The unfolded protein response

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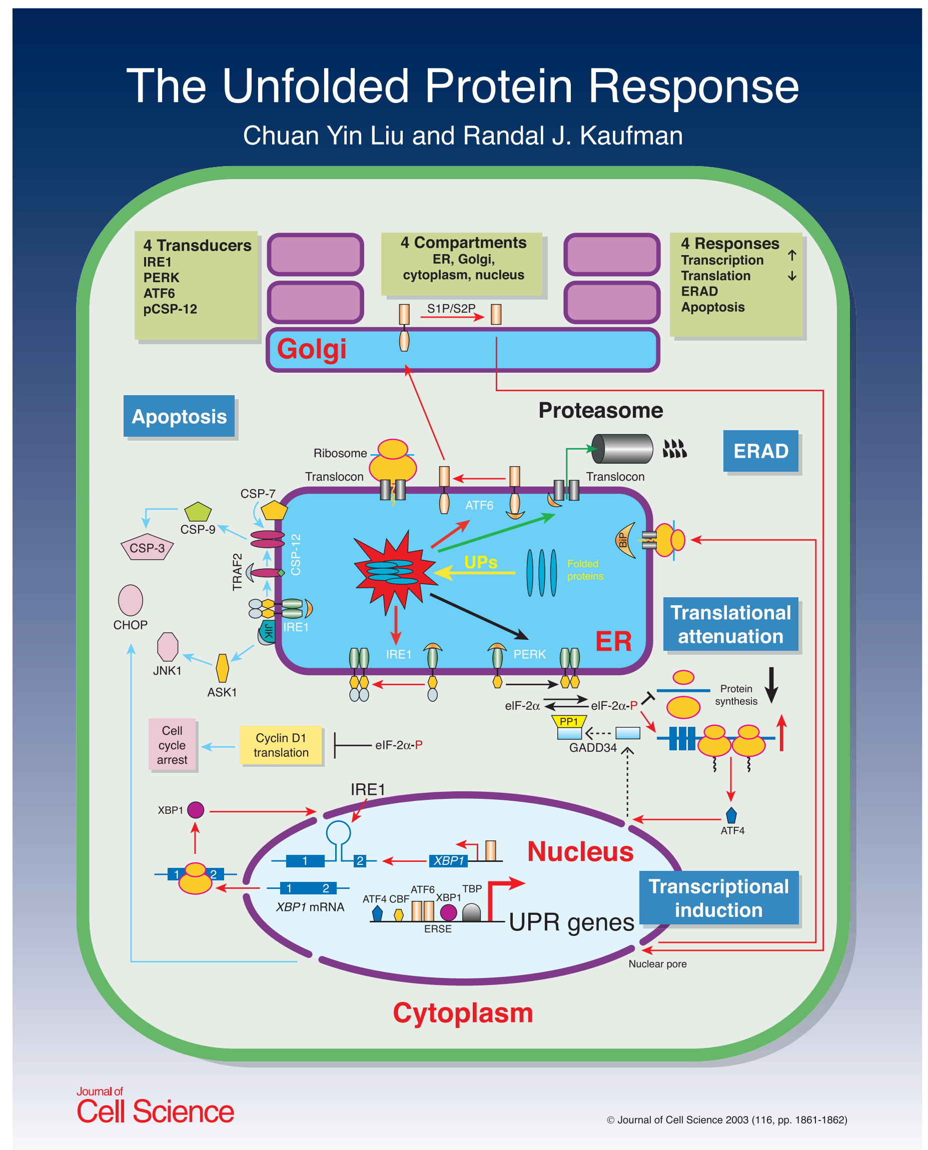
The endoplasmic reticulum (ER) is a principal site for folding and maturation of transmembrane, secretory and ER-resident proteins. Perturbations that alter ER homeostasis can lead to accumulation of unfolded proteins (UPs), which is a threat to all living cells. To cope with the stress, cells activate an intracellular signaling pathway – the unfolded protein response (UPR). The UPR is an integrated intracellular signaling pathway that transmits information about the protein folding status in the ER lumen to the cytoplasm and the nucleus. The UPR includes transcriptional induction of UPR genes (red arrows), translational attenuation of global protein synthesis (black arrows) and ER-associated degradation (ERAD) (green arrows). These divergent outputs provide adaptive responses for survival. If the protein-folding defect is not corrected, cells undergo apoptosis (light-blue arrows). The three major transducers of the UPR are PERK, IRE1 and ATF6.

PERK is an ER transmembrane protein kinase that phosphorylates the α subunit of translation initiation factor 2 (eIF2α) in response to ER stress. Phosphorylation of eIF2α reduces the formation of translation initiation complexes, which leads to reduced recognition of AUG initiation codons and therefore general translational attenuation. This translational control provides an efficient mechanism to reduce the number of unfolded proteins in the ER. Paradoxically, the translation of selective mRNAs that have a lower requirement for eIF2 and the translation initiation complex is enhanced, such as the mRNA encoding the activating transcription factor ATF4. GADD34 transcription is induced by the UPR through ATF4, and the protein product recruits protein phosphatase 1 (PP1) to dephosphorylate eIF2α-P and reverse the translational attenuation.

ATF6 is an ER transmembrane-activating transcription factor. Upon ER stress, ATF6α and ATF6β transit to the Golgi compartment where they are cleaved by S1P and S2P proteases to yield a cytosolic fragment. The free ATF6 fragment migrates to the nucleus to activate transcription.

IRE1 is an ER transmembrane glycoprotein and it contains both kinase and RNase activities in the cytoplasmic domain. ER stress leads to its autophosphorylation and the subsequent activation of its RNase activity. The substrate of IRE1α and IRE1β in mammals, XBP1 mRNA, encodes a basic leucine-zipper-containing transcription factor. Splicing of XBP1 mRNA is initiated by the RNase activity of IRE1 to generate mature XBP1 mRNA. Whereas the ATF6 and PERK pathways are not conserved in lower eukaryotes, the IRE1 signaling pathway is conserved in all known eukaryotic cells.

The signalling from downstream effectors of IRE1, PERK and ATF6 merges in the nucleus to activate transcription of UPR target genes. The mammalian ER stress element (ERSE) is present in the promoter regions of many,



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but not all, UPR target genes. XBP1, ATF6 and the CAAT-binding factor (CBF), all of which bind to ERSE, along with ATF4, activate transcriptional induction of target genes. ATF6 also induces XBP1 transcription, providing a positive feedback for the UPR. In particular, upregulation of molecular chaperones and folding catalysts increases the folding capacity of the ER, providing a protective effect for cell survival. In addition, activated Ire1p in yeast induces transcription of genes, such as *INO1*, that mediate phospholipid biosynthesis to increase the ER volume.

The UPR also induces transcription of genes encoding proteins that mediate ERAD. This important component of the UPR stimulates the degradation and clearance of unfolded proteins in the ER lumen. Several target genes appear to encode proteins that remodel the secretory pathway to decrease the concentration of UPs.

BiP, the ER chaperone, is the master regulator of the activation of the three proximal ER stress transducers – IRE1, PERK and ATF6. All transducers contain a lumenal domain that interacts with BiP. Under normal conditions, BiP serves as a negative regulator of IRE1, PERK and ATF6 activation. Upon ER stress, BiP binds to UPs, thereby allowing BIP release from the transducers. BiP release from IRE1 and PERK permits their homodimerization and activation. BiP release from ATF6 permits its transport to the Golgi compartment for regulated intramembrane proteolysis. This BiP-regulated activation provides a direct mechanism to sense the folding capacity of the ER.

Prolonged UPR activation leads to apoptotic cell death, in which IRE1 serves a proapoptotic function. Activated IRE1 recruits Jun N-terminal inhibitory kinase (JIK) and TRAF2 to activate apoptosis-signaling kinase 1 (ASK1), which in turn activates JNK and mitochondria/Apaf1-dependent caspases. Procaspase-12 (pCSP-12) is an ER-associated proximal effector of apoptosis. TRAF2 release from pCSP-12 permits the clustering and activation of CSP-12. Activated CSP-12 activates CSP-9, which in turn activates CSP-3, leading to apoptosis. Upon ER stress, activated CSP-7 can cleave pCSP-12 to generate active CSP-12. In addition, UPR activation induces CHOP/GADD153 expression through the PERK and ATF4 pathways. CHOP is a proapoptotic transcription factor that potentiates apoptosis. Finally, in response to prolonged ER stress, attenuation of cyclin D1 translation through PERK leads to cell cycle arrest during G1 phase. This provides an ER checkpoint to prevent cells from progressing through the cell cycle.

Tremendous progress has been made in understanding the components and mechanisms of the UPR in recent years. Current studies are focusing on aspects of the pathological and physiological roles of the UPR.

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