

# Mammalian Unfolded Protein Response Transducers

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The unfolded protein response (UPR) bears an evolutionary conserved, dual sensitivity to both protein-folding imbalances in the endoplasmic reticulum (ER) lumen and aberrant compositions of the ER membrane, referred to as lipid bilayer stress (LBS). Through transcriptional and non-transcriptional mechanisms, the UPR upregulates the protein folding capacity of the ER and balances the production of proteins and lipids to maintain a functional secretory pathway.

Keywords: UPR ; IRE1 ; PERK ; ATF6 ; ER ; lipid bilayer stress

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## 1. Introduction

The endoplasmic reticulum (ER) spans eukaryotic cells as a membrane-bound organelle with functionally and structurally distinct subdomains. Its membrane includes both the nuclear envelope (NE) separating the nucleoplasm from the cytoplasm, and the peripheral ER forming an elaborate network of tubules and cisternae <sup>[1]</sup>. The ER has important functions in cellular signaling, secretion, membrane protein biogenesis, and lipid metabolism. In most eukaryotic cells, the ER acts as a storage compartment for intracellular  $\text{Ca}^{2+}$ , which can be released into the cytosol as an important second messenger in a wealth of signaling pathways <sup>[2]</sup>. A large portion of the ER surface contributes to membrane contact sites (MCSs), which provide a physical link to other organelles for exchanging ions and small molecules such as lipids <sup>[3]</sup>.

The ER is a hotspot for protein folding and membrane biogenesis <sup>[4][5]</sup>. It is the entry point to the secretory pathway and contributes to the biogenesis of peroxisomes, lipid droplets, and autophagic membranes. All proteins entering the endomembrane system via the secretory pathway are synthesized by cytosolic ribosomes. In mammalian cells, the ER handles roughly 10,000 different proteins (about 30% of the proteome), thereby accumulating between 0.1 and 2.0 million client proteins every minute in some cell types <sup>[6]</sup>. Most proteins entering the secretory pathway in *Saccharomyces cerevisiae* (*S. cerevisiae*) are membrane proteins. They are co- or post-translationally inserted into the lipid bilayer and folded with the help of molecular chaperones. Probably the most prominent chaperone in the lumen of the ER is the immunoglobulin heavy-chain binding protein (BiP; GRP78; Kar2p in *S. cerevisiae*) <sup>[7]</sup>. In a similar way to all HSP70 chaperones, it binds and hydrolyzes ATP in its nucleotide binding domain (NBD), whilst undergoing cycles of binding and releasing client proteins at its substrate binding domain (SBD). This dynamic interaction with unfolded proteins prevents their unfavorable interactions and co-aggregation with other folding intermediates. Nucleotide exchange factors and J-domain-containing co-chaperones (ERdj1-8) modulate the activity of BiP and help recruit clients <sup>[7][8]</sup>. When a protein fails to fold in the ER, it can be subjected to the ER-associated degradation (ERAD) machinery and degraded via the ubiquitin-proteasome system <sup>[9]</sup>. Successfully folded proteins and properly glycosylated proteins, however, can exit the ER via COPII vesicles for their transport to the Golgi apparatus <sup>[10][11]</sup>.

A carefully orchestrated machine for endomembrane trafficking guarantees the distribution of soluble and membrane proteins to their final, subcellular destination. Cargo sorting relies on specific cargo receptors, but also—in the case of membrane proteins—on the physicochemical properties of the transmembrane domains <sup>[10][11][12]</sup>. The dynamic partitioning of a transmembrane protein between an emerging transport vesicle and its donor organelle provides a means to concentrate it in one or the other compartment. The hydrophobic thickness of a transmembrane domain and its membrane environment is particularly relevant for such mismatch-based sorting mechanisms <sup>[12][13]</sup>. A gradual increase in membrane stiffness along the secretory pathway facilitates a step-by-step sorting of transmembrane proteins with increasing hydrophobic thicknesses at each station along the secretory pathway from the ER to the plasma membrane <sup>[10][12][13][14][15]</sup>. In this context, the ER membrane fulfils a special role, because it has to insert, fold and assemble all sorts of transmembrane proteins, irrespective of their largely distinct transmembrane domains (on average ~20.3/20.6 hydrophobic residues in a transmembrane helix for proteins of the early secretory compared with ~24.4/27 for proteins of the late secretory pathway in mammals/fungi) <sup>[13]</sup>. To provide a suitable environment for this diverse set of membrane proteins, the ER membrane must be particularly soft and deformable; to this end, sensitive surveillance systems keep the

sterol concentration in the ER low (~5–10 mol%) <sup>[16][17]</sup> and the proportion of poorly packing, mono-unsaturated fatty acyl chains high (>70 mol%) <sup>[18]</sup>.

The ER is also a hotspot of lipid biosynthesis and hosts a vast repertoire of lipid metabolic enzymes <sup>[19][20]</sup>. Lipogenic enzymes in the ER include fatty acid desaturases and elongases, as well as dozens of enzymes for producing glycerophospholipids, sterols, ceramides (the precursors for more complex sphingolipids), and neutral storage lipids <sup>[19][20]</sup>. In contrast to secretory and membrane proteins, which commute between organelles via vesicular carriers, lipids are distributed also by lipid transfer proteins <sup>[3]</sup>. However, despite the continuous and rapid exchange of membrane material via vesicular and non-vesicular transport mechanisms, each organelle of the endomembrane system pathway maintains its own, characteristic membrane properties as a means to establish its identity <sup>[21][22]</sup>.

## 2. The Conventional Role of the Unfolded Protein Response (UPR) Is Proteostasis

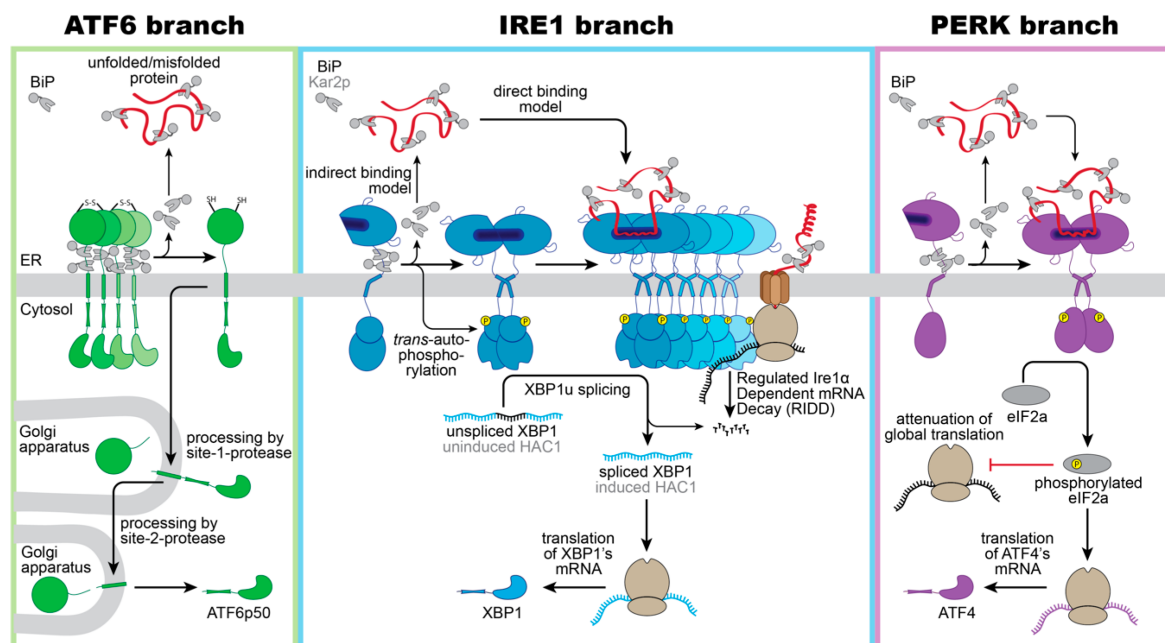
Cells need to adapt when the folding machinery of the ER is overwhelmed and when unfolded or misfolded proteins accumulate—a situation referred to as ER stress. The UPR was originally identified as a signaling pathway that senses ER stress to upregulate ER-resident chaperones <sup>[23][24][25]</sup>. Soon, it became clear that the UPR regulates not only the folding machinery in the ER, but also the processes with relevance for the entire secretory pathway, including lipid metabolism, protein translocation, ER-associated protein degradation (ERAD), ER-to-Golgi transport and Golgi-to-ER retrieval, protein glycosylation in the ER and the Golgi apparatus, vacuolar targeting, distal secretion, and cell wall biogenesis <sup>[26]</sup>. In mammals, the UPR relies on three single-pass, transmembrane proteins in the ER; namely, the activating transcription factor 6 (present as the isoforms ATF6 $\alpha$ / $\beta$  in mammals), the inositol-requiring enzyme 1 (with two mammalian isoforms IRE1 $\alpha$ / $\beta$ ), and the double-stranded RNA-activated protein kinase (PKR)—such as ER kinase (PERK) <sup>[27]</sup>. IRE1 constitutes the most conserved branch of the UPR and represents the only UPR transducer in *S. cerevisiae* (ScIRE1).

When activated, the UPR (1) lowers the global rate of protein production, (2) upregulates the rate of membrane lipid biosynthesis, (3) induces the production of ER-luminal chaperones and components of the ERAD machinery, and (4) expands the capacity of the secretory pathway <sup>[27]</sup>. If these adaptive responses are insufficient to restore ER homeostasis, the prolonged activity of the UPR can lead to cell death <sup>[27]</sup>. Given the broad transcriptional and non-transcriptional effector functions of the UPR, its crucial role in cell fate decisions between life, death, and differentiation, is unsurprising <sup>[27][28][29][30]</sup>.

The upregulation of membrane lipid biosynthesis via UPR signals in *S. cerevisiae* causes an expansion of the ER membrane network <sup>[31][32]</sup>. Likewise, all three branches of the mammalian UPR regulate key steps of lipid metabolism and contribute to the ER membrane expansion via transcriptional and non-transcriptional mechanisms <sup>[33][34][35][36]</sup>. How the composition and properties of the ER membrane contribute to UPR activation in return has been lagging. Meanwhile, it is clear that a variety of signals originating from the ER membrane serve as potent signals for UPR activation in lipid metabolic adaptation and disease <sup>[28][37][38]</sup>. It is true, for example, that insulin-producing  $\beta$ -cells rely on UPR signals for their normal differentiation into professional, secretory cells <sup>[39]</sup>, but it is the chronic stress caused by the excess of saturated fatty acids that kills them <sup>[40]</sup>. Before going into a more detailed discussion of the signals that lead to UPR activation, we will introduce the three branches of the mammalian UPR.

## 3. Three Musketeers—The Mammalian UPR Transducers

ATF6 is a single-pass, type II transmembrane protein. Its C-terminal, ER-luminal domain forms intermolecular disulfide bonds that stabilize homo-oligomeric, inactive assemblies <sup>[41][42]</sup>. This way, ATF6 is directly sensitive to reducing conditions that would interfere with the normal oxidative folding in the ER. Furthermore, ATF6 is associated with the molecular ER chaperone BiP <sup>[43]</sup>. Under conditions of ER stress, BiP is released from ATF6 and unmasks two conserved Golgi localization signals <sup>[43]</sup>. BiP dissociation can be induced in vitro by supplementing ATP-Mg<sup>2+</sup> to immuno-isolated complexes, yet additional factors such as co-chaperones are proposed to control ATF6 activation in vivo by regulating the ATPase cycle of BiP <sup>[44]</sup>. Following BiP dissociation, ATF6 is packaged in COPII vesicles <sup>[45]</sup> and transported to the Golgi apparatus, where it is proteolytically processed and activated via the site-1-protease and site-2-protease <sup>[46][47]</sup>. Released from its membrane anchor, the transcriptionally active ATF6p50 fragment enters the nucleus and triggers a broad transcriptional program to reestablish the protein folding homeostasis in the ER (**Figure 1**, left panel) <sup>[48][49][50]</sup>.



**Figure 1.** Schematic overview of proteotoxic ER stress signaling by the UPR. Three branches of the UPR sense proteotoxic stress in the ER to control adaptive transcriptional and non-transcriptional responses: ATF6, IRE1 (IRE1 $\alpha$  in mammals/ ScIRE1 in *S. cerevisiae*) and PERK. **(Left panel):** Intermolecular disulfide bonds stabilize inactive homo-oligomers of ATF6 thereby limiting the pool of ATF6 that can be activated. In the absence of ER stress, ATF6 interacts with its negative regulator BiP. Notably, various regions of the ER-luminal domain of ATF6 contribute to BiP binding, but only a membrane-proximal binding region is indicated here for simplicity. Current models suggest a dissociation of BiP from ATF6 upon ER stress. The unmasking of Golgi localization signals allows for packaging of ATF6 into COPII vesicles for a transport to the Golgi apparatus. Processing by the site-1-protease and site-2-protease releases a transcriptionally active fragment (ATF6p50) for regulating UPR target genes in the nucleus. **(Middle panel):** Inactive monomers of IRE1 $\alpha$ /ScIRE1 associate with BiP/Kar2p via various interaction sites. Proteotoxic ER stress causes a dimerization of IRE1 $\alpha$ /ScIRE1, the release of BiP/Kar2p, and the formation of higher oligomeric assemblies of IRE1 $\alpha$ /ScIRE1. The enforced proximity of the cytosolic effector domains enables a *trans*-autophosphorylation of the cytosolic kinase domain and activation of the RNase domain. Oligomers of IRE1 $\alpha$  and ScIRE1 cleave the mRNA of unspliced XBP1 and uninduced *HAC1*, respectively, as the committed step for unconventional splicing. Translation of the spliced mRNA yields an active transcription factor XBP1/HAC1 upregulating hundreds of UPR target genes in the nucleus. Oligomers of the mammalian IRE1 $\alpha$  oligomers can reduce the load of the ER with unfolded proteins via the regulated IRE1 $\alpha$ -dependent mRNA Decay (RIDD). **(Right panel):** Proteotoxic ER stress causes a dissociation of BiP from PERK and facilitates the formation of PERK dimers and oligomers. *Trans*-autophosphorylation activates PERK's cytosolic kinase domain, which then phosphorylates the eukaryotic initiation 2 $\alpha$  (eIF2 $\alpha$ ). This causes a global attenuation of translation, but also selectively promotes the production of the transcription factor ATF4. ATF4 controls both pro-survival and pro-apoptotic signals.

A recent study suggested that the ER-resident oxidoreductase ERp18 associates with ATF6 and forms mixed disulfides specifically under conditions of ER stress to ensure optimal processing [51]. In fact, ERp18-depletion accelerates the rate ATF6 ER-to-Golgi trafficking, but causes aberrant processing and releases a non-productive fragment, which is not further processed by the site-2-protease [51].

Precisely how unfolded proteins and BiP 'monomerize' ATF6, despite a fully developed basic leucine zipper on the cytosolic side of the ER membrane, remains unexplored. Unlike the other two branches of the UPR, ATF6 cannot lower the flux of unfolded proteins into the ER. Instead, ATF6p50 induces an expansion of the ER membrane [34][35] and upregulates numerous genes encoding for ER chaperones, ER-luminal disulfide oxidoreductases, and ERAD components [35][48][49][50]. Notably, ATF6p50 and the transcription factor X-box-binding protein 1 (XBP1s), generated by the IRE1 branch of the UPR, act synergistically and can hetero-dimerize [48].

ScIRE1/IRE1 $\alpha$  is a type I transmembrane protein conserved from yeast to humans. When unfolded proteins accumulate in the ER, ScIRE1/IRE1 $\alpha$  oligomerizes [52], thereby juxtaposing the cytosolic kinase/RNase domains. This triggers the *trans*-autophosphorylation of the kinase domain and the activation of the RNase domain [24][53][54][55][56][57]. IRE1 $\alpha$  excises a small intron from the *XBP1* mRNA and initiates an unconventional splicing reaction, which ultimately provides a template for the transcription factor XBP1s ('s' stands for spliced) [56][58]. After the cleavage and ejection of the intron, the two exons of the *XBP1* mRNA zipper up, form an extended stem, and become ligated by the catalytic subunit of the tRNA ligase

complex RTBC [59][60]. Similarly, ScIRE1 initiates the unconventional splicing of the *HAC1* mRNA for generating an active transcription factor Hac1p (**Figure 1**, middle panel) [54][61]. XBP1s in mammals and Hac1p in *S. cerevisiae* control large transcriptional programs with hundreds of target genes involved in various aspects of membrane biogenesis, protein folding, trafficking, and degradation [26][49][50][62]. IRE1 $\alpha$  can also lower the influx of proteins by degrading mRNAs associated with the ribosome-translocon complex in a process known as IRE1-dependent mRNA decay (RIDD) [63][64]. Furthermore, the downregulation of the biogenesis of lysosome-related organelles 1 subunit 1 (*Blos1*) mRNA via RIDD causes an impressive clustering of lysosomes to the perinuclear region in stressed cells, which is crucial to efficiently remove protein aggregates via late endosome-mediated microautophagy [65].

PERK is an ER-resident, type I transmembrane kinase [66]. When unfolded proteins accumulate in the ER, PERK oligomerizes and its cytosolic effector domains are activated through *trans*-autophosphorylation [66]. The activated PERK phosphorylates the eukaryotic translation initiation factor 2 $\alpha$  (eIF2 $\alpha$ ) at serine 51, thereby rapidly inhibiting the global rate of mRNA translation and lowering the flux of proteins into the ER [66][67]. The activating transcription factor 4 (ATF4) escapes this inhibition and is selectively upregulated (**Figure 1**, right panel) [68]. ATF4 upregulates genes involved in amino acid metabolism, tRNA charging, and glutathione biosynthesis [69], the production of the pro-apoptotic transcription factor C/EBP homologous protein (CHOP)—also known as growth arrest—the DNA damage-inducible gene 153 (GADD153), and the growth arrest and DNA damage-inducible gene 34 (GADD34) [68][70]. CHOP/GADD153 and GADD34 orchestrate the PERK-dependent signaling output, which can be either cytoprotective or pro-apoptotic. The cytoprotective GADD34 provides a negative feedback loop that terminates the PERK-signaling downstream of eIF2 $\alpha$  phosphorylation, by forming a complex with the protein phosphatase 1 (PP1c) [70]. CHOP/GADD153, on the other hand, provides pro-apoptotic signals [71] by inducing the expression of the death receptor 5, leading to ligand-independent signaling via Caspase 8 [72]. The transient activation of IRE1 $\alpha$  during acute ER-stress, on the contrary, attenuates the death receptor 5 mRNA level via RIDD, so that two opposing UPR signals control the death receptor 5 level, and thus apoptosis [72].

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