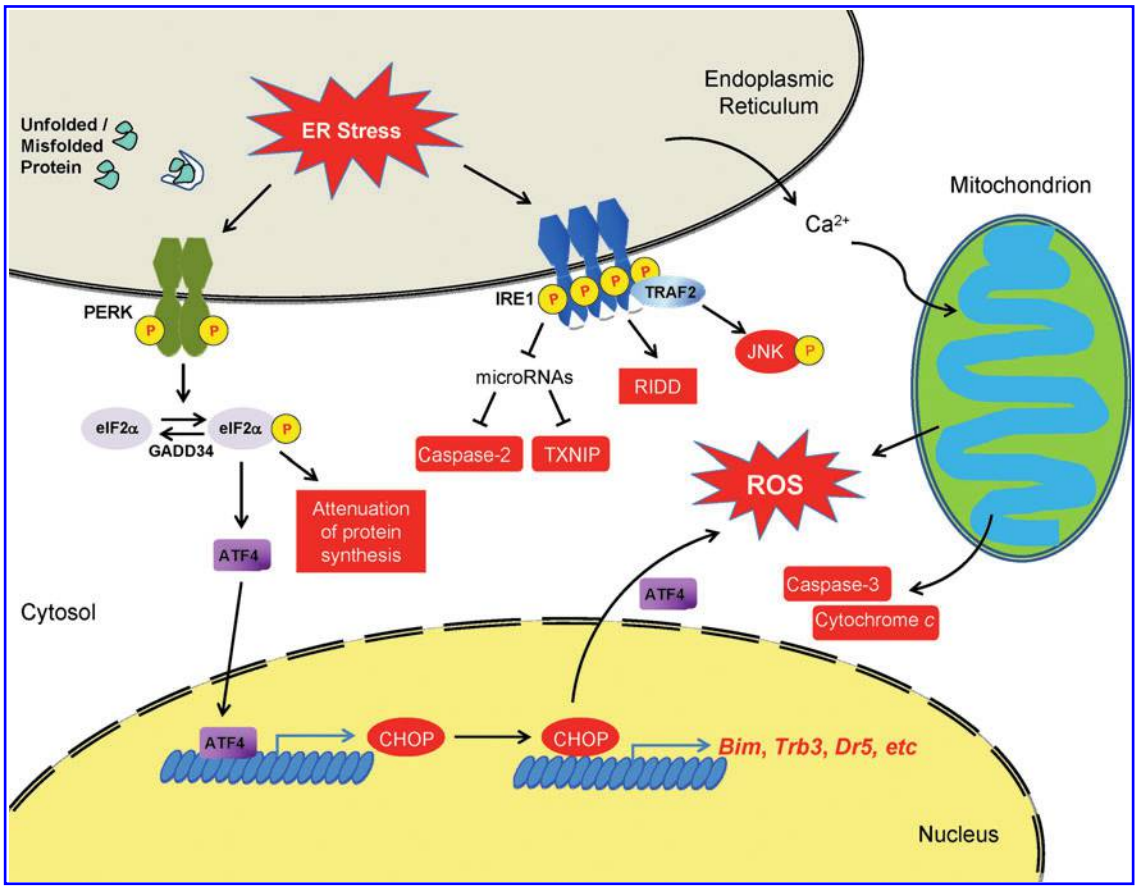

FIG. 3. ER stress-mediated cell death. ER stress leads to apoptotic cell death at transcriptional, post-transcriptional, translational, and post-translational levels. Pro-apoptotic components induced during ER stress are labeled red. See ''ER Stress and Oxidative Stress in Cellular Homeostasis and Apoptosis'' for details.

eIF2α dephosphorylation to restore global mRNA translation. An increase in protein synthesis under conditions where protein folding is defective causes more misfolding and further exacerbates cell death signaling through oxidative stress (65, 107). CHOP has also been involved in oxidative stress induction, which will be discussed in the next section ''Cross-talk between ER stress and oxidative stress in apoptosis.''

IRE1 is the ER stress sensor conserved from yeast to mammals. The IRE1-XBP1 pathway is required for murine embryonic development as well as for optimal UPR activation and normal function in many secretory cells, including pancreatic acinar and β cells, plasma cells, and intestinal Paneth cells (20). However, increasing evidence suggests that IRE1 may contribute to apoptotic cell death, especially on chronic ER stress. First, IRE1α can contribute to apoptotic cell death by activating the JNK pathway through a direct interaction with TRAF2. Activated JNK can induce cell death in different ways, including the phosphorylation of Bcl-2, which inhibits its anti-apoptotic function in regulating Ca^{2+} flux from the ER and inhibiting pro-apoptotic BH3-only-containing Bcl2 family members such as Bax and Bak. The IRE1α-TRAF2 complex may also activate caspase-12 on ER stress. In addition, IRE1 may cause cell death by interacting with factors involved in apoptosis. In mammalian cells, activated IRE1α can bind Bax and Bak on the ER membrane and initiate the mitochondrial-dependent apoptotic cascade. IRE1α is also linked to the activation of PUMA and BH3 interacting-domain death agonist (Bid), two pro-apoptotic proteins. During ER stress, RIDD could help mitigate the ER protein-folding burden and restore ER homeostasis. However, this process may contribute to cell death during prolonged ER stress by degrading mRNAs encoding pro-survival functions (75, 161). Recently, IRE1α was shown to degrade specific microRNAs that target the mRNA encoding caspase-2, thereby boosting caspase-2-dependent apoptosis during ER stress (169).

One key event of ER stress-induced apoptosis is the processing of caspases. So far, the activation of caspases-2, -3, -4, -6, -7, -8, -9, and -12 has been reported in different *in vitro* and/or *in vivo* models of ER stress. Among these caspases, the deletion of caspase genes 3, -7, -9, or -12, as well as APAF1 protects against ER stress-induced cell death (62). However, the activation cascade of some caspase pathways during the execution phase of ER stress is still elusive (Fig. 3).

Cross-talk between ER stress and oxidative stress in apoptosis

Both ER stress and oxidative stress are involved in a variety of physiological and pathophysiological conditions. Studies in the past decade indicate that these two cellular stresses are closely linked events in cell homeostasis and apoptosis.

First, some forms of ROS can disturb ER protein folding and induce ER stress. Exogenous oxidants such as ROS producers, peroxides, metal ions, and lipid oxidation products may activate some aspects of the UPR. 7-ketocholesterol, a major oxidation product of cholesterol in atherosclerotic plaque, induces the full UPR in macrophages and vascular smooth muscle cells (97, 131). The 7-ketocholesterol-activated UPR is suppressed by N-acetyl-cysteine, an antioxidant, suggesting that this ER stress induction is oxidative stress dependent. However, other forms of ROS, such as H_2O_2, can only stimulate mild or specific components of the UPR (145). Therefore, a general conclusion that can be drawn from these findings is the nature of the oxidative stress; for example, strength and location may determine whether it is sufficient to induce potent ER stress. Given the importance of redox state in ER homeostasis, the sensing of altered redox is essential to ER protein folding machinery. A recent study demonstrated that non-selenocysteine containing phospholipid hydroperoxide glutathione peroxidase (NPGPx), a member of glutathione peroxidase family, senses oxidative stress in the ER lumen, then forms a disulfide bond with BiP, and promotes its chaperone activity. The loss of NPGPx in mice led to oxidative stress-induced tissue damage, increased tumorigenesis, and impaired longevity (179).

Given the role of disulfide bond formation in the ER as an important source of ROS, protein misfolding in the ER could contribute to oxidative stress. GSH can reduce disulfide bonds in proteins with improperly paired disulfide bonds to enable proper disulfide bond formation by the PDI-Ero1 cycle. When the microenvironment of ER protein folding is severely disrupted, or when a misfolding-prone protein is expressed in the cell, a futile cycle of disulfide bond formation and reduction could lead to oxidative stress by generating a large amount of H_2O_2 and depleting ER GSH levels (72). As an adaptive response during ER stress, ERAD requires the breakage of disulfide bonds by disulfide reductase ERdj5 before retrotranslocation and degradation of substrate protein, which may also compromise ER redox balance (171). In spite of these relevant data of ER protein misfolding in the induction of oxidative stress, recent studies used novel ER-redox sensors to show that some ER stress inducers did not alter ER redox state, or even rendered the ER lumen more reduced (149). These discrepancies might result from differences in the strength and/or timing of the ER stress, as well as by the different experimental systems utilized, such as cell type and method of redox measurement.

As a major pro-apoptotic factor of the UPR, CHOP also induces oxidative stress in different manners. In mammalian cells, Ero1α is transcriptionally activated by CHOP and can increase ROS production during ER stress. In addition, Ero1α causes inositol-1,4,5-trisphosphate receptor (IP3R)-mediated Ca^{2+} leakage from the ER, which activates Ca^{2+} sensing kinase CaMKII in the cytosol, leading to the activation of pro-apoptotic pathways, including Fas and mitochondrial membrane permeability transition (20, 75, 161). CaMKII also induces NOX subunit Nox2 and causes oxidative stress, which results in PKR-dependent CHOP induction as a positive feed-forward cycle during ER stress (97). CHOP contributes to cell death by restoring global mRNA translation during ER stress, which may lead to protein misfolding and mitochondrion-dependent induction of oxidative stress (7, 65, 107).

Mitochondria are another important site for ROS production during ER stress. In ER-stressed cells, Ca^{2+} released from the ER is taken up by mitochondria, leading to opening of the permeability transition pore to release cytochrome c from the mitochondrial matrix. The loss of cytochrome c inhibits complex III of the ETC and enhances ROS production by increasing the ubisemiquinone radical intermediate. In addition, increased Ca^{2+} in the mitochondria stimulates

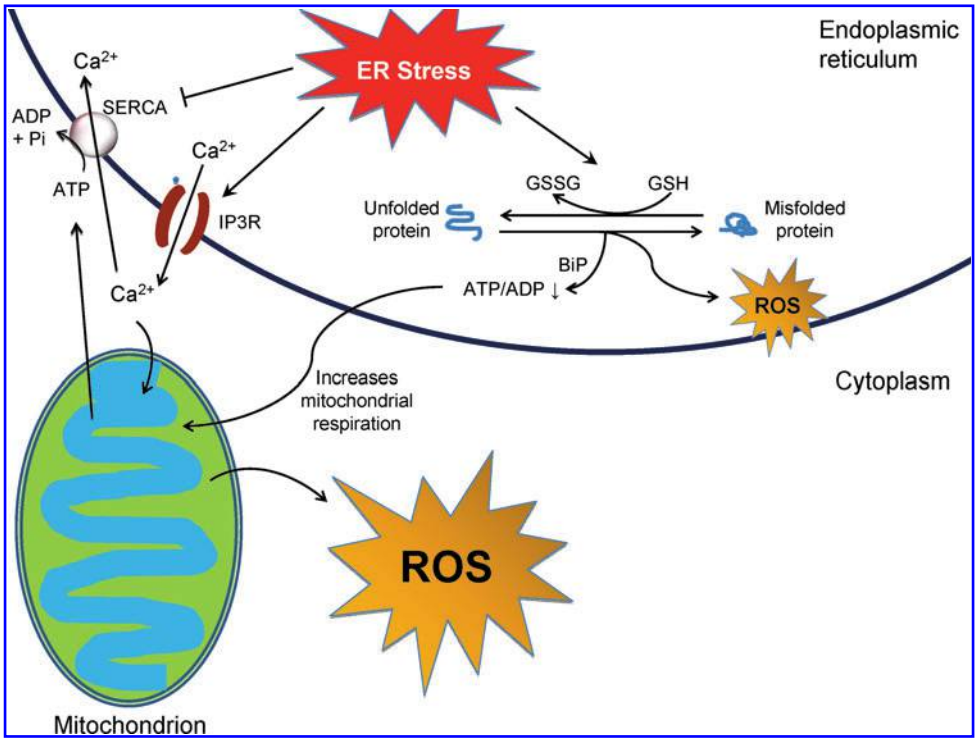

FIG. 4. ER stress-induced ROS production in the cell. ROS are usually generated by cellular processes, including oxidative protein folding and mitochondrial respiration, which can be augmented to disrupt cell function and survival during ER stress. See "Cross-talk between ER stress and oxidative stress in apoptosis" for details. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

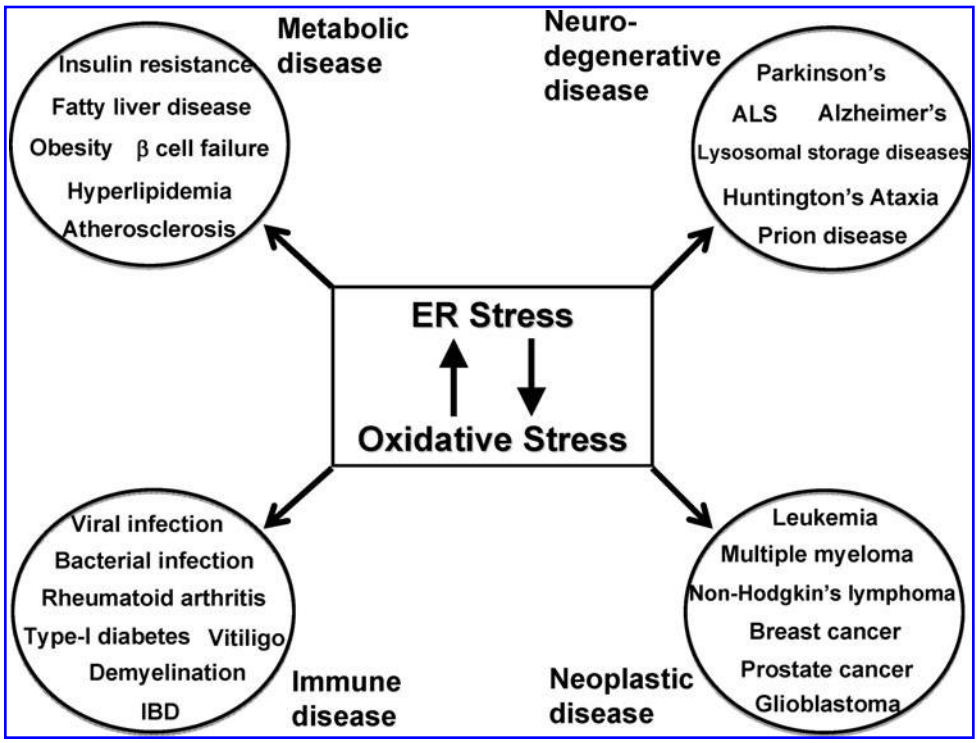

FIG. 5. ER stress and oxidative stress in human diseases. ER stress and oxidative stress are linked to multiple human pathologies, including metabolic, neurodegenerative, immune/inflammatory, and neoplastic diseases. Studies on the two cellular stresses have not only contributed to our understanding of the pathogenesis, but also opened new avenues to next-generation therapies for these debilitating illnesses. See ''ER Stress and Oxidative Stress in Human Diseases'' for details.

Krebs cycle dehydrogenases, thereby boosting oxygen consumption and ROS production. Mitochondrial Ca^{2+} also activates nitric oxide synthase, whose product disturbs the ETC and enhances ROS generation (16, 159). During ER stress, Ca^{2+} release from the ER and mitochondrial ROS production creates a vicious cycle that impairs cellular homeostasis and induces apoptosis. ROS opens the ER Ca^{2+} channels IP3Rs and ryanodine receptors and releases more ER Ca^{2+}, which further disturbs ER protein folding and induces mitochondrial oxidative stress and dysfunction. ER and mitochondria are interconnected physically and functionally by mitochondria-associated ER membranes (MAMs), a structure that may be important for Ca^{2+} uptake by the mitochondria (17). Recent studies showed that ER Ca^{2+} channels, including the IP3Rs and the mitochondrial voltage-dependent anion channel, are enriched in MAMs, which might facilitate Ca^{2+} flow between the two organelles (160). In addition, the ER stress sensor PERK resides in MAMs and helps maintain the ER-mitochondria junction that plays a critical role in mitochondrial dysfunction and apoptosis (174). In addition to Ca^{2+}-mediated mitochondrial ROS production, the futile cycle of disulfide bond formation and breakage during ER stress could deplete cellular energy and stimulate mitochondrial respiration, which may also increase ROS production in mitochondria (Fig. 4).

Given the deleterious impact of oxidative stress induced during protein misfolding in the ER, eukaryotic cells have evolved antioxidative stress responses to restore cellular redox homeostasis. The PERK branch of the UPR induces ATF4 and NRF2, two transcription factors that transactivate antioxidative stress response genes, including SODs, heme oxygenase-1, glutathione transferase, and uncoupling mitochondrial protein 2 (145). In addition, small-molecular antioxidants, such as butylated hydroxyanisole (BHA), can prevent ER stress-induced apoptosis and promote proper protein folding and secretion (104, 105), which further demonstrates the crucial role of oxidative stress in protein misfolding-related cellular dysfunction.

ER Stress and Oxidative Stress in Human Diseases

The previous decade has witnessed an increase in our knowledge of protein misfolding-induced human diseases through animal studies and clinical investigations. The pathogenesis is further complicated by the fact that oxidative stress is usually induced during ER stress and contributes dramatically to cell dysfunction and apoptosis (Fig. 5). Next, we discuss how understanding the two cellular stresses develop and cross-talk in human disease will provide insights for novel prevention and treatment strategies. We have not covered neurodegenerative disease, as this topic was recently reviewed (30, 39, 80, 115).

Metabolic disease

Diabetes. Pancreatic β cells are the primary source of insulin, which accounts for about half of the protein production in these professional secretory cells. High protein secretion predisposes β cells to the challenge of ER stress. Meanwhile, β cells are sensitive to oxidative stress due to their high energy consumption and low levels of antioxidant enzymes (108). Both type 1 and type 2 diabetes involve β-cell dysfunction and/or apoptosis, which are associated with ER stress and oxidative stress (6, 178). Several pathological, environmental, and genetic causes are proposed to induce ER stress and oxidative stress in β cells, including glucotoxicity, lipotoxicity, and inflammatory challenge (51, 178). Indeed, a high-fat diet alone increases proinsulin misfolding in C57Bl6/J mice (148). Chronic high-glucose challenge (glucotoxicity) induces the pro-apoptotic UPR, including CHOP and IRE1α-JNK, and oxidative stress in β cells in both *in vitro*

and *in vivo* models. Free fatty acids, such as palmitate, induce ER stress and oxidative stress and cause apoptosis in β cells (6, 51, 99). Proinflammatory cytokines, including interferon-γ and interleukin (IL)-1β, also induce ER stress in β cells and contribute to the pathogenesis of type 1 diabetes (24).

Since oxidative stress is usually coupled with ER stress, the UPR has evolved to handle both protein folding defects and oxidative challenge. The PERK-eIF2α pathway plays a crucial role in β-cell function and survival. Patients with Wolcott–Rallison syndrome, an autosomal-recessive disease, harbor loss-of-function mutations in the *PERK* gene and suffer from infancy-onset β-cell failure (35, 74, 191). Later, murine studies demonstrated that deletion of *Perk* or expression of non-phosphorylatable Ser51Ala mutation in eIF2α (*AA*) impairs adaptive UPR signaling, disturbs intracellular trafficking from the ER to the Golgi, reduces expression of β-cell-specific genes, diminishes insulin granule number, and increases apoptosis in pancreatic β cells (67, 147). In addition, β cells with a defective PERK-eIF2α pathway also exhibit oxidative stress (7). This phenotype may be explained by at least two different mechanisms: (i) unregulated protein synthesis in $Perk^{-/-}$ and *AA* β cells exacerbates ER protein misfolding and increases ROS production; (ii) a compromised ATF4-dependent antioxidative stress response in the absence of a functional PERK-eIF2α pathway. The importance of oxidative stress in β-cell pathology in the *AA* model was demonstrated by showing that feeding of antioxidant BHA alone alleviates β-cell dysfunction and restores glucose homeostasis in these mice. In contrast to *Perk*, *Chop* deletion improves β-cell function and reduces apoptosis in genetic- and diet-induced diabetes in mice (157). Similarly, the protective effect of *Chop* deletion in β cells is phenocopied in murine diabetic models by feeding of BHA, which is consistent with previous findings that CHOP disrupts cellular homeostasis by inducing oxidative stress. The IRE1α-XBP1 pathway is required for the biosynthesis, folding, and maturation of proinsulin (92, 100). IRE1α directly attenuates the translation of insulin mRNA through RIDD, which may protect β cells from ER stress and oxidative stress induced by hyperactivated insulin synthesis [2].

Insulin resistance. Insulin resistance (IR), a major characteristic of obesity and type 2 diabetes, is caused by impaired insulin signaling in multiple organs, including the liver, adipose tissue, and muscle. Animal and clinical studies indicate that ER stress and oxidative stress may be important contributors to IR (50). In mammals, the liver orchestrates the homeostasis of glucose and lipid metabolism. Hepatic IR leads to hyperglycemia and hyperlipidemia by inducing gluconeogenesis and lipogenesis, respectively (178). ER stress and the UPR contribute to hepatic IR through different mechanisms. IRE1α induces hepatic IR through activation of JNK and IKK, which blocks insulin signaling by serine phosphorylation of insulin receptor substrate 1 and 2 (6, 18, 162, 170). In addition to IRE1α, ER stress can also activate JNK through CAMKII and PKR and induce hepatic IR (122, 163). Free fatty acids are an important metabolic signal that induces both ER stress and oxidative stress in hepatocytes and adipocytes, which then leads to increased lipolysis, induction of proinflammatory mediators and IR. However, the underlying mechanism is still poorly understood. ROS play a causative role in IR; while antioxidants, including N-acetylcysteine, SOD, and catalase, can improve insulin sensitivity in cultured muscle cells (81).

Nonalcoholic fatty liver disease. Nonalcoholic fatty liver disease (NAFLD) is characterized by excessive accumulation of triacylglycerol in the liver due to increased influx of free fatty acids and/or *de novo* lipogenesis in the absence of significant alcohol consumption. ER stress is linked to multiple hepatic dysfunctions, including IR, lipotoxcity, inflammation, cell death, and steatosis (53, 103) (Fig. 2). The presence of ER stress and oxidative stress was demonstrated in the livers of animal models of nonalcoholic steatohepatitis (NASH) as well as in the livers of patients with NAFLD or NASH (128, 134). Recent studies using genetic murine models suggest that ER stress plays a causal role in the pathogenesis of hepatosteatosis. Induction of ER stress caused hepatosteatosis in mice, and this hepatosteatosis was much more severe in mice that had mutations in the three UPR pathways, *Ire1α*, *Atf6α*, as well as Ser51Ala eIF2α (144, 190). A point mutation in *Sec61α1*, which encodes the aqueous channel for protein translocation into the ER, disrupted the ER secretory pathway and increased the susceptibility to hepatic steatosis and fibrosis on metabolic challenge in mice (101). Forced expression of *Gadd34* in murine liver reduced eIF2α phosphorylation and protected against ER stress and hepatosteatosis on the feeding of a high-fat diet (126). Recently, the IRE1α-XBP1 pathway was shown to play an important role in the assembly and secretion of very-low-density lipoprotein in the liver. Mice deleted in *Ire1α* in hepatocytes displayed more severe steatosis on fasting or challenge of a high fructose diet (177). The IRE1α-XBP1 pathway was required to induce expression of PDI that is essential for microsomal triglyceride transfer protein activity to promote triglyceride assembly with ApoB. Finally, the hepatocyte-specific ATF6 family member CREBH regulates liver lipid metabolism and patients with nonsynomenous mutant hypomorphic alleles of CREBH exhibit severe hypertriglyceridemia (95, 188). Several animal and clinical studies showed strong correlations between oxidative stress such as serum oxidative markers and hepatic lipid peroxidation and severity of NAFLD/NASH. During the pathogenesis of NAFLD, accumulation of lipid in hepatocytes induces β oxidation of fatty acids, which overwhelms the ETC in the mitochondria and promotes ROS production. Oxidative damage of mitochondrial membrane proteins, such as the components of ETC, impairs mitochondrial function and exacerbates ROS overproduction. Accumulation of fatty acids also stimulates extramitochondrial fatty acid oxidation in organelles, including peroxisomes and microsomes, which also contributes to ROS production and oxidative stress. In addition, a reduced antioxidative stress response, such as coenzyme Q10, Cu-Zn SOD, and catalase, was observed in both patients and animal models of NASH (140). A recent study linked fatty acid oxidation to ER stress by showing that pharmacological inhibition of fatty acid oxidation in hepatocytes increases cellular redox potential and protects against ER stress (168). However, the functional interaction between ER stress and oxidative stress in hepatocyte homeostasis and pathogenesis of NAFLD/NASH is still elusive.

Inflammatory disease

ER stress and oxidative stress are observed in several inflammatory diseases, including inflammatory bowel disease

(IBD), chronic obstructive pulmonary disease, chronic kidney disease, alcoholic liver disease, hepatitis, pancreatitis, and rheumatoid arthritis (1, 2, 36, 47, 57, 70, 85, 89, 103, 124, 129, 138, 186, 187). These two stresses can contribute to inflammatory pathologies in various organ systems by causing cellular dysfunction and inducing ''cell autonomous'' inflammation. Accumulated evidence suggests that the UPR is a crucial inducer of pro-inflammatory signals in the cell. The IRE1-XBP1 pathway, the most conserved UPR signaling, promotes cellular inflammation through several different mechanisms. The kinase domain of IRE1α can activate JNK-AP1 and NF-κB signaling through a physical interaction with adaptor protein TRAF2 (86, 170). XBP1s can transactivate pro-inflammatory genes *Tnf*α and *Il6* in macrophages by directly binding to their promoter/enhancer regions (112). The PERK-eIF2α-CHOP pathway also plays important roles in the inflammatory response. Phosphorylation of eIF2α facilitates the nuclear translocation of NF-κB by attenuating the synthesis of IκB protein (183). In dendritic cells, CHOP induces the transcription of gene encoding IL-23, an inflammatory cytokine that stimulates the maturation of Th17 cells (61). In macrophages, CHOP is important for the induction of caspase-11 mRNA and subsequent activation of pro-caspase-1 and the inflammasome (44). Recently, the IRE1α and PERK pathways were linked to inflammasome activation in pancreatic β cells through increasing thioredoxin interacting protein (TXNIP) to inhibit thioredoxin and cause oxidative stress (125). In addition, ATF6α and CREBH also contribute to inflammatory response. ER stress induces cleavage and activation of ATF6α and CREBH that act to increase transcription of the systemic arm of the inflammatory response, the acute phase response (APR) genes in the liver (189). ROS production has long been associated with cellular inflammation. ROS function as second messengers and activate a number of signal transduction pathways, including JNK, p38 MAPK, ERK, PI3K/Akt, PKC, Src family kinases, and growth factor tyrosine kinase receptor pathways, all of which can lead to the induction of inflammatory genes. Furthermore, ROS also stimulate redox-sensitive transcription factors, including NF-κB, AP1, and hypoxia-inducible factor-1 (HIF-1), which play crucial roles in inflammatory responses (94). In addition to inducing inflammation at the cellular level, ER stress and oxidative stress can also contribute to the pathogenesis of inflammatory disorders in various tissue/organ systems in a ''non-cell autonomous'' manner. IBD is an example where ER stress and ROS induce inflammatory disease in both ''cell autonomous'' and ''non-cell autonomous'' manners.

IBD, including Crohn's disease and ulcerative colitis, is a group of inflammatory conditions in the gastrointestinal tract. Murine and human intestines harbor four intestinal epithelial cells (IEC), including Paneth and goblet cells, which secrete large amounts of antimicrobial peptides and mucins, respectively, and are crucial for intestinal barrier function and mucosal homeostasis. Accumulated evidence suggests that IECs, particularly Paneth and goblet cells, are sensitive to alterations in ER protein folding homeostasis due to environmental challenge and/or genetic defects (46, 114). ER stress markers are induced in the mucosal tissues of patients with IBD as well as in several murine models of colitis and Crohn's ileitis (12, 23, 73, 82, 90, 152). Mice that express a misfolding-prone mutant of MUC2 mucin, the major mucin in the large intestine, displayed ER stress, goblet cell dysfunction, and spontaneous colitis (73). The anti-inflammatory cytokine IL-10 ameliorated the misfolding of mutant MUC2 mucin, reduced ER stress, and improved mucin secretion in colonic goblet cells both *in vitro* and *in vivo* (71). Glucocorticoids, a family of drugs that have been used in IBD therapies for decades, were recently shown to reduce ER stress in colonic epithelial cells by transactivating ER chaperones and ERAD components (33). So far, several studies using murine genetic models have demonstrated the crucial role of specific UPR components in IEC function and mucosal homeostasis. The IEC-specific ablation of *Xbp1* caused progressive Paneth cell death, reduced goblet cell number, as well as spontaneous inflammation in the ileum of $\sim$60% of the mice (90). In addition, several nonsynonymous SNPs in the coding region of *XBP1* were identified by deep sequencing of IBD patients and control individuals, which raised the possibility that hypomorphic function of *Xbp1* may contribute to IBD by impairing IEC homeostasis and intestinal barrier function (90). The deletion of *Chop*, a pro-apoptotic transcription factor, is protective against dextran sodium sulfate (DSS)-induced colitis in mice (123). Deletion of *Ire1*β exacerbates epithelial cell death and mucosal inflammation on the challenge with DSS (9). Recent studies suggest that IRE1β degrades *Muc2* mRNA in colonic goblet cells in mice, thereby optimizing the biosynthesis of Muc2 mucin. In the absence of IRE1β, ER stress was induced in colonic epithelial cells, probably due to increased translation of *Muc2* mRNA that overwhelms ER protein folding capacity (166). In contrast, IRE1β promotes mucin production in respiratory epithelial cells by mediating *Xbp1* splicing (111). PKR can be activated by ER stress and multiple inflammatory stimuli (56). PKR protects against DSS colitis by activating eIF2α-phosphorylation-mediated UPR signaling and pro-survival components, including STAT3 and AKT in colonic epithelial cells (22). A recent study demonstrated that ER cochaperone $P58^{IPK}$ and ATF6α, a master transactivator of ER chaperone genes, are important for the function and survival of colonic epithelial cells by reducing ER stress and suppressing the pro-apoptotic UPR on DSS challenge (19, 23). So far, there have been limited studies that provide insights into how ER stress and the UPR affect cell-autonomous inflammation in IECs and inflammatory cells in the pathogenesis of IBD (25). However, previous findings support the general conclusion that ER stress-induced epithelial dysfunction may be sufficient to cause intestinal inflammation by compromising mucosal homeostasis and barrier function in the gut.

Increased production of ROS and reactive nitrosative species (RNS) were observed in the mucosal tissues of both chemical-induced and genetic models of IBD, as well as in patients with IBD. Oxidative and nitrosative stress cause damage to macromolecules in cells, as indicated by the formation of lipid peroxidation products and protein modifications, including carbonyls in the mucosa. During the initiation and progression of mucosal inflammation, multiple cell types in the gut can generate ROS/RNS. Neutrophils, macrophages, and IEC can produce a large amount of superoxide and nitric oxide *via* the activation of NOXs and inducible nitric oxide synthase, respectively, in the pathogenesis of IBD. Overproduction of ROS/RNS contributes to intestinal inflammation by causing epithelial cell death and

mucosal tissue injury, as well as by stimulating cell-autonomous inflammation in both IEC and inflammatory cells (192). Depletion of antioxidants is also observed in inflamed mucosal tissues in both human and animal models. The endogenous antioxidative stress defense plays a critical role in the homeostasis of the intestinal mucosa, highlighted by studies of mice deficient in glutathione peroxidase-1/2 or Nrf2 (48, 91). In a small case-controlled study, a polymorphism in the paraoxonase 1 gene (PON1 R192 allele) was associated with both Crohn's disease and ulcerative colitis in an Ashkenazi Jewish population from Israel (87). In addition, polymorphisms in genes encoding Mn-SOD, epoxide hydrolase, NAD(P)H:quinone oxidoreductase, and Hrf2 are associated with ulcerative colitis in different populations (192). Nrf2, a transcription factor that plays a central role in the antioxidative stress response in the gut, is activated by both ER stress and oxidative stress. On ER stress, Nrf2 is phosphorylated and activated by PERK and then migrates into the nucleus to induce antioxidative stress response genes (32). Given the coexistence of ER stress and oxidative stress in inflamed mucosa, it is still to be determined whether the two cellular stresses reciprocally induce each other in the gut, or whether either one is sufficient as an initiating event in the induction of IBD.

Neoplastic disease

One important hallmark of neoplastic disease is the uncontrolled growth of transformed cells in the body. Carcinogenesis is a process in which precancerous and cancerous cells resist multiple stresses, including ER stress and oxidative stress during their growth and expansion. Primary human tumor cells of various origins, including breast, lung, liver, colon, prostate, and brain, show increased UPR signaling, while peritumoral cells do not. Limited supplies of oxygen and nutrients due to poor vascularization constantly challenge solid tumor cells *in vivo*. Hypoxia activates UPR components, including BiP, XBP1, ATF4, and CHOP, in multiple tumor cell types. In transgenic mice with spontaneous mammary carcinogenesis, splicing of *Xbp1* mRNA correlates with the degree of hypoxia in the tumor (40). In addition, a high rate of glycolysis in cancer cells and insufficient blood supply combine together to limit the glucose available to solid tumors (158). BiP is an essential ER chaperone for both normal cells and transformed cells. In primary human melanoma, liver, colon, and breast cancer tissues, the level of BiP was found to positively correlate with tumor progression. The physiological significance of BiP was demonstrated by studies that *Bip* heterozygosity significantly reduces the cancer cell proliferation, survival, as well as angiogenesis in breast tumors (37). In addition, conditional knockout of *Bip* in the prostate of mice with *Pten* inactivation suppressed prostate cancer growth (54). Finally, sublitase, a bacterial cytotoxin that selectively cleaves BiP, can kill glioblastoma cells (133).

The IRE1-XBP1 pathway also plays an important role in carcinogenesis. Knocking down *Xbp1* in human fibrosarcoma cells inhibits their growth and angiogenesis in a xenograft model (141). Later, it was shown that IRE1α is essential for the expression of vascular endothelial growth factor A (VEGF-A) and lung cancer growth both *in vitro* and *in vivo* (40). The importance of PERK in tumorigenesis is supported by the findings that loss of PERK in mouse fibroblasts and human colon cancer cells reduced tumor growth and angiogenesis when grafted into immunodeficient mice (10, 11). The PERK-eIF2α-ATF4 pathway can promote cancer cell survival and expansion by inducing the hypoxic response and autophagy (69, 173). The UPR is linked to the production of several proinflammatory, tumorigenic cytokines, including IL-6, TNFα, and IL-23. On ER stress challenge, murine lymphoma cells showed transcriptional induction of several inflammatory genes, including *Il-6*, *Tnfα*, *Il-23*, *Tlr2*, and *Cebpβ* (180). More interestingly, macrophages cultured in the conditioned medium of ER-stressed cancer cells displayed induction of the UPR and proinflammatory signals, including IL-6, TNFα, IL-23, MIP-1α, and MIP-1β, which suggests that ''transmissible'' ER stress initiated in cancer cells may be exploited to modify the tumor microenvironment through activation of inflammatory cells (102).

Oxidative stress plays an important role in almost every hallmark of cancer as defined by Hanahan and Weinberg (49, 66). A review of recent studies suggests that ER stress and oxidative stress have overlapping as well as intertwined functions in carcinogenesis. Both ER stress and oxidative stress promote epithelial mesenchymal transition, a key step of metastasis and tissue invasion of many tumor cells. Both stresses activate VEGF signaling and angiogenesis. HIF-1, an essential transcription factor during the hypoxic response, is regulated by both ER stress and oxidative stress. While the tumor suppressor PTEN can be inactivated by oxidative stress during tumorigenesis, PTEN activity requires PKR-eIF2α signaling (120). Moreover, the detachment of mammary epithelial cells from extracellular matrix activates the PERK-eIF2α-ATF4-CHOP branch of the UPR, which protects mammary tumor cells from anoikis by stimulating both autophagy and antioxidative stress responses (5). Later, it was found that oxidative stress causes induction of c-Myc and n-Myc, which improve cancer cell survival through PERK/eIF2α/ATF4-dependent induction of autophagy (69). Oxidative stress induces mutations and aerobic glycolysis by disrupting mitochondrial function, leading to the Warburg effect, which is characterized by increased glycolysis and altered lipid metabolism, by activating mitophagy and inhibiting mitochondrial respiration in cancer cells (58, 109, 110, 172). Pharmacological inhibition of fatty acid oxidation protects cells against ER stress (168); however, its link to the Warburg effect has not been determined. In addition, ER stress and oxidative stress have profound impacts on cell autonomous and non-cell autonomous inflammation, which are critical to both tumor cell expansion and anti-tumor immunity (49). In spite of these inter-related functions, it is still unknown how ER stress and oxidative stress cross-talk with each other during the different stages of carcinogenesis.

Therapeutic Implications

Previous studies indicate that ER stress and oxidative stress form a vicious cycle in many human pathologies, including metabolic, neurodegenerative, and inflammatory diseases (104). Therefore, therapies that target both stresses may be more effective to treat these diseases. Previous findings suggest that antioxidants can suppress both oxidative stress and ER stress for these diseases (21). The overexpression of the misfolding-prone coagulation factor VIII in

cultured cells and mouse liver leads to the induction of ER stress, oxidative stress, and cell death. BHA, an antioxidant wildly used in the food industry, alleviated ER stress, oxidative damage, and apoptosis, and enhanced the folding and secretion of factor VIII both *in vitro* and *in vivo* (105). In addition, BHA protected β cells that were genetically engineered for increased proinsulin synthesis which caused both ER stress and oxidative stress (7). Similarly, Mitoquinone and MitoTempol, two mitochondrial-targeted antioxidants, reduced mitochondrial oxidative stress, ER stress, energy depletion, and cell death in β cells with glucotoxicity or glucolipotoxicity. Clinical trials demonstrated that Mitoquinone protects against Parkinson's disease and cardiac ischemia-reperfusion injury with excellent safety profile in patients (98, 154).

Tauroursodeoxycholate (TUDCA) and 4-phenylbutyrate (PBA), two small-molecular ''chemical chaperones,'' impede protein misfolding and aggregation as well as promote intracellular trafficking and secretion. The Food and Drug Administration (FDA) approved UDCA, the unconjugated form of TUDCA, and PBA for the treatment of primary biliary cirrhosis and urea-cycle disorders, respectively. Recently, TUDCA and PBA compounds demonstrated therapeutic potential in preclinical/clinical studies for multiple diseases associated with ER stress, including IR (45, 88, 127, 128, 136, 184), alcoholic/nonalcoholic liver disease (84), Alzheimer's disease (139, 181), neuronal cell apoptosis (116), as well as acinar cell death and pancreatitis (151). Many of these diseases are also associated with oxidative stress, which may play a causal role in the pathogenesis. Given the excellent safety profiles of TUDCA and PBA in humans, these compounds deserve further exploration for mono-therapies or combinatorial therapies with antioxidants for diseases associated with both ER stress and oxidative stress (106).

In addition to antioxidants and chemical chaperones, small molecules that activate endogenous components of the adaptive UPR and antioxidative stress response may exhibit therapeutic potential for these diseases. The PERK-ATF4 branch of the UPR not only induces ER chaperones and intracellular trafficking machinery, but also activates antioxidative stress defenses in the cell. Therefore, pharmacological activation of the PERK-ATF4/Nrf2 pathway may improve cellular homeostasis by suppressing both ER stress and oxidative stress. Salubrinal and guanabenz, two structurally unrelated small-molecular compounds, have been identified to prevent the dephosphorylation of eIF2α by disrupting PP1 complex, thereby sustaining PERK-ATF4 signaling during ER stress (15, 165). Salubrinal alleviated protein aggregation and apoptosis in cell culture models of Alzheimer's, Huntington's, and Parkinson's disease by inducing the eIF2α phosphorylation-mediated adaptive UPR (93, 155, 156). In several rodent models of Parkinson's disease and α-synucleinopathies, salubrinal reduced the accumulation of α-synuclein in the ER and delayed the onset of disease (27, 28). In a mouse model of familial ALS, salubrinal reduced the accumulation of poly-ubiquitinated protein inside motor neurons, improved motor neuron and muscle function, and prolonged survival (146). In addition, salubrinal protected against neuronal injury on excitotoxic challenge in the rat brain (156). In several other disease models, salubrinal improved cellular homeostasis by suppressing oxidative stress, ER stress, and mitochondrial dysfunction (38, 182, 193). Guanabenz is an FDA-approved α2-adrenergic agonist that is used to treat hypertension for decades. Before its UPR-regulating function was discovered, guanabenz was shown to reduce the accumulation of prion in both yeast and mammalian cells *in vivo* (164). In *Akita* mice that express mutant, misfolding-prone insulin, guanabenz reduced β-cell dysfunction and apoptosis (165). In a *Drosophila* model of oculopharyngeal muscular atrophy, guanabenz prevented nuclear inclusion formation and muscular degeneration by inhibiting the aggregation and toxicity of poly(A) binding protein nuclear 1 (8). In addition, guanabenz ameliorated cell death and preserved light detection function in a murine model of ciliopathies, a rare genetic disorder caused by protein trafficking defects (118).

The killing power of ER stress and oxidative stress has demonstrated therapeutic potential for several cancers. Ras-driven tumors are refractory to conventional treatments as well as to monotherapy of the ER stress inducers tunicamycin and thapsigargin. However, combining tunicamycin or thapsigargin with rapamycin showed a rapid suppression of tumor growth in mice. It was demonstrated that rapamycin inhibits the synthesis of glutathione, an essential antioxidant in the cell, by repressing the transcription of glucose 6-phosphate dehydrogenase of the pentose phosphate pathway. A combination of an HSP90 inhibitor IPI-504, an ER stress inducer currently in clinical trials, and rapamycin, which exacerbates oxidative stress, suppressed the growth of two Ras-driven tumors both *in vitro* and *in vivo* by stimulating progressive ER stress and mitochondrial damage (34). The findings suggest that some cancer therapies may require both ER stress and oxidative stress to be successful. Recently, a novel PERK kinase inhibitor (GSK2656157) was shown to inhibit the growth of tumor xenografts in mice (3). Several IRE1 endoribonuclease inhibitors, which prevent *Xbp1* mRNA splicing and RIDD, exhibited a therapeutic effect against multiple myeloma *in vitro* and/or *in vivo* (117, 130, 137). In future, it will be worthwhile to test the combinatorial effects of the oxidative stress inducer, for example, rapamycin, and ER stress stimulators such as bortezomib, brefeldin A, and sublitase, as well as novel UPR regulators, including PERK and IRE1 inhibitors, in cancer therapy (173).

Conclusions

Recent insights indicate that ER stress and oxidative stress are highly inter-related biological processes which regulate a wide range of signaling pathways in the cell. This is not only demonstrated by the fact that the two stresses coexist and induce each other, but also reflected by the multi-functional stress responses which target both ER protein misfolding and redox imbalance. The two cellular stresses profoundly impact normal physiology as well as many human pathologies, including metabolic, neurodegenerative, inflammatory, and neoplastic diseases. Recently, studies suggest that the two stresses and their downstream signaling pathways are promising targets for novel therapeutics. In spite of the exciting findings in the past decade, a number of questions still remain: (i) how do ER stress and oxidative stress act on components at the molecular and cellular level to alter physiology? (ii) how do these stress responses cross-talk with each other in different cell types and disease models? and (iii)

how can we design compounds and therapies that selectively target ER stress and/or oxidative stress in specific tissues/organs? Current efforts to disentangle these puzzles are impeded by the complex nature of both ER stress and oxidative stress. More mechanistic and physiological studies using newly developed high-throughput technologies, a real-time *in vitro* and *in vivo* imaging system, and novel conditional genetic animal models are needed.

Acknowledgments

The authors acknowledge the grant support from NIH HL057346, HL052173, DK042394, and DK088227 and the Crohn's and Colitis Foundation of America (R.J.K.).

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Date of first submission to ARS Central, January 14, 2014; date of final revised submission, March 26, 2014; date of acceptance, April 5, 2014.

Abbreviations Used

APR = acute phase response
ATF6 = activating transcription factor 6
BHA = butylated hydroxyanisole
DSS = dextran sodium sulfate
eIF2α = eukaryotic translation initiation factor 2
ER = endoplasmic reticulum
ERAD = ER-associated protein degradation
Ero1 = ER oxidoreductase 1
ETC = electron transport chain
FDA = Food and Drug Administration
GSH = glutathione
GSSG = glutathione disulfide
H_2O_2 = hydrogen peroxide
HIF-1 = hypoxia-inducible factor-1
IBD = inflammatory bowel disease
IEC = intestinal epithelial cells
IL = interleukin
IP3R = inositol-1,4,5-trisphosphate receptor
IR = insulin resistance
JNK = c-Jun N-terminal kinase
MAM = mitochondria-associated ER membrane
NAFLD = nonalcoholic fatty liver disease
NASH = nonalcoholic steatohepatitis
NF-κB = nuclear factor-kappaB
NOX = NADPH oxidase
NPGPx = non-selenocysteine containing phospholipid hydroperoxide glutathione peroxidase
PBA = 4-phenylbutyrate
PDI = protein disulfide isomerases
PERK = pancreatic ER eIF2α kinase
PKR = dsRNA-activated protein kinase
PUMA = p53 upregulated modulator of apoptosis
QSOX = quiescin sulfhydryl oxidase
redox = reduction–oxidation
RNS = reactive nitrosative species
ROS = reactive oxygen species
S1P = site-1 protease
SOD = superoxide dismutase
TNFα = tumor necrosis factor alpha
TRAF2 = TNFα receptor-associated factor 2
TUDCA = tauroursodeoxycholate
TXNIP = thioredoxin interacting protein
UPR = unfolded protein response
VEGF = vascular endothelial growth factor
XBP1 = X-box-binding protein 1

This article has been cited by:

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