Editorial

The viability of a cell strictly depends on the functional and structural integration between different subcellular compartments. At each organelle, different molecular sentinels permanently sense stressful cellular conditions and initiate a complex molecular response. This response aims either to adapt to the new conditions or to activate specific cell death signaling pathways if a critical threshold of damage has been reached. The endoplasmic reticulum (ER) is the subcellular compartment where membrane-spanning and secreted proteins are synthesized. This organelle is responsible for regulating and executing many post-translational modifications, ensuring proper protein folding and facilitating formation of protein complexes. The ER is also the place where the biosynthesis of steroids, cholesterol, and other lipids occurs, playing a crucial role in organelle biogenesis and signaling through the generation of lipid second messengers. The ER is well-known as a major calcium store in the cells and thus constitutes a signaling organelle that modulates many cellular processes including proliferation, cell death and differentiation via calcium release. A number of stress conditions, such as perturbed calcium homeostasis or redox status, elevated rate of secretory protein synthesis, altered glycosylation and cholesterol overloading, can interfere with ER functioning. These alterations lead to the accumulation of unfolded or misfolded proteins in the ER lumen, which has been referred as a cellular condition denominated “ER stress”.

ER stress triggers a complex adaptive reaction known as the unfolded protein response (UPR), which aims the restoration of the homeostasis of this organelle. Activation of the UPR affects the expression of proteins involved in nearly every aspect of the secretory pathway, including protein entry into the ER, folding, glycosylation, ER-associated degradation (ERAD), ER biogenesis, lipid metabolism and vesicular trafficking. The UPR restores the folding capacity to decrease unfolded protein load. The protective response of the UPR acts transiently to maintain homeostasis within the ER, but sustained ER stress ultimately leads to apoptosis by the activation of specific cell death programs. Increasing evidence indicates that the UPR is crucial for maintaining tissue homeostasis. Different physiological conditions can induce the UPR by increasing the demand of protein synthesis/secretion or by the generation of excessive misfolded proteins as described for B lymphocytes and pancreatic β cells. Also, abnormal metabolic conditions, such as glucose deprivation can trigger the UPR. Components of the ER stress pathway have been shown to be an important factor for tumor survival and growth due to an adaptation to hypoxia conditions. In addition, in different neurodegenerative conditions associated with protein misfolding (including Huntington's disease, Alzheimer's, Prion-related disorders, Amyotrophic Lateral Sclerosis and others), irreversible alteration of ER homeostasis has been proposed to be a critical mediator of neuronal dysfunction.

In higher eukaryotes, ER stress stimulates three distinct signaling pathways mediated by the sensors IRE1α (inositol-requiring transmembrane kinase/endonuclease), PERK (double-stranded RNA activated protein kinase-like ER kinase), and ATF6 (activating transcription factor 6) (Fig. **1A**). IRE1α is a Ser/Thr protein kinase/endoribonuclease that upon activation initiates the unconventional splicing of the mRNA encoding the transcriptional factor X-Box-binding protein 1 (XBP-1). This leads to the expression of a more stable and potent transcriptional activator, XBP-1s, a basic leucine zipper (bZIP) transcription factor that controls the upregulation of a subset of UPR-related genes. XBP-1 expression also controls organelle biogenesis. In addition, activated IRE1α can bind to the adaptor protein TRAF2 (TNF-associated factor 2), triggering the activation of the c-Jun N-terminal kinase (JNK) pathway (Fig. **1B**). PERK directly phosphorylates and inhibits the translation initiation factor eIF2α decreasing the overload of misfolded proteins in this organelle (Fig. **1B**). Conversely, eIF2α phosphorylation activates translation of ***ATF4*** (activating transcription factor 4), a transcription factor that induces expression of genes that function in amino acid metabolism, the antioxidant response and apoptosis. A third UPR pathway is initiated by ATF6 (Fig. **1B**), a type II ER transmembrane protein encoding a bZIP transcriptional factor on its cytosolic domain and localized in the ER in unstressed cells. Upon ER stress induction, ATF6 is exported to the Golgi, where it is processed. Cleaved ATF6 then translocates to the nucleus where it increases expression of some ER chaperones and XBP-1 transcription. Current models for the activation of ER stress sensors propose that under normal conditions Grp78/BiP binds to the ER luminal domain of PERK, ATF6 and IRE1α, maintaining the proteins in an inactive state. During an UPR, Grp78/BiP is preferentially bound to misfolded proteins, thereby releasing PERK and IRE1α to multimerize and become autophosphorylated, leading to its enzymatic activation. After release of ATF6, the protein translocate to the Golgi compartment where it gets activated.

The inability of cells to adapt to extensive ER stress result in cell death by specific mechanisms. Apoptosis ultimately depends upon the activation of cysteine proteases of the caspase family which execute cellular suicide. Activation of caspase-12 in rodents has been linked with ER stress-mediated apoptosis. Procaspase-12 is localized in the ER membrane and upon proteolytical processing the active form is released to the cytosol. Alternatively, procaspase-12 is cleaved by the calcium dependent protease m-calpain increasing its enzymatic activity. Despite caspase-12 activation has been shown in many ER stress experimental systems, its role in cell death is controversial since human procaspase-12 gene acquired deleterious mutations. The closest homolog of procaspase-12 in humans, procaspase-4, was recently shown to participate on ER stress-mediated

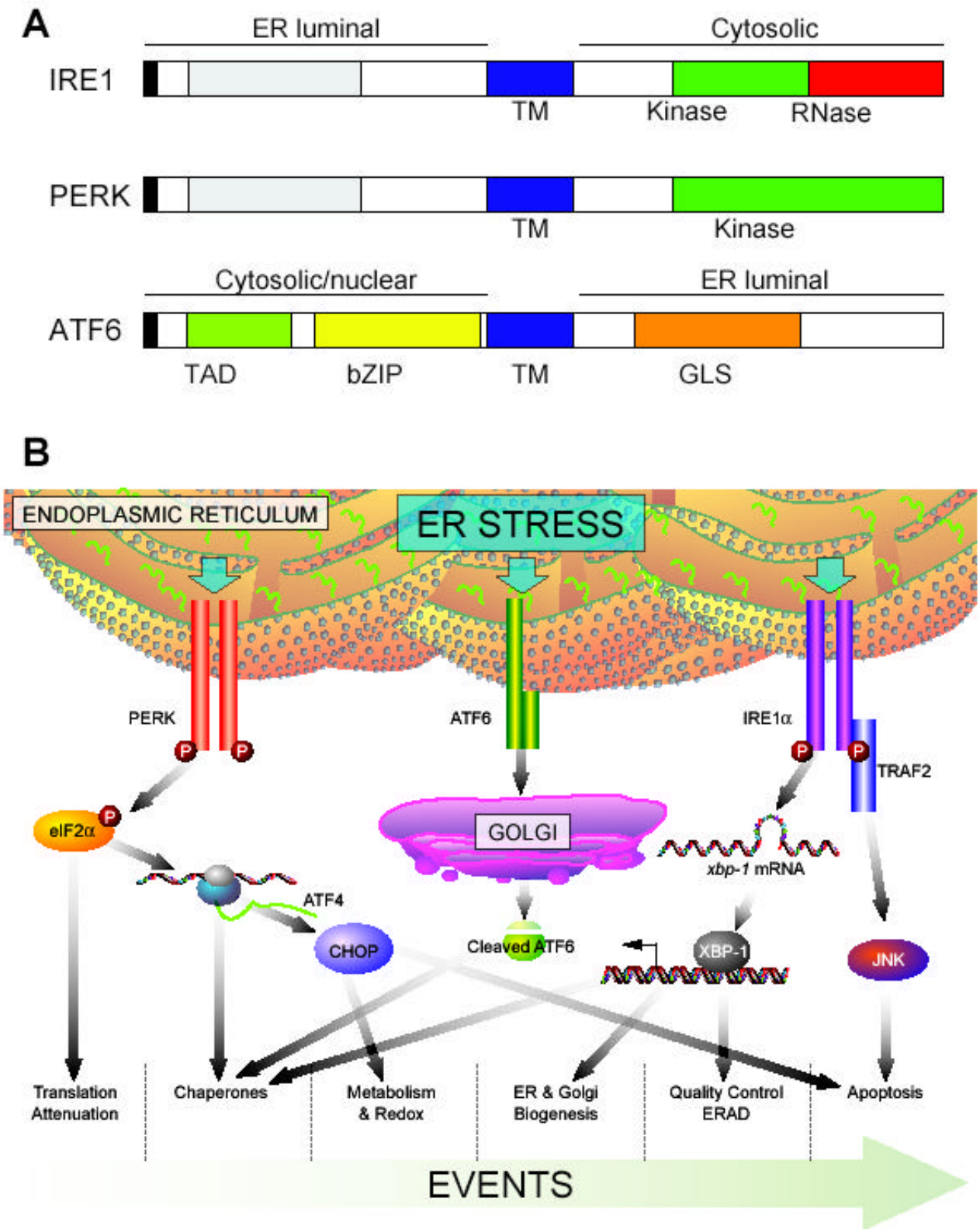

Fig. (1). UPR signal transducers. (A) Schematic representation *of the ER stress sensors*: Inositol requiring kinase 1 (IRE1α), protein kinase-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6). Gray bars represent conserved regions between the two sensors. The other abbreviations are bZIP, basic leucine zipper; GLS1 and GLS2, Golgi localization sequences 1 and 2; TAD, transcriptional activation domain; and TM, transmembrane domain. **(B) *UPR signaling*:** Summary of the general signaling pathways and the cellular effect initiated by the activation of the stress sensors IRE1α, PERK and ATF6.

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apoptosis suggesting that an alternative pathway may exist in humans. ER stress triggers the activation of the pro-apoptotic kinases JNK and ASK1 through an IRE1α/TRAF2 complex formation. However, the targets of JNK under ER stress conditions are not clear and may include some members of the BCL-2 protein family. Recent evidence indicates that many members of the BCL-2 family are located in the ER membrane where they have a crucial role in regulating cell death. Finally, upregulation of CHOP/GADD153 by ATF4 has been shown to have pro-apoptotic effects.

This special edition of the ***Current Molecular Medicine*** contains a selection of reviews focused on different aspects of the UPR to provide an overview of the relevance of these stress pathways in many physiological and pathological conditions. In this volume of the ***Curr. Mol. Med.***, Fumico Urano gives a comprehensive summary of the experimental data supporting the role of different branches of the UPR signaling in the function of the pancreas and its possible role in pathological conditions such as diabetes. Crucial mediators in the alleviation of the stress in the ER are protein chaperones and foldases of the Glucose Regulated Protein (GRPs) family. Amy Lee, one of the pioneers in the study of GRPs in apoptosis and ER stress, presents an overview of the multiple functional roles of this family of proteins. Randal Kaufman and Martin Schroder prepared a detailed analysis of the function and interconnection between different UPR signaling pathways.

The inability of a cell to adapt to prolonged perturbations on the homeostasis of the ER ends with the activation of specific cell death pathways. Members of Stanley Korsmeyer's laboratory, Scott Oakes, Stephen Lin and Michael Bassik review the emerging role of the BCL-2 protein family in the regulation of different aspects of ER physiology in addition to apoptosis. This is complemented by an article from Hidenori Hichijo, describing the involvement of the ASK1/MAP kinase pathway on ER stress-mediated apoptosis.

Accumulation of abnormal protein aggregates composed of misfolded proteins is a common denominator in many neurological disorders. Julie Atkin and Bradley Turner discuss recent evidences suggesting that mutant SOD1 proteins genetically linked to Amyotrophic Lateral Sclerosis may induce motoneuron dysfunction by alteration in the function of ER and Golgi. A related article is presented by Takashi Momoi depicting a unifying model for the neurotoxicity of Huntington's polyglutamine rich protein, linking ER stress, proteasome dysfunction and autophagy/apoptosis. Othman Ghribi reviews the relationship between ER stress and cholesterol homeostasis in the etiology of Alzheimer's disease. Finally, we discuss recent data about the involvement of UPR and ER stress-mediated apoptosis in prion-related disorders, also called Transmissible Spongiform Encephalopathies. These articles pretend to reinforce the notion that irreversible alteration of ER function has deleterious effects to the cell and the organism. But, as initially described in yeast models, the UPR is a prosurvival pathway and its beneficial effect can be also translated into pathological conditions. Costas Koumenis summarizes the growing evidence supporting a role of the UPR in hypoxia tolerance and tumor progression. As the reader will conclude from this selected group of reviews, pharmacological targeting of different components of the UPR/ER stress pathway may have therapeutic application for the treatment of many pathological conditions, such as diabetes, cancer and neurological disorders.

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