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Cellular Mechanisms of Endoplasmic Reticulum Stress Signaling in Health and Disease. 1. An overview

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Dufey E, Sepúlveda D, Rojas-Rivera D, Hetz C. Cellular Mechanisms of Endoplasmic Reticulum Stress Signaling in Health and Disease. 1. An overview. *Am J Physiol Cell Physiol* 307: C582–C594, 2014. First published August 20, 2014; doi:10.1152/ajpcell.00258.2014.—Increased demand on the protein folding capacity of the endoplasmic reticulum (ER) engages an adaptive reaction known as the unfolded protein response (UPR). The UPR regulates protein translation and the expression of numerous target genes that contribute to restore ER homeostasis or induce apoptosis of irreversibly damaged cells. UPR signaling is highly regulated and dynamic and integrates information about the type, intensity, and duration of the stress stimuli, thereby determining cell fate. Recent advances highlight novel physiological outcomes of the UPR beyond specialized secretory cells, particularly in innate immunity, metabolism, and cell differentiation. Here we discuss studies on the fine-tuning of the UPR and its physiological role in diverse organs and diseases.

ER stress; UPR; protein misfolding

MAINTAINING PROTEIN HOMEOSTASIS or proteostasis is essential for sustaining cell function. In eukaryotic cells, secreted and membrane proteins fold and mature in the lumen of the endoplasmic reticulum (ER) and Golgi apparatus. Secretory proteins are synthesized by ribosomes attached to the ER membrane and are then folded and modified by a large spectrum of chaperones and foldases in the ER lumen. Correctly folded proteins exit the ER and traffic through the secretory pathway to their final destination. This process is precisely coordinated by efficient quality control mechanisms to ensure that functionally folded proteins exit the ER (28). Misfolded glycoproteins are retained in the ER through the calnexin-calreticulin cycle and delivered to the cytosol for proteasomal-mediated degradation via the ER-associated degradation (ERAD) system (28).

Different cellular perturbations can alter ER function and lead to the abnormal accumulation of misfolded proteins. These alterations include, for example, the expression of disease-related mutant proteins, high secretory demands in endocrine and exocrine cells, viral infections that overload the ER with viral-encoded proteins, or loss of calcium homeostasis that affects calcium-dependent chaperones. ER stress activates a conserved signaling pathway to cope with protein folding alterations, that is collectively known as the unfolded protein response (UPR). The UPR transmits information about the protein folding status at the ER lumen to the cytosol and nucleus to engage adaptive responses (134). UPR signaling increases the biogenesis of the ER and other organelles, enhances folding and quality control mechanisms at the level of gene expression, and fine-tunes protein translation. However, unresolved ER stress results in cell death. Thus, UPR stress sensors can integrate information about the duration and intensity of stress stimuli toward determining cell fate either to adapt and survive or to enter into an apoptotic program.

Accumulating evidence has implicated the UPR in important processes that seem to be independent of its traditional role in the protein folding stress response. Components of the UPR can be differentially engaged to regulate various physiological processes such as lipid metabolism, glucose homeostasis, innate immunity, and cell differentiation (136). Moreover, as demonstrated in a variety of studies in preclinical models, failure of the UPR to sustain ER proteostasis contributes to the development of several pathologies, including metabolic, neurodegenerative, and inflammatory diseases. In agreement with this concept, drug discovery efforts have recently validated ER stress as a therapeutic target to treat several disease conditions (51). Thus, it has become increasingly important to develop a precise understanding of the mechanism of signal transduction of the UPR and its impact on distinct pathologies. This article gives a global view of the signaling mechanism behind the UPR and provides a context to understanding the impact of ER stress in human disease. We review mechanistic aspects of signal transduction by specific UPR stress sensors and how the pathway integrates information in the context of the global proteostasis network to determine cell fate. Finally, we briefly discuss novel physiological outputs of the UPR in different cell types and organs and its possible involvement in the development of human diseases.

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UPR Signaling Branches

In mammals, the UPR is mediated by at least three classes of stress sensors expressed at the ER membrane: PERK (PKR-like ER kinase), IRE1α and -β (inositol-requiring transmembrane kinase/endonucleases), and ATF6α and -β (activating transcription factor 6) (158) (Fig. 1). PERK is a type I transmembrane protein containing an NH_2-terminal domain that detects luminal ER stress and a cytosolic kinase domain. PERK activation involves its dimerization, autotransphosphorylation, and further oligomerization (96). Activated PERK inhibits protein translation through inactivation by phosphorylation of the eukaryotic translation initiation factor eIF2α, thus reducing protein synthesis and decreasing misfolded protein load (43). However, some mRNAs containing short open reading frames in their 5′-untranslated regions are preferentially translated when eIF2α is limiting. One of them is ATF4 mRNA, a transcription factor that positively regulates a cluster of UPR target genes involved in amino acid metabolism, antioxidant response, folding, and the regulation of apoptosis (41, 74, 77). Two important target genes driven by ATF4 are CHOP (C/EBP homologous protein) and GADD34 (growth arrest and DNA damage-inducible 34). GADD34 encodes a regulatory subunit of the phosphatase protein PP1C that counteracts PERK activity by dephosphorylating eIF2α under prolonged ER stress (101). CHOP promotes transcription of *BIM* and decreases the expression of *BCL-2*, triggering apoptosis (145, 152). Attempts to define the impact of PERK signaling on gene expression in mammalian cells revealed that nearly half of PERK-dependent targets are ATF4 independent (44), suggesting the existence of other PERK downstream effectors that have not yet been explored. In a pathway that is less well understood, PERK signaling also activates by phosphorylation the transcription

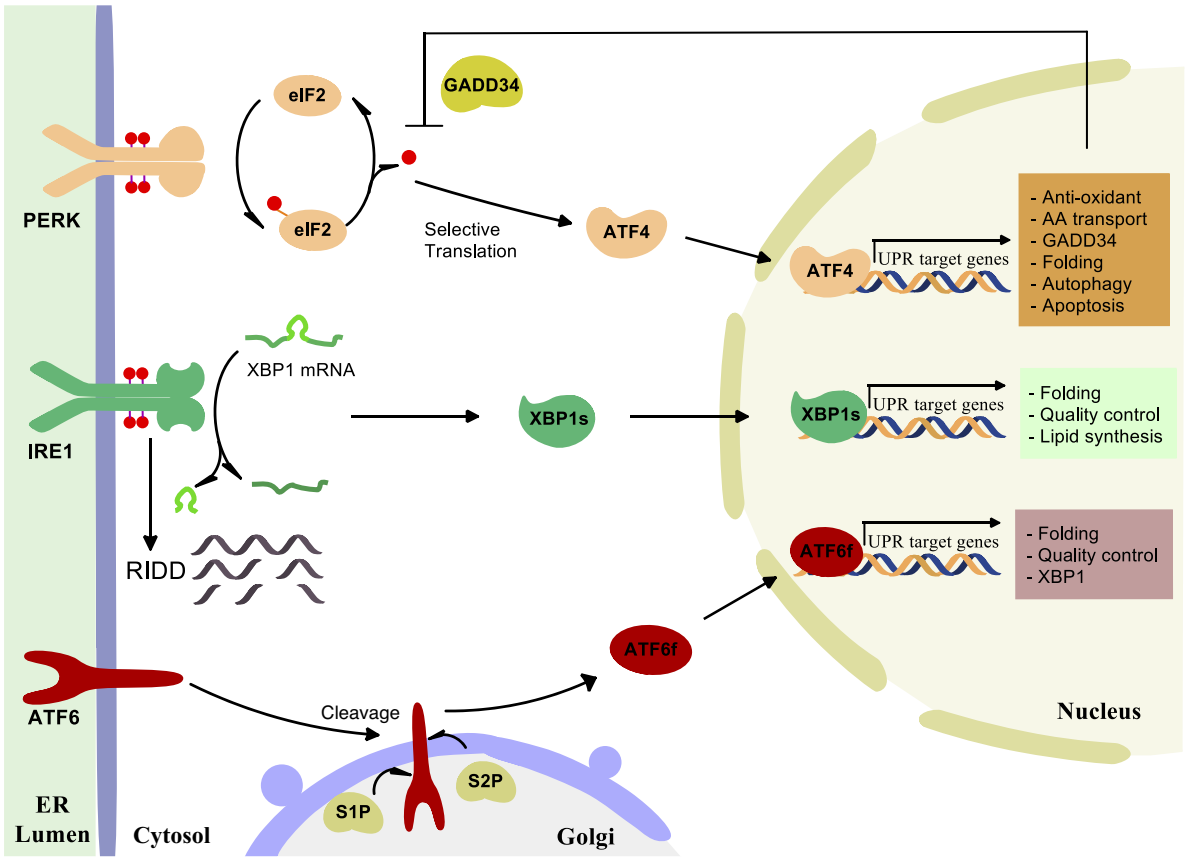

Fig. 1. The unfolded protein response (UPR) signaling. The UPR is mediated by three types of ER stress sensors: IRE1, PERK, and ATF6. Activation of PERK decreases the rate of protein synthesis through phosphorylation of the eukaryotic translation initiation factor eIF2α. As a consequence, eIF2α phosphorylation increases the selective translation of the mRNA encoding for ATF4, a transcription factor that induces the expression of genes involved in amino acid (AA) metabolism, antioxidant responses, apoptosis, autophagy, and GADD34. GADD34 counteracts PERK activity by dephosphorylating eIF2α under prolonged ER stress. Under ER stress conditions, IRE1 dimerizes and autophosphorylates, leading to the activation of its endoribonuclease activity in the cytosolic domain. Active IRE1 processes the mRNA encoding XBP1, a transcription factor that upregulates a subset of UPR target genes related to folding, quality control, and ER-associated degradation (ERAD). IRE1 also degrades certain mRNAs through regulated IRE1-dependent decay (RIDD). ATF6 encodes a transcription factor in its cytosolic domain that localizes to the ER in unstressed cells. Upon the induction of ER stress, ATF6 is processed at the Golgi apparatus, releasing its cytosolic domain which then translocates to the nucleus where it increases the expression of some ER chaperones, ERAD-related genes, and XBP1. See text for definitions of abbreviations.

factors NRF2 (nuclear factor erythroid 2-related factor) and NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), which may have consequences in regulating redox metabolism and inflammatory processes, respectively (141).

IRE1 is the most conserved branch of the UPR from yeast to higher eukaryotes (63). IRE1 has two enzymatic activities in its cytosolic region, a serine/threonine kinase (18) and an endoribonuclease (RNase) (15). Under ER stress conditions, IRE1 autotransphosphorylates and homodimerizes, inducing a conformational change that activates its RNase domain (3, 11, 81, 88). IRE1 signals through a unique mechanism: it catalyzes the unconventional splicing of the mRNA encoding XBP1 (X-box binding protein 1), removing 26 nucleotide intron that changes the reading frame (15, 87, 166). Spliced XBP1 mRNA encodes a potent transcription factor called XBP1s, which modulates the expression of a subset of UPR-target genes including ER chaperones, glycosylation enzymes, ERAD components, components of the ER translocon, or involved in the synthesis of phospholipids (87, 134). Additionally, other RNAs are targets of IRE1 through a process termed regulated IRE1-dependent decay (RIDD) (39, 59). RIDD is conserved in mammals, yeast, and plants (58, 78, 110), and its substrates are defined in a cell-type- specific manner (24, 31, 108, 127). IRE1 is also involved in the degradation of certain microRNAs that have been linked to the regulation of apoptosis, cell migration, energy metabolism, and inflammation (107, 150). IRE1 can also control distinct signaling events that cross talk with other classical stress pathways, highlighting the MAP kinases. The cytosolic domain of IRE1 binds the adapter protein TRAF2 (TNF receptor-associated factor 2), promoting the activation of ASK1 (apoptosis-signal-regulating kinase 1) and the JNK (c-Jun NH_2-terminal kinase) pathway (116, 151). IRE1 also modulates other "alarm pathways" including p38, ERK (114), and NF-kB (60). In general, these signaling events are independent of XBP1 and could have an impact on a wide range of physiological processes ranging from apoptosis/survival, macroautophagy, proliferation, metabolism, and inflammation.

ATF6 is a type II glycoprotein that contains a single transmembrane domain. Under ER stress conditions, ATF6 is transported to the Golgi apparatus where it is processed by the site-1 and site-2 proteases (45, 120, 140). This processing event releases the cytosolic fragment of the protein ATF6f, which acts as a transcription factor and regulates the expression of a subgroup of target genes related to ERAD and protein folding at the ER, in addition to controlling the transcription of XBP1 (1, 45). Furthermore, ATF6f forms heterodimers with XBP1s (166) and thereby, can regulate specific gene expression patterns (143). Moreover, UPR transcription factors can heterodimerize with other transcription factors such as CREB, PCAF, and others (8, 90, 169), resulting in distinct effects on gene expression of a cell-type and stimuli-dependent manner (49), demonstrating the complex and dynamic transcriptional programs activated by the UPR.

Cell Fate and ER Stress

Under ER stress, it is possible to distinguish two temporal and global phases in the UPR. In cells undergoing ER stress, both PERK and IRE1 control immediate reactions to stress before any transcriptional reaction is engaged. One of the fastest consequences triggered by PERK activation is the repression of global protein translation through the control of the phosphorylation stage of eIF2α (41). Similarly, IRE1-RNase activity degrades mRNA coding for secretory proteins that are predicted to be difficult to fold (39, 58, 59, 107). However, this concept is still evolving and there are increasing examples showing that IRE1 also targets mRNAs encoding for proteins localized in the nucleus and cytosol (107), having an immediate impact on RNA stability and as a consequence protein translation.

ER stress also attenuates the translocation of secretory and membrane proteins in a signal sequence-selective manner to reduce ER lumen protein overload, a system termed "preemptive quality control" (69), mediating the cotranslational degradation of diverse ER proteins at the cytosol (124). In addition, early stages of the ER stress response could modulate the transfer of calcium from the ER to mitochondria, which stimulate mitochondrial bioenergetics and ATP production (13, 71).

Under ER stress conditions, autophagy is also activated as a survival pathway. Autophagy is involved in many physiological processes and is essential to maintain metabolic homeostasis. Cells undergoing ER stress activate autophagy to eliminate damaged cellular components and aggregated proteins by the lysosomal pathway. Usually, autophagy is induced as a protective mechanism; however, when autophagy is overactive it can be deleterious to cellular survival (9). ER stress-dependent autophagy is mediated by the binding of IRE1 to the adaptor protein TRAF2, followed by the downstream activation of JNK that modulates Beclin 1 activity (118), an essential autophagy regulator (82). In addition, ATF4 can also induce genes involved in autophagy such as *ATG12*, *ATG5*, and *BECN1* (4). Besides, autophagy-defective cells show upregulation of essential ER chaperones (105), suggesting a close homeostatic balance between the autophagy and UPR pathways. The increase in both autophagy and mitochondrial bioenergetics contributes to the restoration of proteostasis. Together, these immediate responses represent a first barrier to cope with ER stress.

The second phase in the adaptive response controlled by the UPR involves reprogramming of gene expression in part through XBP1s, ATF4, and ATF6f. As mentioned, these factors regulate the expression of a large range of partially overlapping target genes that contribute to an increase in the folding capacity of the ER and an improvement in the efficiency of quality control and protein degradation mechanism (152). Under chronic or irreversible ER stress, apoptosis is triggered as a late event, a process dependent on the canonical intrinsic mitochondrial pathway (Fig. 2). Transcriptional and posttranscriptional mechanisms are activated to regulate proapoptotic members of the BCL-2 family that facilitate cytochrome *c* release from the mitochondria and calcium release from the ER to engage downstream apoptotic signaling events (130). The molecular events that determine how the UPR switches its signaling from an adaptive reaction to activate cell death programs are poorly understood.

Diverse UPR signals emerging from the ER converge into the mitochondrial outer membrane permeabilization (MOMP) to release apoptogenic factors (123, 168). The BCL-2 family of proteins is a group of upstream regulators of MOMP that comprises both anti- and proapoptotic components (22, 167). Antiapoptotic BCL-2 family members are characterized by the presence of four BH domains (BH1–4), and their mechanism of action is the inhibition of the conformational activation of BAX and BAK through direct or indirect mechanisms (147).

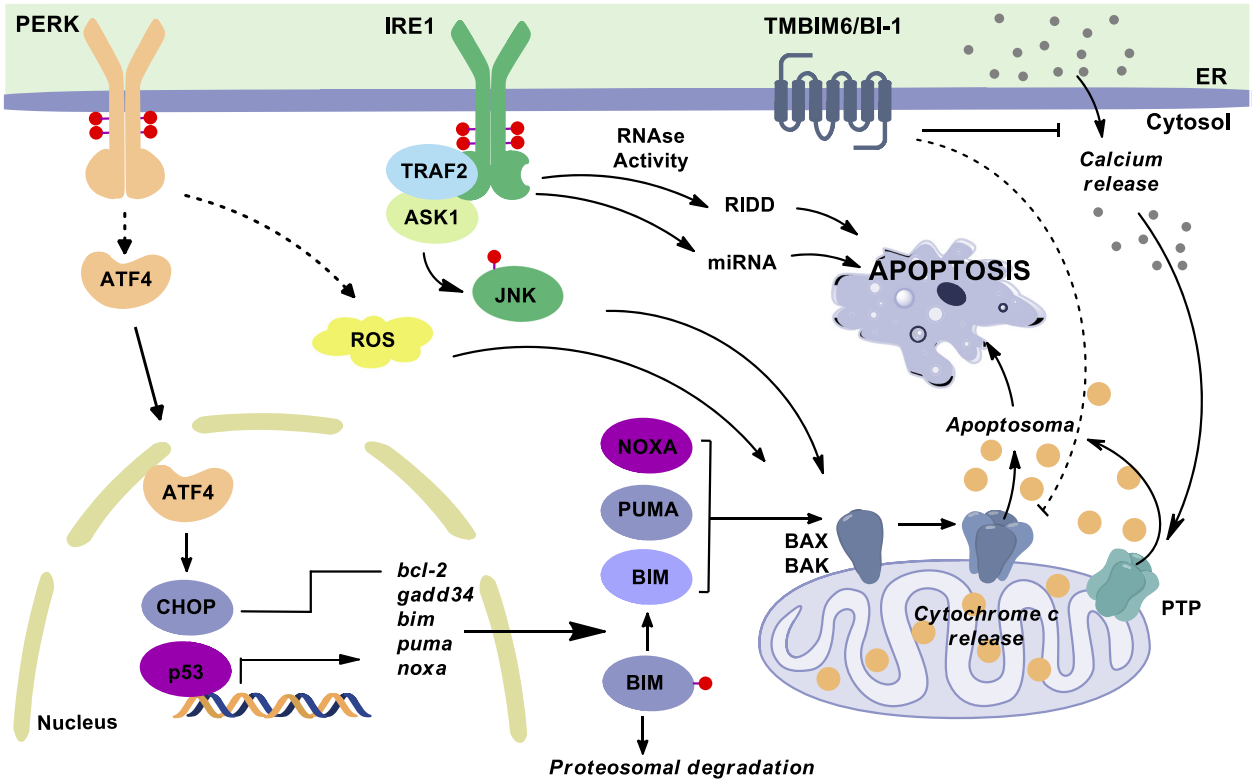

Fig. 2. ER stress-mediated apoptosis. The BCL-2 family of protein plays an essential role in the control of apoptosis under chronic ER stress. Activation of the proapoptotic BCL-2 family members BAX and BAK at the mitochondria is a key step in the induction of apoptosis, leading to the release of cytochrome *c* and activation of downstream caspases. Upstream regulators of BAX and BAK are the BH3-only proteins, another subset of proapoptotic members of the BCL-2 family. Activation of the UPR stress sensor PERK induces the transcriptional induction of the transcription factor CHOP, which downregulates the antiapoptotic protein BCL-2 and induces GADD34. In addition, the UPR controls the transcriptional upregulation of BH3-only proteins (i.e., PUMA, BIM, and NOXA) possibly through p53, CHOP, and ATF4. BIM protein levels can be regulated by phosphorylation, ubiquitination, and proteasomal degradation. The BH3-only protein BID also activates apoptosis when it is cleaved by caspase-2. In addition, PERK is required at the mitochondrial-associated ER membranes (MAMs) to modulate cytochrome *c* release and apoptosis by controlling calcium signaling and ROS production. Active IRE1 also binds TRAF2, leading to the activation of the proapoptotic kinases JNK and ASK. Thus, IRE1 degrades several mRNAs through a process known as RIDD. RIDD has a prosurvival function degrading mRNA coding for proteins with a high tendency to misfold and also has a proapoptotic activity by degrading mRNAs coding for key ER chaperones. Also, the endoribonuclease activity of IRE1 can cleave miRNAs that regulate the expression of proapoptotic proteins. At the ER membrane, TMBIM6/BI-1 inhibits Ca^{2+} release. Mitochondrial Ca^{2+} overload induces opening of the permeability transition pore (PTP), which leads to loss of mitochondrial inner membrane potential ($\Delta\psi$), ionic unbalances, matrix swelling, and mitochondrial inner and outer membrane permeabilization (MOMP). PTP has been associated with cytochrome *c* release. See text for definitions of abbreviations.

Proapoptotic components of the family can be subdivided into "multidomain" members displaying homology in the BH1–3 domains, such as BAX, BAK, and BOK, and the "BH3-only" members, which are characterized by the presence of only one BH3 domain critical for apoptosis activation (72). Chronic ER stress leads to the transcriptional and posttranslational upregulation of proapoptotic BH3-only proteins, such as BIM, PUMA, BID, and NOXA. This engages the activation of downstream proapoptotic proteins BAX and BAK (89). The control of expression of BCL-2 members under chronic ER stress has been attributed in part to the PERK-ATF4-CHOP axis (109). Thus, CHOP represses the expression of BCL-2 and upregulates the transcription of BIM, promoting apoptosis. Interestingly, p53 is also involved in the upregulation of BH3-only proteins such as PUMA and NOXA under ER stress (92). GADD34 expression enhances reactive oxygen species (ROS) production possibly by promoting protein synthesis overloading, which may increase proteotoxicity (80). This event triggers cell death possibly due to augmented ROS production and ATP depletion (40). The BH3-only protein BID can be posttranscriptionally activated via cleavage mediated by caspase-2 (130, 146). ER stress-dependent apoptosis is also highly controlled by another family of cell death regulators, known as the Bax-inhibitor 1 (BI-1) or TMBIM protein family (133). The TMBIM family has a well-described impact on UPR signaling and ER calcium homeostasis under ER stress. Both TMBIM6/BI-1 (20, 161) and TMBIM3/GRINA have antiapoptotic activity under chronic ER stress, but only the mRNA coding for TMBIM3/GRINA is upregulated by ER stress through the PERK-ATF4 branch (132). Another complementary mechanism involved in cell death induced by prolonged ER stress is ER calcium release (54, 146), which sensitizes mitochondria to undergo MOMP.

Prolonged activation of IRE1 has been associated with the induction of apoptosis, possibly due to the activation of ASK1/JNK (151) and by the occurrence of RIDD of certain mRNAs and miRNAs that encode ER chaperones and regulators of cell death such as caspase-2 (150). Although many distinct mechanisms have been shown to engage apoptosis by ER stress, the effects of these individual events are only partial, suggesting that the apo-

ptosis programs triggered by the UPR are highly complex and dependent on the cross talk between different signaling pathways.

Regulation of UPR Stress Sensors

The first step in the induction of the UPR is the detection of abnormal levels of unfolded proteins in the ER lumen. A few models have been proposed to explain how UPR stress sensors monitor unfolded protein load. The mechanism of activation of IRE1 has been primarily studied in yeast (75). This model suggested that binding of BiP, an ER-resident chaperone, to IRE1 and PERK, or IRE1p, retains the sensors in a monomeric and inactive state, thereby preventing their oligomerization. Under ER stress conditions, BiP preferentially interacts with unfolded proteins, releasing its association with IRE1 and PERK luminal domains, enabling their spontaneous oligomerization (11, 75, 121, 134). In this model, BiP is the actual sensor because of its ability to detect misfolded proteins, whereas PERK and IRE1 operate as signal transducers. Further studies in yeast, however, have shown that IRE1p or BiP mutants that disrupt their binding do not dramatically alter the activation of the UPR (11, 75). An alternative "direct-recognition" model has emerged based on structural and biochemical analysis of yeast IRE1p. The crystal structure of the yeast IRE1 luminal domain (19) and recent biochemical evidence has shown that IRE1p directly binds to unfolded proteins, triggering IRE1p activation and oligomerization (32). In yeast, BiP dissociation and reassociation to IRE1p may help fine-tune its activation but also modulate the inactivation phase that is observed after prolonged ER stress (75).

The luminal event mediated by IRE1β involves direct interaction with unfolded proteins, whereas IRE1α activation is mediated by association/dissociation with BiP (119). The three-dimensional structure of the mammalian IRE1α luminal domain is similar to the yeast IRE1; however, the binding of IRE1α to unfolded proteins is theoretically incompatible because the binding pocket is narrow in the crystal structure reported (172) and this binding has not been recapitulated in vitro when compared with the yeast IRE1p luminal domain (75). Besides, in contrast to the yeast UPR, mutations in IRE1α that reduce its ability to bind BiP enhance the ability of this sensor to be activated, even in the absence of stress (76).

Little is known about how ATF6 responds to ER stress. ATF6 also associates with BiP under resting conditions, and this binding masks a Golgi apparatus localization signal, retaining ATF6 at the ER membrane (142). Upon ER stress, BiP is released, thus allowing the translocation of ATF6 to the Golgi apparatus where it undergoes proteolytic processing. The ATF6 luminal domain also contains intramolecular and intermolecular disulfide bonds that may serve as redox sensors to monitor the ER environment. Interestingly, one study indicated that ATF6 could be selectively activated by the overload of the ER membrane with proteins (100). It remains to be determined whether PERK or ATF6 activation also involves the direct recognition of unfolded proteins. These models require further biochemical analysis to fully understand ER stress-sensing mechanisms.

Fine-Tuning ER Stress Signaling: The UPRosome

The kinetics of activation and signal attenuation between the three UPR stress sensors could differ depending on the nature and duration of the stress stimuli and the cell type analyzed, suggesting the existence of modulatory mechanisms that fine-tune the UPR beyond the accumulation of misfolded proteins at the ER (49). Interestingly, accumulating evidence suggests that the UPR may be engaged, even, in the absence of stress through signal transduction mechanisms that affect UPR stress sensors, mediated in part by the binding of cofactors or posttranslational modifications. Thus, the mechanisms underlying the activation of the UPR may differ from yeast to mammals and may involve distinct selective modulatory events.

The integration of UPR signaling determines cell fate under ER stress. As mentioned, increasing evidence indicates that the selective modulation of specific UPR branches impacts the balance between adaptation/survival and cell death under ER stress. Although PERK and IRE1 share functionally similar luminal sensing domains (96), depending on the cell type, the signaling kinetics of these sensors is markedly different. For example, in certain conditions, IRE1 signaling is turned off by prolonged ER stress (93), whereas PERK signaling can be sustained until apoptosis occurs (94). Attenuation of IRE1 signaling under chronic ER stress is predicted to reduce the expression of XBP1s and as a consequence its prosurvival effects, whereas sustained PERK signaling favors the upregulation of proapoptotic factors. The differences between the regulation of these sensors has been explained by a mechanism that involves structural changes in their cytosolic domains and the physical association of positive and negative regulators. These regulatory factors could specifically affect their activation and modulate the intensity of downstream signaling outputs. Most of the studies on protein-protein interactions have been performed with IRE1, leading to the definition of a dynamic signaling platform that has been referred to as the "UPRosome" (52). In this section we discuss a few regulatory mechanisms that fine-tune the amplitude and kinetics of individual UPR signaling branches.

Several studies have uncovered an interesting cross talk between IRE1 and the apoptosis machinery (50). An initial discovery from our group indicated that IRE1 signaling is selectively enhanced by the expression of BAX and BAK, involving the formation of a protein complex with the cytosolic domain of IRE1 (50). Similarly, expression of the proapoptotic BH3-only proteins BIM and PUMA at the ER membrane triggers the activation of the JNK pathway in an IRE1- and BAK-dependent manner (79). These BCL-2 family members also modulate the maintenance of IRE1 signaling under prolonged ER stress (131). In this context, a subgroup of proapoptotic BCL-2 family members may have a dual function: They operate as prosurvival factors, instigating early adaptive responses to cope with ER stress via IRE1 and XBP1 signaling, and also mediate downstream and late effecter functions in apoptosis at the mitochondria. Several other components of the UPRosome complex have been reported (49), including the recent discovery of the nonmuscle myosin IIB, which controls the formation of the IRE1 clusters (46) and the disulfide isomerase PDIA6, which modulates the redox status of IRE1 through its luminal region (27, 37). In addition, indirect evidence suggests that XBP1 mRNA splicing and RIDD activity may also be differentially modulated (107), adding an additional layer of complexity to the regulation of IRE1.

As mentioned, under constant ER stress, IRE1 is turned off. Inactivation of IRE1 involves the dissolution of IRE1 clusters and dephosphorylation of IRE1, leading to a decline of XBP1

mRNA splicing (91). Bax-inhibitor 1 (BI-1) is a central mediator of IRE1 attenuation as demonstrated in different studies in cell culture and animal models of ER stress (6, 7, 95, 135). In other experimental systems the opposite behavior has been observed, where XBP1 mRNA splicing is sustained over time while eIF2α phosphorylation is attenuated through a feedback loop that induces its phosphatase (14, 98, 117). Thus, the UPR is fine-tuned in a dynamic manner through the assembling of distinct factors to the UPRosome, which potentially establishes a stress threshold to engage the UPR.

In addition to the negative regulation of eIF2α phosphorylation by GADD34 (117), PERK can also be modulated by other components by a physical interaction. For example, under ER stress conditions, p58 IPK expression is upregulated and binds to PERK, reducing its kinase activity (156, 165). Recent evidence has also shown that mitofusin 2 interacts with PERK and that deficiency of mitofusin 2 enhances PERK phosphorylation, impacting apoptosis and autophagy (113). Other components also selectively modulate PERK, in particular Nck1 (164), a splicing variant of BiP (115) and the calcium-dependent phosphatase calcineurin (12). Although less well studied, ATF6f is also modulated through interactions with other factors. The UPR target gene *WFS1* represses ATF6 signaling possibly by inducing its proteasome-dependent degradation (29). ATF6 is also modulated by redox changes of its luminal cysteine and also by glycosylation, where the protein disulfide isomerase PDIA5 modulates ATF6 activation (57).

Systematic studies are needed to define the interactome of UPR stress sensors and to understand how their composition is modulated by ER stress in different contexts. We predict that the identification of distinct UPRosomes will emerge from these studies, where their identity may depend on the cell type and stimuli analyzed. All these examples demonstrate the highly regulated and dynamic nature of the UPR. Assembling of specific UPRosomes may allow the integration of information regarding the type and intensity of the stress stimulus toward reinforcing specific outputs of the UPR according to the cell's needs.

UPR in Physiology and Disease

UPR activation is observed in many physiological processes beyond the homeostatic control of protein folding. Components of the UPR play a central role in the normal development and differentiation of specialized secretory cells, including B cells, pancreatic β-cells and salivary glands. In addition, recent studies have associated the UPR with the control of innate immunity and in the control of energy metabolism and the synthesis of cholesterol and lipids. Furthermore, abnormal ER stress levels are involved in several diseases including diabetes mellitus, neurodegeneration, cancer, and other pathologies (Fig. 3). In this section, we describe some examples that highlight the impact of the UPR to the development of disease and its participation in the homeostatic control of diverse tissues (Table 1).

During the differentiation of B cells to antibody-secreting plasma cells, XBP1s is required to induce cell differentiation in addition to enhancing the folding capacity of the cell (65, 129). Professional secretory immune cells lacking XBP1 display severe abnormalities in their development and function as initially reported in plasma B cells (65) and dendritic cells (66). ATF6 is also activated during plasma cell differentiation (33), while PERK remains inactive (34). In contrast, pancreatic β-cells require PERK signaling to maintain endocrine function. In fact, genetic targeting of PERK/eIF2α signaling leads to β-cell deficiency, altering insulin production and glucose metabolism, which results in early-onset diabetes mellitus (42, 139, 171). Similarly, developmental ablation of XBP1 triggers a collapse in the exocrine pancreas and salivary glands, whereas endocrine pancreas in adults is also altered, leading to hypoglycemia (50, 84, 85). XBP1 conditional deletion in pancreatic β-cells causes hyperglycemia, glucose intolerance, and markedly decreases the number of insulin granules, in addition to impaired proinsulin processing (2, 85). Interestingly, insulin mRNA is a RIDD target and its expression is also controlled by XBP1 (39). XBP1-deficient animals present hypoplastic fetal livers, with reduced hematopoiesis triggering early death during development due to anemia (128). Postnatal XBP1 liver-specific knockout mice do not show any spontaneous abnormalities, with no evidence of liver damage; however, a dramatic alteration in lipid synthesis is observed (86). In the liver, IRE1α controls lipogenesis and lipoprotein metabolism through the RIDD pathway (144).

UPR components have a crucial role in bone development and osteoblast function. PERK-deficient animals develop drastic osteopenia involving a reduction of trabecular bone thickness and volume (138, 159, 171). Interestingly, targeting XBP1 in intestinal epithelial cells triggers spontaneous enteritis, augmenting the susceptibility to colitis and chronic inflammation (70). Moreover, a polymorphism in the *XBP1* gene was found in patients with Crohn's disease (35). In addition, emerging roles of the UPR in innate immunity have been described, involving activities in macrophage and dendritic cell differentiation and function (103, 122). XBP1 is induced downstream of Toll-like receptors, modulating the production of proinflammatory cytokines in macrophages (103). Genetic manipulation of key UPR components has also demonstrated a crucial role of the pathway in gastric zymogenic cell differentiation (61) and intestinal epithelial cell differentiation (47), among many other relevant physiological roles (reviewed in Ref. 17).

In relation to the phenotypes observed in UPR target mouse models, PERK knockout animals are viable, allowing the early characterization of its function in vivo in the field (42). IRE1α null mice develop dramatic defects during development, leading to lethality at 12.5 days of gestation (170). These mice show a decrease of vascular endothelial growth factor and abnormalities in the blood vessels of the placenta (27). Remarkably, there is a rescue of the embryonic lethality in conditional knockout mice when IRE1α is reconstituted in the placenta (68). Surprisingly, these animals did not develop hypoplasia in the liver (68) as described for XBP1-deficient mice (68) and, in contrast to the phenotypes described for XBP1-deficient animals, IRE1α deletion caused only mild abnormalities of exocrine tissues and only slightly altered blood glucose level and serum immunoglobulin levels (67). One possible explanation is that the deletion of XBP1 produces the overactivation of IRE1α activity that decreases some RIDD target genes, compensating for XBP1 loss-of-function (62). In addition, neither ATF6α nor ATF6β is essential for embryonic development and single knockout animals do not show evident growth defects and develop normally into adulthood (160, 162). Importantly, ATF6α and ATF6β double deficiency results in full embryonic lethality, suggesting that these proteins

have functional redundancy, with essential functions during mouse development (162). However, ATF6α knockout animals are hypersensitive to experimental ER stress as revealed by the unexpected lethality observed after the intraperitoneal injection of the ER stress agent tunicamycin, associated with the generation of acute liver and kidney damage (160, 162). ATF6α plays an important role in glucose and lipid homeostasis under both pharmacologically induced and physiological ER stress. Moreover, ATF6α-deficient mice showed augmented hepatic triacylglycerol levels, fat deposits, and increased lipid droplets, which are associated with liver microvesicular steatosis (137, 163). In agreement with this concept, this abnormal hepatic phenotype is observed during the genetic ablation of any of the three UPR branches (137).

The physiological role of the UPR in many organs translates into the development of several diseases when the ER proteostasis is irreversible damaged. For example, increased levels of ER stress are observed in models of obesity and diabetes, leading to inflammatory reactions and insulin resistance (30). Suppression of insulin signaling pathways occurs through IRE1-dependent hyperactivation of JNK and subsequent phosphorylation of insulin receptor substrate on serine residues (125). Wolcott-Rallison syndrome (childhood diabetes) mutations in PERK have been associated with abnormal function of pancreatic islets (25), consistent with the phenotypes described in *perk*-deficient animals (43).

One of the major areas of therapeutic development in the UPR field is cancer. Early studies demonstrated that the UPR is essential for the survival and growth of tumor cells into solid tumors, providing an adaptive capacity to the adverse microenvironmental conditions generated by hypoxic conditions (23, 99). In addition, accumulating evidence indicates that the UPR contributes to tumor growth, metastasis, and angiogenesis (5, 16, 26, 111, 153). Importantly, genomic screening of cancer cells has revealed that IRE1 is one of the kinases most frequently mutated in cancer (36, 38, 126). More recently, XBP1- dependent gene signatures were proposed as a predictor of the aggressiveness of different types of cancer (21, 73). Many different drug screening efforts have identified small molecules that selectively inhibit PERK or the RNAse activity of IRE1, exhibiting potent antitumor activity in a variety of cancer models in vivo (51).

Another area of active research in the UPR field is neuroscience. Conditional deletion of XBP1 in the central nervous system has been performed to test its contribution to neurodegeneration in many disease models (55). In addition, deletion of PERK in the adult forebrain resulted in reduced eIF2α phosphorylation and ATF4 expression, leading to altered be-

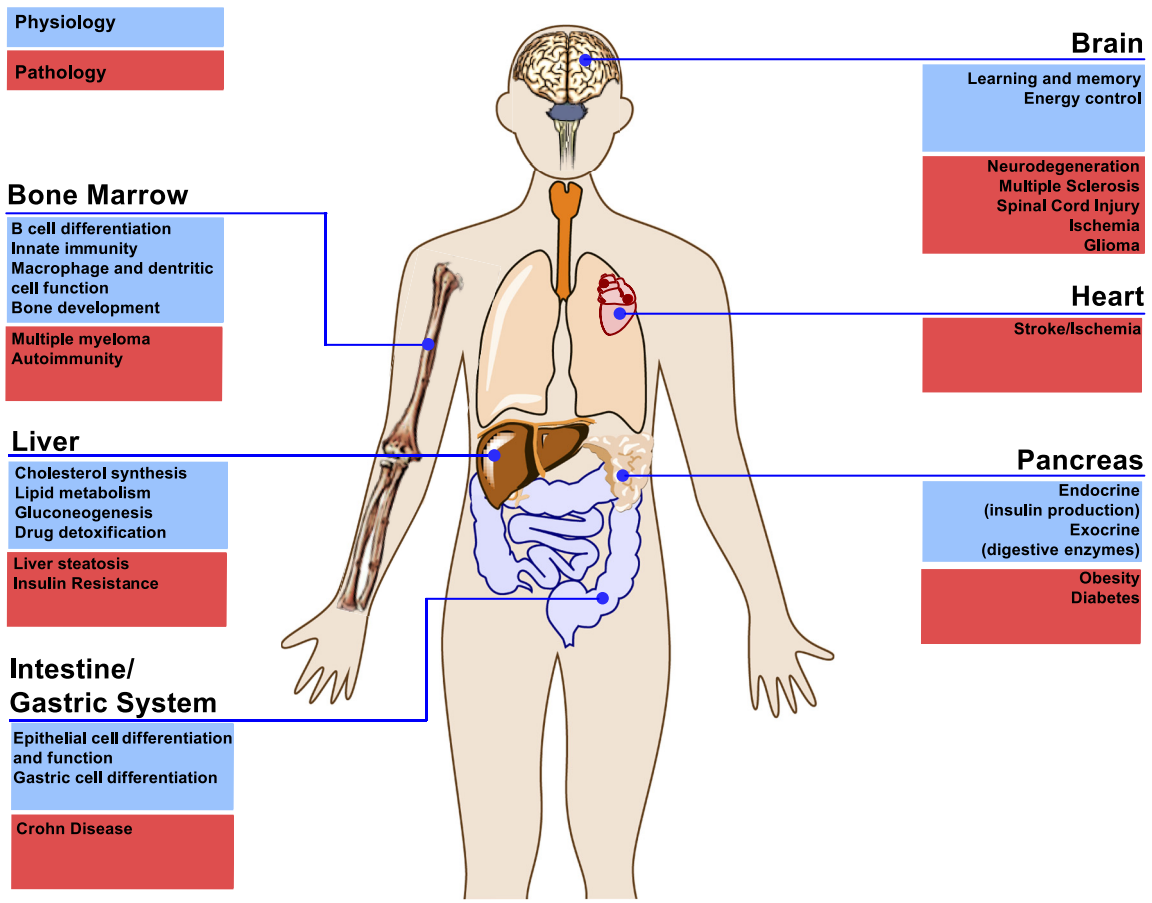

Fig. 3. Role of the UPR in physiology and diseases. Genetic manipulation of major UPR components has revealed its relevance in the function of diverse organs and cell types, in addition to its contribution to a variety of diseases using preclinical mouse models. Important functions have been reported in brain, bone marrow, heart, liver, pancreas, intestine, and gastric system (blue boxes). Pathologies where abnormal ER stress levels play a relevant role in disease include diabetes, neurodegeneration, ischemia, cancer, and other diseases (red boxes).

Table 1. *UPR mouse models and associated phenotypes*

UPR Member	Animal Model	Phenotype	Reference
IRE1α	Full knockout	Embryonic lethality after 12.5–13 days of gestation.	(68, 170)
IRE1α	Conditional embryo-specific knockout	Hyperglycemia, mild hypoinsulinemia. Abnormal histological structure of the acinar pancreas and salivary serous tissues.	(67)
IRE1β	Full knockout	Increased susceptibility to experimental colitis.	(10, 64, 102, 149)
XBP1	Full knockout	Hypoplastic fetal liver, reduced hematopoiesis, and embryonic death from anemia at 12.5 days of gestation.	(128)
XBP1	Adult liver-specific knockout	No gross liver abnormalities. Reduced plasma levels of cholesterol and triglycerides due to decreased hepatic lipid synthesis and secretion.	(86)
XBP1	Conditional β-cell-specific knockout	Mild hyperglycemia and glucose intolerance due to impaired proinsulin processing and reduced insulin secretion.	(85)
PERK	Full knockout	Hyperglycemia, impaired synthesis of insulin, and digestive enzymes. β-Cell loss. Growth retardation and skeletal dysplasia.	(42, 171)
PERK	Brain-specific knockout	Cognitive deficits in information processing.	(148)
ATF4	Full knockout	Defective eye lens development. Severe anemia due to impaired fetal-liver hematopoiesis.	(48, 83, 104)
ATF6α	Full knockout	Hypoglycemia, insulin resistance, and liver steatosis in response to pharmacologically induced ER stress.	(154, 163)
ATF6β	Full knockout	No obvious phenotype.	(162)
ATF6α and -β	Double knockout	Embryonic lethality.	(162)

UPR, unfolded protein response; IRE1, inositol-requiring transmembrane kinase/endonuclease 1; ER, endoplasmic reticulum; PERK, PKR-like ER kinase; ATF4, activating transcription factor 4.

havior in several tests (148). Interestingly, disruption of PERK improves learning and memory in an Alzheimer's disease mouse model (97). Although the role of the UPR in the physiology of the nervous system remains poorly understood, the occurrence of chronic ER stress is widely described in most models of neurodegeneration and human postmortem studies (55). ER stress is found in the brain of patients affected with diseases such as Alzheimer's, Parkinson's, Huntington's, amyotrophic lateral sclerosis (ALS), and prion-related disorders. These diseases have different clinical manifestations; they all involve the accumulation of protein aggregates containing misfolded proteins. Initially, it was proposed that UPR activation in neurodegenerative diseases represents a pathogenic event; however, the scenario is much more complex because genetic manipulation of distinct UPR signaling components in preclinical models of neurodegeneration have revealed contrasting and sometimes opposing results (55). Activation of the UPR may enhance or prevent neurodegeneration in different diseases, and in some cases may have opposite effects depending on the signaling branch activated. For example, we have reported that targeting XBP1 in ALS (56) or Huntington's disease (157) provides protection through upregulation of autophagy, whereas in spinal cord injury it reduces motor recovery (155). In prion diseases, XBP1 deficiency did not have any effects (53). In contrast, targeting PERK/ATF4 signaling in ALS (106) or prion diseases (112) protects against degeneration; it has no effects in Huntington's disease (157) and exacerbates the effects of spinal cord injury (155). The relevance of the UPR in brain disorders seems to be specific to distinct diseases, therefore, a systematic study of the functional significance of ER stress is needed to understand the contribution of UPR in neurodegeneration. In summary, overall, the UPR is emerging as a relevant homeostatic network that could contribute to the pathogenesis of many common human diseases.

Perspectives

The adaptive capacity to protein folding stress is fundamental to sustain the physiological function of specialized secretory cells. The UPR constitutes an extremely dynamic and complex network of signals, whose impact on cell fate depends heavily on a larger cellular context. Mechanistic studies have revealed that the effector consequences of UPR signaling (outputs) are diverse and have effects beyond its classical role as an adjustor of the protein folding status. In addition, understanding the way in which the UPR is fine-tuned is acquiring more relevance because of its fundamental impact to understanding how cells transit from an adaptive to an apoptotic phase. We believe that defining the UPR stress sensor interactome is needed to uncover the composition of the UPRosome and how the pathway is connected to other signaling events.

The UPR has been involved in several diseases with a high prevalence and mortality, and studies continue to identify novel connections between ER stress and disease. Modulating the activity of the UPR on a disease context has been validated using pharmacology and gene therapy approaches in a variety of preclinical models (51). Owing to the impact of ER stress signaling on the sustenance of various organ functions, it is difficult to predict the side effects of targeting the pathway with chronic administration of UPR-targeting small molecules. Future clinical trials will unveil the true potential of this pathway as a therapeutic target. Applications in the area of biomarkers for diagnosis and prediction of disease prognosis are also emerging in the field which we believe will represent an enormous advance to monitor clinical trials in the future as a mirror of the health of the proteome.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

E.D. conception and design of research; E.D., D.S., and D.R.-R. prepared figures; E.D., D.S., D.R.-R., and C.H. drafted manuscript; E.D., D.S., D.R.-R., and C.H. edited and revised manuscript; E.D. and C.H. approved final version of manuscript.

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