The unfolded protein response

A stress signaling pathway critical for health and disease

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Abstract—The endoplasmic reticulum (ER) is an intracellular organelle consisting of a membranous labyrinth network that extends throughout the cytoplasm of the cell and is contiguous with the nuclear envelope. In all eukaryotic cells, the ER is the site where folding and assembly occurs for proteins destined to the extracellular space, plasma membrane, and the exo/endocytic compartments. The ER is exquisitely sensitive to alterations in homeostasis, and provides stringent quality control systems to ensure that only correctly folded proteins transit to the Golgi and unfolded or misfolded proteins are retained and ultimately degraded. A number of biochemical and physiologic stimuli, such as perturbation in calcium homeostasis or redox status, elevated secretory protein synthesis, expression of misfolded proteins, sugar/glucose deprivation, altered glycosylation, and overloading of cholesterol can disrupt ER homeostasis, impose stress to the ER, and subsequently lead to accumulation of unfolded or misfolded proteins in the ER lumen. The ER has evolved highly specific signaling pathways called the unfolded protein response (UPR) to cope with the accumulation of unfolded or misfolded proteins. Recent discoveries of the mechanisms of ER stress signaling have led to major new insights into the diverse cellular and physiologic processes that are regulated by the UPR. This review summarizes the complex regulation of UPR signaling and its relevance to human physiology and disease.

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Backbone of the unfolded protein response. The history of the unfolded protein response (UPR) started from the identification of a set of genes that were upregulated upon glucose deprivation of fibroblasts.[1-6] The products of these genes were termed glucose-regulated proteins (GRPs).[7,8] The most abundant member of this family, GRP78 (also known as BiP) was the first endoplasmic reticulum (ER) molecular chaperone that was shown to bind incompletely assembled immunoglobulin (Ig) intermediates and prevent their transport from the ER.[9,10] Subsequently, it was demonstrated that overexpression of an unfolded mutant of the influenza hemagglutinin protein was sufficient to induce expression of BiP and another ER chaperone protein, GRP94,[11] leading to the designation of this signaling pathway as the unfolded protein response (UPR). In addition, overexpression of a wild-type protein, coagulation factor VIII, was also shown to induce expression of BiP and GRP94.[12,13] Thereafter, researchers characterized the basic components of the UPR pathway in the budding yeast *Saccharomyces cerevisiae*. A 22-bp UPR element *cis*-acting element (UPRE) was characterized as necessary and sufficient for ER stress induction of a reporter gene in yeast.[14] Following this work, a genetic screen was used to isolate an ER transmebrane bifunctional serine/threonine protein kinase/endoribonuclease (Ire1p/Ern1p) as a proximal UPR transducer required for the induction of yeast BiP (KAR2) and other ER chaperones and for survival upon ER stress.[15,16] Ire1p has an N-terminal lumenal domain that senses the ER stress signal and a C-terminal cytoplasmic domain that has a serine/threonine kinase and site-specific endoribonuclease (RNase) activity required for activating KAR2 transcription.[16-18] The only known substrate for the Ire1p RNase activity is *HAC1* mRNA. The presence of unfolded proteins in the ER lumen promotes dimerization and *trans*-autophosphorylation of Ire1p, activating its RNase activity to remove a 252-base intron from the *HAC1* mRNA through an unconventional splicing reaction.[19-21] Spliced *HAC1* mRNA encodes a basic leucine zipper (b-ZIP) transcription factor that ultimately activates transcription of approximately 381 UPR target genes in yeast.[22]

All eukaryotic cells have conserved the essential and unique properties of the UPR in yeast, but have also evolved additional sensors to generate a diversity of responses. In mammals, the counterpart of yeast Ire1p has two isoforms: IRE1α and IRE1β. Although IRE1α is expressed in most cells and tissues, IRE1β expression is primarily restricted to intestinal epithelial cells.[23,24] The UPR in mammals has two additional stress sensors: PKR-like ER-associated kinase (PERK) and activating transcription factor 6 (ATF6). PERK contains a large ER lumenal "stress sensing" domain that is functionally interchangeable with the IRE1α lumenal domain, and a cytosolic eukaryotic translation-initiation factor 2α kinase

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domain.[25-27] ATF6 is transcription factor with a b-ZIP domain in the cytosol that also contains a large ER lumenal domain to sense ER stress.[28] Each UPR sensor protein is localized to the ER membrane, and is constitutively expressed in all cell types.

The most upstream event for the UPR is the activation of the ER stress sensors by a common stimulus, the accumulation of unfolded proteins in the ER lumen. Current studies support that BiP serves as a master UPR regulator that plays essential roles in activating all three transducers IRE1, PERK, and ATF6 in response to ER stress.[29-31] Under non-stressed conditions, BiP binds to IRE1, PERK, and ATF6 to prevent their signaling. When the ER is overloaded by newly synthesized proteins or is "stressed" by agents that cause accumulation of unfolded proteins, BiP binds to the unfolded proteins in the ER and prevents their transport to the *cis*-Golgi. As unfolded proteins bind and sequester BiP, IRE1 and PERK are released to permit homodimerization and autophosphorylation, leading to their activation.[30,32] Concomitantly, release of ATF6 from BiP permits ATF6 transport to the Golgi compartment where it is cleaved to generate the cytosolic activated form of ATF6 that translocates to the nucleus.[31] Thus, this BiP-regulated activation provides a direct mechanism for the three UPR transducers to sense the "stress" in the ER. However, in certain cells, different stresses or physiologic conditions can selectively activate only one or two of the ER stress sensors. For example, in B cell differentiation, the IRE1α-mediated UPR pathways are activated and indispensable while the PERK-mediated UPR pathway through phosphorylation of eIF2α is not activated and not required for the B-cell differentiation process.[33,34] In contrast, in pancreatic β cells, glucose limitation appears to activate PERK prior to activation of IRE1 (Scheuner and Kaufman, unpublished observation). It will be important to elucidate how a general BiP repression mechanism permits the selective activation of individual components of the UPR that mediate various downstream effects.

In general, UPR signaling is an adaptive mechanism for cells to survive accumulation of unfolded proteins in the ER lumen. The UPR reduces the amount of new protein translocated into the ER lumen, increases retrotranslocation and degradation of misfolded ER-localized proteins, and bolsters the protein-folding capacity of the ER. The UPR is orchestrated by transcriptional activation of multiple genes mediated by IRE1 and ATF6, a general decrease in translation initiation and a selective translation of several specific mRNAs mediated by PERK.

Transcriptional regulation under ER stress. To cope with accumulation of unfolded or misfolded protein in the ER lumen, the UPR is activated to alter transcriptional programs through IRE1 and ATF6 (figure 1). In yeast, ER stress induces IRE1 homodimerization and transautophosphorylation to activate its RNase activity to initiate removal of a

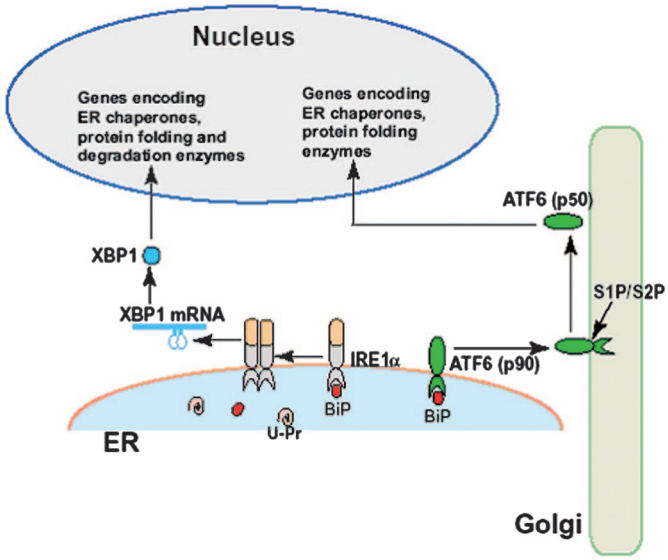

Figure 1. Transcriptional regulation upon ER stress. Upon accumulation of unfolded protein in the ER lumen, BiP release from IRE1 permits dimerization to activate its kinase and RNase activities to initiate XBP1 mRNA splicing. Spliced XBP1 mRNA encodes a potent transcription factor that binds to UPRE or ERSE sequences in many UPR target genes. BiP release from ATF6 permits ATF6 transport to the Golgi compartment where full-length ATF6 (90KD) is cleaved by S1P and S2P proteases to yield a cytosolic fragment (50KD) that migrates to the nucleus to activate transcription of UPR responsive genes. U-Pr, unfolded protein.

252-bp intron from the *HAC1* mRNA.[35] Spliced *HAC1* mRNA encodes a potent transcriptional activator that binds to the UPR element (UPRE, minimal motif TGACGTGC/A) upstream of many UPR target genes and activates transcription.[2,36] In mammals, the promoter regions of many UPR-inducible genes, such as BiP, GRP94, and calreticulin, contain a mammalian ER stress response element (ERSE, minimal motif: CCAAT(N_9)CCACG) that is necessary and sufficient for ER stress-induced gene transcription.[37] Using ERSE as a probe in a yeast one-hybrid screen, researchers isolated two UPR-specific b-ZIP transcription factors, the X-box DNA binding protein 1 (XBP1) and ATF6.[37] XBP1 was identified as a homologue of yeast HAC1 that is a substrate for mammalian IRE1 RNase activity.[38-40] On activation of the UPR, IRE1 RNase cleaves *XBP1* mRNA to remove a 26-nucleotide intron, generating a translational frame-shift. As the precedent of HAC1 regulation in yeast, the spliced *XBP1* mRNA encodes a protein with a novel carboxy-terminus that acts as a potent transcriptional activator for many UPR target genes.

ATF6 is a UPR transducer that can bind ERSE motifs in the promoter regions of UPR responsive genes.[37] There are two forms of ATF6, ATF6α (90 kDa) and ATF6β (110 kD, also known as CREB-RP), both of which require the presence of the transcription factor NF-Y to bind to the ERSE.[28,41,42] On acti-

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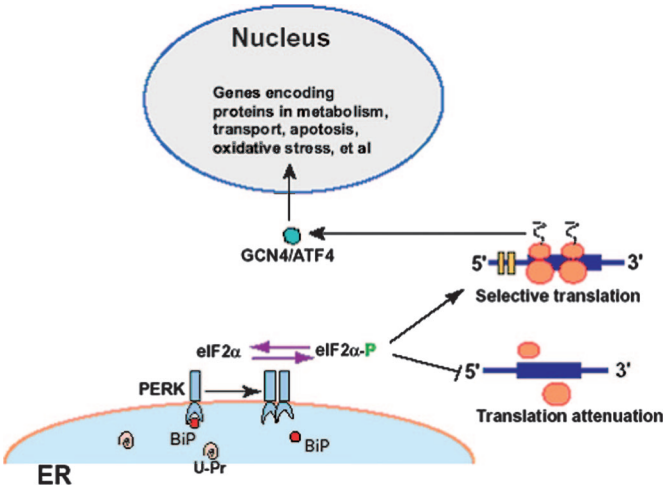

Figure 2. Translational regulation upon ER stress. Upon accumulation of unfolded protein in the ER lumen, PERK is released from BiP, thus permitting its dimerization and activation. Activated PERK phosphorylates eIF2α to reduce the frequency of the mRNA translation initiation in general. However, selective mRNAs, such as GCN4 or ATF4 mRNA, are preferentially translated in the presence of phosphorylated eIF2α. U-Pr, unfolded protein.

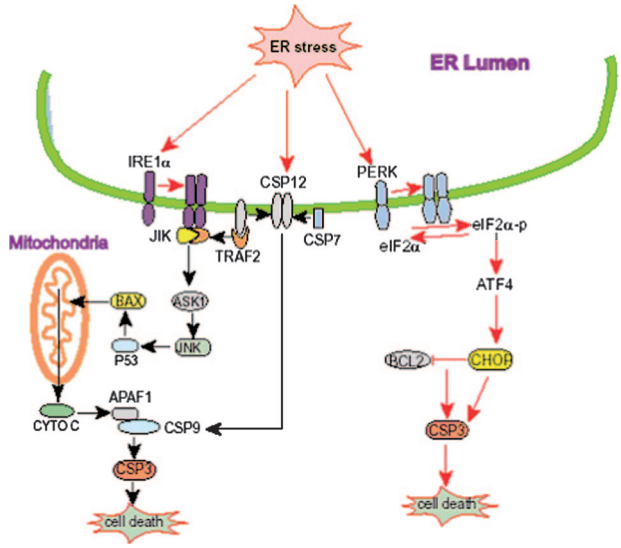

Figure 3. Apoptosis mediated by UPR signaling. Upon ER stress, activated IRE1 can recruit JIK and TRAF2 to activate ASK1 and JNK, leading to activation of mitochondria/Apaf1-dependent caspases. Upon activation of the UPR, c-Jun-N-terminal inhibitory kinase (JIK) release from procaspase-12 permits clustering and activation of procaspase-12. Caspase-12 activates procaspase-9 to activate procaspase-3, the executioner of cell death. Activated PERK phosphorylates eIF2α, that enhances translation of ATF4 mRNA. ATF4 induces transcription of the pro-apoptotic factor CHOP, that can inhibit expression of apoptotic suppressor BCL2. CSP, caspase; CYTO C, cytochrome C.

vation of the UPR, ATF6 transits to the Golgi where it is cleaved by site-1 protease (S1P) and site-2 protease (S2P) to generate a 50 kD cytosolic b-ZIP-containing fragment that migrates to the nucleus to activate transcription of UPR target genes[31,43] (figure 2). Notably, ER stress-induced cleavage of ATF6 is processed by the same proteases S1P and S2P that cleave the ER-associated transmembrane sterol-response element binding protein (SREBP) upon cholesterol deprivation.[43]

ATF6 regulates a group of genes encoding ER-resident molecular chaperones and folding enzymes, whereas XBP1 regulates a subset of ER resident chaperone genes that are essential for protein folding, maturation, and degradation in the ER.[44,45] It was previously proposed that *XBP1* mRNA is induced by ATF6 in response to ER stress to generate more substrate *XBP1* mRNA for IRE1-mediated splicing.[38,41,46] However, UPR induction of *XBP1* transcripts and proteins was not altered in the cells having defective or reduced ATF6 cleavage.[45,46] Induction of *ATF6* mRNA upon ER stress was partially compromised in the absence of XBP1, therefore it was proposed that ATF6 lies downstream of XBP1 in some cases.[45] These results suggest that XBP1 and ATF6 are situated largely in parallel pathways and may interact with each other upon ER stress.

Translational regulation under ER stress. When mammalian cells are subjected to ER stress, an immediate response is activation of PERK to inhibit protein biosynthesis through phosphorylation of eukaryotic translation initiation factor eIF2α.[47] When eIF2α is phosphorylated, the formation of the ternary translation initiation complex eIF2/GTP/Met-tRNA$_i^{Met}$ is prevented, leading to attenuation of translation in general. The ER-resident kinase PERK phosphorylates eIF2α on Ser51, thereby attenuating protein synthesis to reduce the workload on the ER[48-50] (figure 2). Murine cells deleted in PERK or mutated at Ser51 in eIF2α to prevent phosphorylation did not attenuate protein synthesis upon ER stress. As a consequence, these cells were not able to survive ER stress.[48] Whereas phosphorylation of eIF2α by PERK leads to attenuation of global mRNA translation, phosphorylated eIF2α selectively stimulates translation of a specific subset of mRNAs in response to stress (see figure 2). In yeast, the phosphorylation of eIF2α upon amino acid starvation promotes translation of *GCN4* mRNA that encodes a b-ZIP transcription factor required for induction of genes encoding amino acid biosynthetic functions.[51] *GCN4* mRNA contains multiple upstream open reading frames (uORFs) in its 5′ UTR. These uORFs, which ordinarily prevent translation initiation at the authentic GCN4 ORF, are bypassed only when eIF2α is phosphorylated, thus allowing translation of the *GCN4* ORF.[47] This control mechanism is also utilized in mammalian cells to regulate translation in response to ER stress and amino acid starvation. For example, upon ER stress, phosphorylated eIF2α selectively promotes translation of activating transcription factor 4 (ATF4) mRNA.[50] ATF4 subsequently activates transcription of genes in-

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volved in amino acid metabolism and transport, oxidation-reduction reactions, and ER stress-induced apoptosis.[52,53]

ER stress-associated protein degradation and programmed cell death. Protein folding in the oxidizing environment of the ER is an energy-requiring process.[53,54] Under nonstressed conditions, newly synthesized proteins exist as unfolded intermediates along the protein-folding pathway. Once ER stress is imposed, such as by depletion of energy, many folding intermediates become irreversibly trapped in low-energy states and accumulate. These unfolded proteins are retained in the ER through interactions with BiP, calnexin, and calreticulin. Eventually, unfolded or misfolded proteins in the ER lumen are retrotranslocated to the cytoplasm, where they are ubiquitinated and degraded by the proteasome.[55] This process is called ER-associated degradation (ERAD), and is regulated by the UPR. Proteasomal degradation of ER-associated misfolded proteins is required to protect from UPR activation. Proteasomal inhibition is sufficient to activate the UPR, which can, in turn, induce transcription of genes encoding several components of ERAD, such as, DER1, HRD1/DER3, HRD3, and UBC7 in yeast.[22] The IRE1-XBP1 UPR pathway seems to be critical in regulating ERAD. In mammalian cells, induction of the gene encoding the ER degradation-enhancing a 1, 2-mannosidase-like protein (EDEM), an important ERAD component that is essential for degradation of glycoproteins misfolded in the ER, depends solely on the IRE1-XBP1 UPR signaling.[56-59] On the other hand, if the overload of unfolded or misfolded proteins in the ER is not resolved, prolonged UPR activation will lead to programmed cell death.

Three known proapoptotic pathways emanating from the ER are mediated by IRE1, caspase-12, and PERK/CHOP, respectively (figure 3). Under the ER stress, activated IRE1 can bind c-Jun-N-terminal inhibitory kinase (JIK) and recruit cytosolic adapter TRAF2 to the ER membrane.[60,61] TRAF2 activates the apoptosis-signaling kinase 1 (ASK1), a mitogen-activated protein kinase kinase kinase (MAPKKK).[62] Activated ASK1 leads to activation of the JNK protein kinase and mitochondria/Apaf1-dependent caspase activation.[60,62,63] Caspase-12 is an ER-associated proximal effector of the caspase activation cascade, and cells defective in this enzyme are partially resistant to ER stress-induced apoptosis.[64] Under ER stress, activated caspase-12 activates caspase-9, which in turn activates caspase-3, leading to apoptosis.[64,65] Finally, a second death-signaling pathway activated by ER stress is mediated by transcriptional activation of genes encoding proapoptotic functions. Activation of the UPR transducer PERK leads to translation of transcription factor ATF4, which subsequently activates transcription of CHOP/GADD 153, a b-ZIP transcription factor that potentates apoptosis, possibly through repressing expression of apoptotic repressor BCL2.[50,66]

UPR in health and diseases. During cell growth, differentiation, and environmental stimuli, there are different levels of protein-folding load imposed upon the ER. Cells have evolved the ability to augment their folding capacity and remodel their secretory pathway in response to developmental demands and physiologic changes. Accumulating evidence suggests that the UPR plays important roles in differentiation and function of specialized cells. Moreover, pathologic conditions that interfere with ER homeostasis produce prolonged activation of the UPR that may contribute to the pathogenesis of many diseases.

UPR in B-cell differentiation. On terminal differentiation of B lymphoid cells to plasma cells, the ER compartment expands approximately fivefold to accommodate the large increase in immunoglobulin (Ig) synthesis.[67] The UPR transcriptional activator XBP1 is required for plasma cell differentiation.[68] XBP1-deficient B lymphoid cells express Ig genes and undergo isotype switching, but are defective in plasma cell differentiation and do not secrete high levels of Igs. Expression of the spliced form of XBP1 efficiently restores production of secreted Igs in XBP1-deficient B cells, suggesting a physiologic role for the UPR in high-rate production of secreted antibodies.[69] During plasma cell differentiation, IRE1α-mediated splicing of *XBP1* mRNA was found to depend on increased translation of Ig chains.[34,69,70] These observations support the hypothesis that increased synthesis of Ig produces greater amounts of nascent, unfolded and unassembled subunits that bind and sequester BiP, leading to UPR activation. Indeed, BiP is the most abundantly expressed UPR-dependent gene and was first identified as encoding a protein that binds Ig heavy chains in the absence of light chains.[9] In addition, the UPR transducer ATF6 may be involved in the process of terminal differentiation of B cells by regulating secretion of Igs.[34,71] In addition to the role of the UPR in B lymphocyte differentiation into plasma cells, it is possible that the UPR may signal a B cell differentiation program that occurs prior to increased antibody synthesis. Activation of the UPR may be part of the early B lymphocyte differentiation program that occurs prior to induction of high-level antibody synthesis. Recently, our group demonstrated that mouse IRE1α is required at two distinct steps during B cell lymphopoiesis.[33] IRE1α plays essential roles in both early and late stages of B cell development. In the very early stage, IRE1α regulates transcription of the VDJ recombination–activating genes *rag1*, *rag2* and *TdT*, that is required for initiation of VDJ rearrangement and B cell receptor formation. In the late stage of B cell differentiation, IRE1α is required to splice the *XBP1* mRNA for terminal differentiation of mature B cells into antibody-secreting plasma cells.[33]

UPR in glucose homeostasis and diabetes. The metabolism of glucose is tightly controlled at the levels of synthesis and utilization through hormonal regulation. Glucose not only promotes the secretion

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of insulin but also stimulates insulin transcription and translation.[72-74] UPR signaling has been shown to be essential to maintain glucose homeostasis. It is noteworthy that the UPR was first characterized as transcriptional activation of a set of genes, encoding glucose-regulated proteins, in response to glucose/energy deprivation.[5] We now know that pancreatic β-cells uniquely require the UPR for survival during intermittent fluctuations in blood glucose.[48,49] Humans and mice with deletions in PERK have a profound pancreatic β-cell dysfunction and develop infancy-onset diabetes.[49,75] Mice with a homozygous Ser51Ala mutation at the PERK phosphorylation site in eIF2α display a β cell loss in utero, suggesting that translational control through PERK-mediated phosphorylation of eIF2 is required to maintain β cell survival.[48,49] Pancreatic β cells are exquisitely sensitive to physiologic fluctuations in blood glucose, because they lack hexokinase, an enzyme with a high affinity for glucose as a substrate. We propose that blood glucose levels influence the protein-folding status in the ER.[48] As glucose levels decline, the energy supply decreases, so protein folding becomes less efficient and IRE1 and PERK are activated. The UPR regulates transcriptional induction of glucose-regulated proteins that might provide a protective function by increasing the cellular capacity for the uptake and use of glucose. Conversely, as blood glucose levels rise, eIF2α would be dephosphorylated so that translation would accelerate to increase proinsulin synthesis.[48] This would allow entry of new preproinsulin into the ER, and is consistent with the glucose-stimulated increase in total protein and proinsulin synthesis observed in isolated β-cell preparations. Eventually, after prolonged proinsulin translation, the UPR would be turned on to inhibit further protein synthesis and prevent overload of the ER folding capacity. In this manner, a balance between glucose level and PERK-eIF2α UPR signaling is essential for the glucose-regulated periodic fluctuations in proinsulin translation, β-cell function and survival.

The UPR may also play an important role in the regulation of cellular responses to insulin. A recent study showed that ER stress serves as a central feature of peripheral insulin resistance and type 2 diabetes and IRE1α-XBP1 UPR pathway is critical for this process.[76] Mice deficient in XBP1 develop insulin resistance. ER stress in obese mice leads to suppression of insulin receptor signaling through hyperactivation of c-Jun N-terminal kinase (JNK) and subsequent serine phosphorylation of insulin receptor substrate–1 (IRS-1).

UPR in organelle expansion. When the protein-folding load exceeds the capacity of the ER to fold proteins, the UPR maintains ER homeostasis by inhibiting protein synthesis and enhancing transcription of resident ER proteins that facilitate protein maturation, secretion and degradation. The UPR is required for ER expansion that occurs upon differentiation of highly specialized secretory cells.[77] During differentiation of certain secretory cells, such as those in the pancreas or liver, membrane expansion is accompanied by a dramatic increase in protein secretion and UPR activation. Recent evidence supports that one role of UPR activation is to expand the quantity of the ER in order to promote more productive protein folding and secretion. In mature B cells, ectopic expression of XBP1 induced a wide spectrum of secretory pathway genes and physically expanded the ER.[78] Overexpression of spliced XBP1 increased cell size, lysosome content, mitochondrial mass and function, ribosome number, and total protein synthesis. Thus, XBP1 coordinates diverse changes in cellular structure and function resulting in the characteristic phenotype of professional secretory cells. Furthermore, another study has showed that spliced XBP1 could induce membrane biosynthesis and ER proliferation in a cell type different from B lymphocytes.[79] Overexpression of spliced XBP1 in NIH-3T3 cells was sufficient to induce synthesis of phosphatidylcholine, the primary phospholipid of the ER membrane. Cells overexpressing spliced XBP1 exhibit elevated levels of membrane phospholipids, increased surface area and volume of rough ER, and enhanced activity of the cytidine diphosphocholine pathway of phosphatidylcholine biosynthesis.

UPR in neurologic diseases. Neurologic disease caused by expansion of polyglutamine repeats and neurodegenerative diseases, such as Alzheimer disease (AD) and Parkinson disease (PD), are associated with accumulation of abnormal protein and dysfunction of the ER. Analysis of the polyglutamine repeat associated with the spinocerebrocellular atrophy protein (SCA3) in Machado-Joseph disease suggests that cytoplasmic accumulation of the SCA3 aggregate can inhibit proteasome function, thereby interfering with ERAD to induce the UPR and elicit caspase-12 activation.[62,80] AD is a progressive neurodegenerative disorder that is characterized clinically by progressive loss of memory and cognitive impairment, and pathologically by the extracellular deposition of senile plaques. Mutations of genes that encode amyloid precursor protein, presenilin-1 (PS1), and presenilin-2 (PS2) were found to cause familial AD.[81-84] Interestingly, it was observed that PS1 bound directly to IRE1α on the ER membrane and that the autophosphorylation of IRE1α in response to ER stress was diminished in cells expressing mutant PS1 compared with cells expressing wild-type PS1.[85,86] Mutant PS1 was also found to suppress the activation of the other two UPR transducers ATF6 and PERK, so the global ER response to stress seems to be reduced by mutant PS1. Indeed, cells expressing mutant PS1 show increased vulnerability to ER stress.[87] The mechanisms by which mutant PS1 affects the ER stress response are attributed to the inhibited activation of the ER stress transducers IRE1, PERK and ATF6. However, in sporadic AD, the spliced isoform of Presenilin-2 (PS2) induces expression of high mobility group A1a protein (HMGA1a), and also downregulates the UPR signal-

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ing pathway in a manner similar to that of PS1 mutant in familial AD.[88] It was suggested that caspase-4, the human homologue of murine caspase-12, plays critical roles in ER stress-induced neuronal cell death in AD.[89]

Autosomal recessive juvenile parkinsonism (AR-JP) results from defects in the Parkin gene,[90] encoding a ubiquitin protein ligase (E3) that functions with ubiquitin-conjugating enzymes UbcH7 or UbcH8 to tag proteins for degradation. Overexpression of Parkin suppresses cell death associated with ER stress.[91] Inherited PD is associated with the accumulation of PAEL-R in the ER of dopaminergic neurons. PAEL-R is a putative transmembrane receptor protein that is detected in an insoluble form in the brains of AR-JP patients.[92] The accumulation of PAEL-R results from defective Parkin that does not maintain the proteasome-degrading activity necessary to maintain ER function.[93] Finally, translational inhibition through UPR activation was observed in cerebral ischemia. PERK is the only eIF2α kinase that is known to be activated after cerebral ischemia[94] and *XBP1* mRNA splicing was detected after transient cerebral ischemia.[95] Together these findings indicate that the etiology of many neurologic diseases is significantly related to impaired ER homeostasis and activation of the UPR.

Finally, sporadic inclusion-body myostis (s-IBM), the most common degenerative muscle disease in humans age 50 years and older, has similar features of AD, including accumulation of amyloid-β, phosphorylated tau, and several other proteins detected in aggregates observed in patients with AD.[96] ER chaperones including calnexin, calreticulin, GRP94, BiP and ERp72 were found to be abnormally multifocally accumulated in s-IBM muscle fibers, where they colocalized with accumulated amyloid-β protein.[97] Furthermore, it was observed that accumulated amyloid-β precursor protein in s-IBM muscle biopsies could physically interact with calnexin, calreticulin, GRP94, BiP and ERp72. These results suggested that ER stress and the UPR activation are parts of the s-IBM pathogenic cascade and that the UPR may play a role in folding and processing of amyloid-β precursor protein.

Summary and future direction. Over the past 10 years, tremendous progress has been made in identifying the mechanisms of UPR signaling under ER stress conditions. However, there remains much to do in understanding physiologic roles of the UPR in maintaining cell homeostasis and in pathogenesis of many diseases. An important subject for future investigation is to elucidate the sensing mechanisms by which selective UPR transducers are activated under different physiologic conditions. Research efforts to understand the upstream events in the UPR pathway promise to expand our knowledge of UPR regulation and its physiologic functions. It is known that a variety of environmental insults and genetic defects result in accumulation of unfolded or misfolded proteins in the ER that contribute to the pathogenesis of different disease states. As new animal models with defects in different signaling components of the UPR are generated, we will gain a more precise knowledge of how these pathways cause or are a consequence of different pathologic conditions. Elucidating which components of the UPR that are beneficial vs those that are detrimental under different conditions of stress represents a major avenue of research for the future. As we gain a greater understanding of the mechanisms and physiologic roles of the UPR, it should be possible to design novel therapies for the diseases associated with abnormal accumulation of unfolded or misfolded proteins by activating or inhibiting UPR signaling as desired.

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