Published in final edited form as:
Gastroenterology. 2011 July ; 141(1): 38–41.e2. doi:10.1053/j.gastro.2011.05.018.

The Cell Biology of the Unfolded Protein Response

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Abstract

The Unfolded Protein Response (UPR) is an ensemble of signal transduction pathways that respond to perturbations in the oxidative, pro-folding environment of the endoplasmic reticulum. During the past decade, ongoing research implicated these pathways in maintaining homeostasis of cells and organisms exposed to various stresses. Herein, we highlight recent findings regarding the functional role of the UPR in both normal and pathophysiological processes.

The lumen of the endoplasmic reticulum (ER) provides an oxidative compartment wherein proteins destined for secretion or insertion into cellular membranes are co-translationally modified with sugar moieties and folded. Stresses that compromise the ER environment impair maturation resulting the accumulation of mis-folded proteins and activation of a stress response termed the Unfolded Protein Response (UPR)[1,2]. While chemicals that inhibit N-linked glycosylation (tunicamycin) or deplete ER calcium (thapsigargin) are frequently used to impair protein folding within the ER, environmental stresses that reduce carbon source availability (glucose), and oxygen, which occurs under pathogenic conditions such as cancer and viral infection, also have a direct impact on secretory homeostasis and thereby trigger the UPR[3,4]. The UPR is characterized by increased transcription of genes encoding ER molecular chaperones including BiP/GRP78 and GRP94, protein disulfide isomerase (PDI), and the pro-apoptotic transcription factor *CHOP* (C/EBP homologous protein), which is also known as growth arrest and DNA damage gene-153 (*GADD153*)[5]. The induction of ER chaperones is in turn coordinated with a marked decrease in the rate of overall protein synthesis and with cell cycle arrest. Inhibition of protein synthesis serves to lower the overall rate of protein traffic into the ER, but the fact that this process is counterbalanced by an increased synthesis of ER chaperones highlights the specificity of the UPR. This mini-review will focus on advances in our understanding of the role of the UPR

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in determining cell fate in response to micro-environmental stresses to which cells must respond.

Signal Transduction from the ER

Ire1 isoforms (α, ubiquitously expressed α and tissue restricted β), are composed of a luminal domain that senses stress, a single transmembrane domain, and a cytosolic tail that contains both a protein kinase domain and an RNase domain[6, 7]. Ire1 triggers increased expression of numerous ER chaperones through activation of the X-box binding protein 1 (Xbp1) transcription factor (Figure 1). Accumulation of Xbp1 is mediated by the RNase function of Ire1, which mediates an alternative splicing event that generates an alternative Xbp1 mRNA that is more efficiently translated[8, 9]. PERK, another ER transmembrane protein kinase activated in a manner analogous to the Ire1[10], catalyzes serine 51 phosphorylation of eIF2α resulting in down-regulation of general protein synthesis[11, 12]. While PERK is one of four distinct eIF2α protein kinases, which includes the heme-regulated kinase (HRI), the interferon-inducible, RNA-dependent protein kinase (PKR) and GCN2, only PERK function is required for cellular response to ER stress. The third signaling components are the transmembrane transcription factors ATF6α/β. While normally tethered to the ER, upon stress, ATF6 migrates to the trans-Golgi, where it is processed by S1P and S2P proteases to release the N-terminal DNA-binding transcription factor domain. The latter regulates transcription of a subset of Xbp1 responsive genes due to their related DNA binding specificities[13].

Activation of both Ire1 and PERK requires dimerization via sequences within luminal domains[14]. Dimerization is antagonized by the ER chaperone BiP, which physically inhibits association. Increased levels of unfolded proteins in the ER lumen titrate BiP thereby permitting dimerization and activation of PERK/Ire1 molecules. ATF6 is also regulated by BiP, unlike Ire/PERK, BiP inhibits movement of ATF6 to the Golgi and thereby determines access to activating protease activity. Thus, the chaperone to misfolded protein ratio is considered a key determinant in UPR status.

At the interface of cell cycle progression

Activation of UPR signaling triggers a rapid arrest in G1 phase of the cell cycle. G1 phase progression requires the activities of one or more of the D-type cyclins (D1, D2, D3) in association with either CDK4 or CDK6 followed by activation of the cyclin E- and A-dependent kinase CDK2. Cell cycle arrest in response to mitogen deprivation or anti-proliferative cytokines can be achieved through degradation of unstable cyclin subunits, by specific post-translational modifications of the CDK subunits, or via association of active cyclin-bound CDKs with polypeptide CDK inhibitors (CKIs)[15]. While mitogen withdrawal inhibits cyclin D gene expression and accelerates cyclin D1 proteolytic degradation[16], UPR-dependent signal transduction intersects with the cell cycle via PERK-dependent inhibition of cyclin D protein synthesis and rather than accelerating cyclin D degradation[17, 18]. Research utilizing genetically defined cells revealed that G1 arrest triggered by ER stress requires PERK-dependent phosphorylation of eIF2α[18]. The resulting inhibition of cyclin D1 translation together with its rapid rate of proteolysis results in its nearly immediate elimination and loss of cyclin D1-dependent kinase activity[19]. The ensuing cell cycle arrest in non-tumorigenic cells is facilitated alsoby p53-dependent increases in the CKI, p21^{Cip1} [20]. ER stress-induced growth arrest likely provides a window of opportunity or checkpoint that prevents cells from continuing their cell division cycle under conditions in which the proper folding and assembly of proteins are significantly compromised. Ultimately, the failure of the UPR to re-establish proper homeostatic balance can trigger apoptosis.

UPR and Metabolism

A primary function of the ER is post-translational folding of proteins destined for membranes or for secretion and a key modification essential for proper folding is asparagine-linked glyclosylation. Thus, tissues whose primary function is secretion are particularly dependent upon UPR signaling for homeostasis. Not surprisingly, significant pathologies in such tissues are caused by inadequacies in PERK function. Children suffering from Wallcot-Rallison disease, a recessive disorder characterized by loss-of-function PERK mutations, develop type I diabetes, a result of reduced beta-cell proliferation and exocrine cell apoptosis[21]. This phenotype is faithfully recapitulated in conventional PERK knockout mouse model[22, 23]. In addition to the pancreas, plasma cells, a B-cell whose function is the secretion of functional antibodies depend also upon UPR components. Rather than PERK however, plasma cells depends upon the combined activities of ATF6 and Ire1-Xbp1[24, 25] that function to maintain a required repertoire of ER chaperones.

Given that increased secretory demand as well as cell division requires membrane expansion, it should not come as a surprise that UPR signaling contributes also to aspect of lipid biogenesis. Ire1-dependent activation of Xbp1 contributes not only to chaperone expression, but contributes to phospholipid biosynthesis via regulation choline cytidyltransferase, a rate-limiting enzyme in the CDP-choline pathway[25]. Synthesis of this enzyme in plasma cells appears to be synergistically regulated by Xbp1 and ATF6[24, 25]. Additionally, Xbp1 also plays a key role in the production of liver-derived plasma lipids[26].

UPR signaling contributes to lipid biogenesis in the context of mammary gland during pregnancy. Knockout of PERK in the murine mammary gland reduced free fatty acid production and lipid deposition in the milk of nursing mice[27]. *Perk* deletion correlated with a loss of sustained of expression of key lipogenic enzymes such as ATP citrate lyase, fatty acid synthase, stearyl-CoA desaturase-1. Expression of these enzymes is acutely dependent upon Sterol Regulatory Element-Binding Protein 1c (SREBP1c) a transmembrane transcription factor whose release from ER membranes requires targeted movement to the Golgi where it is processed by S1P and S2P proteases. PERK loss inhibits SREBP1c Golgi processing, thereby reducing expression of key Lipogenic enzymes[27].

Viral Impact on the UPR

Replication of viruses in eukaryotic cells requires the robust synthesis of viral polypeptides that taxes the folding machinery. Accordingly, many viruses including herpes simplex virus (HSV) and hepatitis C virus (HCV) are associated with UPR activation. This rapidly expanding field is covered by several excellent recent reviews[28, 29]. Viruses are known to both induce UPR and produce the means of inhibiting these responses. The latter might be necessary in order to protect the host cells from ER stress-mediated death, to enable translation of viral proteins and ensuing virus production[28–32]. However, in reality, a number of examples demonstrate poorly understood specificity with regard to which UPR branch is activated by specific viruses.

The most obvious reasons for such selectivity is likely the very need to correct the protein synthesis-controlling and pro-apoptotic branches of the pathway in order to complete the replication. The rapid translation of viral proteins will pose an additional problem for the virus as it challenges the capacity of the host cell to properly fold key proteins. Accordingly, viruses have evolved to ameliorate specific UPR branches that control translation. For example, HSV was shown to express glycoprotein B that specifically inhibits PERK activation[33]. Furthermore, HSV is also generates the $\gamma_1$34.5 protein that is capable of maintaining the low levels of eIF2α phosphorylation through the phosphatase-mediated stimulation of eIF2α de-phosphorylation[34]. The latter mechanism is likely required to

safeguard against activation of other kinases capable of phosphorylation of eIF2α independently of activated PERK (e.g. PKR)[35]. Yet, this kinase can be also inhibited by proteins produced by viruses of medical importance such as HCV[36].

Conversely, the flavivirus West Nile virus strain Kunjin virus can specifically activate Ire1α but has a negligible effect on PERK[37]. In the latter case, synthesis of hydrophobic non-structural proteins inhibits the anti-viral effects of IFNα/β. HCV appears to utilize an analogous mechanism[38]. This relationship between induction/resolution of UPR and responsiveness of cells to anti-viral effects of type I IFN is significant as the UPR may negatively impact local immunity[39]. Although temporally detrimental for viral maturation, activation of PERK also has a side effect of feeding into the ligand-independent pathway that governs downregulation and degradation of IFNα/β receptor. This receptor on cell surface mediates all cellular responses to endogenous IFNα/β or pharmaceutical IFNα used to treat chronic viral infections such as hepatitis C and B[40]. The levels of this receptor are regulated by the ligand-inducible ubiquitination and degradation of the IFNAR1 chain[41]. Ubiquitination of IFNAR1 depends on IFN-induced IFNAR1 phosphorylation by protein kinase D2[42–46]. This pathway negatively regulates IFNα/β signaling in cells previously exposed to IFNα/β and have likely generated a robust anti-viral response to these cytokines. There is also an alternative basal (ligand-independent) pathway that leads to downregulation of IFNAR1 from the surface of cells that have not been yet exposed to IFNα/β[47]. Because this pathway does not require ligand, it can impair the ability of a naïve cell to respond to its future encounters with IFNα/β.

Phosphorylation of IFNAR1 by Casein kinase 1α is key to ligand-independent turnover[48, 49]. Remarkably, the ability of this kinase to phosphorylate IFNAR1 and trigger its ubiquitination and degradation can be greatly increased in cells exposed to ER stress[49]. More importantly, these UPR-induced events required activity of PERK[49]. The functional outcome of this regulation is a tempered ability of already infected cell to react to its future encounters to IFNα/β and to mount an efficient anti-viral state[49, 50]. Intriguingly, whereas the induction of UPR by HCV infection in experimental models has been thoroughly documented[39], a search for upregulated markers of UPR in liver biopsy samples from patients with chronic HCV was inconclusive[51]. The latter results could be explained by localized changes that are limited to rather small clusters of infected cells at a given time[52]. Future concerted efforts are required to investigate the role of UPR in hepatitis C pathogenesis and liver injury.

Apoptotic response to the UPR

In most pathophysiological conditions activation of the UPR has cytoprotective effects, a feature of reduced global protein synthesis with selective increased synthesis of proteins with cytoprotective roles, cells experiencing prolonged or acute ER stress undergo ER-initiated apoptosis. Indeed prolonged exposure of cells to tunicamycin or thapsigargin induce apoptosis[53, 54]. Conversely, cells with a compromised UPR, (e.g. cells deficient for PERK/eIF2α or IRE/XBP-1), are significantly more sensitive to ER-induced cell death than wild-type cells presumably due to the continuous accumulation of misfolded proteins in the ER, a process termed “proteotoxicity”[55, 56]. Although the mechanisms for ER-induced apoptosis are poorly understood, but there is strong evidence that Ca2+ release from ER stores and subsequent caspase activation, including caspase-3 and perhaps caspases 4 and 7 mediate programmed cell death under these conditions[57].

Well known for their contribution to the intrinsic apoptotic pathway through the mitochondria, bcl-2 family members are localized also to the ER. ER localized bcl-2 may contribute to ER membrane permeability by maintaining the pro-death bak and bax in their

inactive conformations[58]. ER stress induces oligomerization of bax and bak to their active states that can then induce an ER Ca^{+2} leak that triggers apoptosis. ER release of calcium is known to activate calpains, and induce cleavage of Bid, a BH-3 only bcl-2 family protein. Cleavage of Bid enhances its capacity to induce mitochondria membrane permeabilization, thereby leading to cytochrome c release and activation of downstream caspases.

UPR and Autophagy

Another emerging role for an ER-dependent pro-survival pathway is the involvement of ER and eIF2α phosphorylation in the autophagic pathway. Previous work[59, 60] has established that ER stress can activate autophagy, a highly conserved lysosome-dependent mechanism for degrading intracellular constituents. It has been proposed that autophagy, as a pro-survival mechanism under short-term nutrient deprivation, can counteract apoptotic mechanisms. However, similar to UPR activation, prolonged or acute activation of autophagy can induce clonogenic cell death[61]. Interestingly, several agents that induce ER stress (e.g., proteasome inhibitors, thapsigargin, etc) induce autophagy. Extreme hypoxia can also induce autophagy, primarily via activation of ATF4[62, 63]. These findings establish autophagy an important adaptive response cells use to survive ER stress, especially in the conditions of the solid tumor microenvironment.

Tumorigenic utilization of the UPR

Accumulating evidence demonstrates activation of the UPR in solid tumors. BiP/GRP78 accumulation in malignant human breast lesions has been observed frequently[64]. With regard to signal transduction from the ER, loss of Ire1[65], as well as its downstream target transcription factor XBP1[66], compromise tumor progression and inhibit neovascularization. Moreover, transgenic mice with directed expression of the XBP-1 spliced isoform (XBP-1s) develop bone lytic lesions and subendothelial Ig deposition - pathologic disorders reminiscent of multiple myeloma in humans[67]. PERK has also been implicated in facilitating tumor progression. Initial work demonstrated that murine fibroblasts derived from PERK null embryos and transformed with SV40 large/small T-antigen and Ki-RasV12 failed to grow in immune compromised mice as did human colorectal carcinoma cells expressing a dominant-negative form of PERK[68]. Subsequently, deletion of PERK in MMTV-Neu mice was found to modestly increased tumor latency, but more profoundly inhibit metastatic spread. Furthermore, deletion of PERK in established tumors, significantly reduced tumor progression[69, 70].

In addition to involvement in tumor progression, recent work has also implicated UPR in Inflammatory Bowel Disease, response to of the GI tract to hypoxic insult increasing susceptibility to bacterial translocation and inflammatory response[71–73]. Adaptive signaling from the UPR has even been implicated in response to alcohol consumption[74] emphasizing the role of this pathway as a sensor of both cellular and environmental stress.

Collectively, the current work supports the concept of developing inhibitors of UPR signaling as anti-neoplastic therapeutics and potentially for a variety of diseases that impact the secretory apparatus of the cell. However, caution must be utilized. Our understanding of the breadth of the UPR signaling with respect to cellular and organismal homeostasis remains limited. Efforts to dissect the molecular role of each component within cellular contexts provide new and exciting avenues of research, but also add to the complexity of downstream effects that must be considered when targeting pathways. As better animal models are generated to assess the function of the UPR in various physiological and pathological diseases, such as cancer, we will be in a position to better anticipate uses and outcomes of targeted therapies.

Acknowledgments

This work was supported by grants from the National Institutes of Health P01 CA104838 and a Leukemia & Lymphoma Scholar award (JAD); CA142425 (SYF); CA 094214 and CA 13962 (CK); and the Abramson Cancer Center (JAD, SYF, CK).

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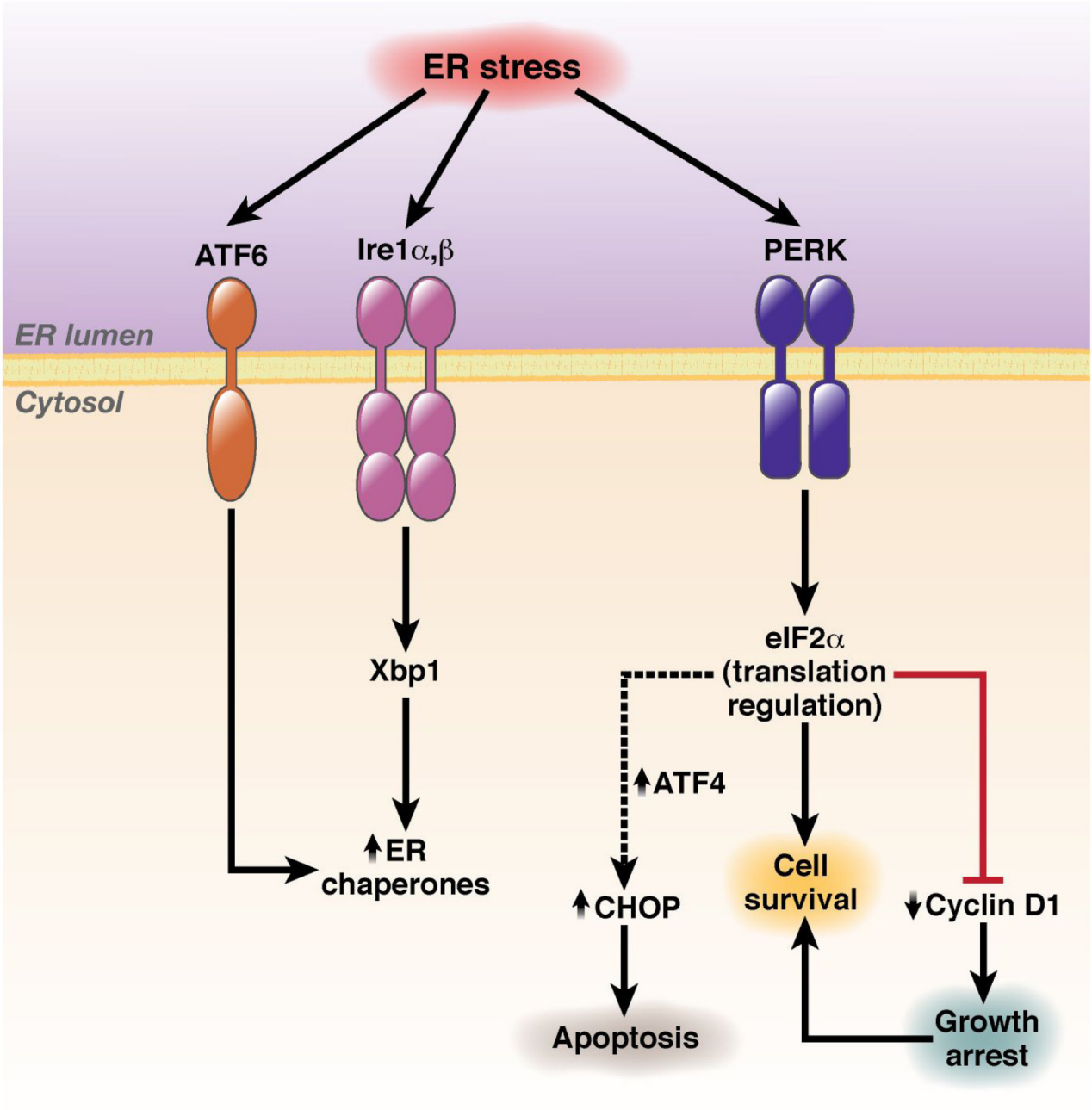

Figure 1. UPR signal transduction

ER stress signals induce UPR via promoting the activation of homologous transmembrane protein kinases, Ire1a/b, and PERK and a transmembrane transcription factor, ATF6. These regulators collectively transduce signals resulting in the upregulation of ER chaperones and CHOP while simultaneously down-regulating cellular protein synthesis and including that of the growth promoter cyclin D1 thereby inducing growth arrest.