Unfolded protein response

- The Neuroprotective Effects of the Crinoid Natural Compound Rhodoptilometrin in Parkinson's Disease Experimental Models: Implications for ER Stress and Autophagy Modulation
- ER stress-related mitochondrial protein-coding gene risk model and in vitro experiments unveil OMA1 as a novel prognostic and therapeutic biomarker for low-grade glioma
- Endoplasmic reticulum stress on glioblastoma: Tumor growth promotion and immunosuppression
- Comprehensive transcriptomic analysis integrating bulk and single-cell RNA-seq with machine learning to identify and validate mitochondrial unfolded protein response biomarkers in patients with ischemic stroke
- Monoallelic TYROBP deletion is a novel risk factor for Alzheimer's disease
- Activation of the PERK Branch of the UPR as a Strategy for Improving Outcomes in Acute Ischemic Stroke
- PSMC2 upregulation enhances epithelial-to-mesenchymal transition in glioblastoma via activating AKT/GSK3β/β-catenin axis
- Unraveling the crucial role of UPR pathway in rat brain development

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The unfolded protein response (UPR) is a cellular stress response mechanism that is activated when there is an accumulation of unfolded or misfolded proteins in the endoplasmic reticulum (ER), a cellular organelle involved in protein synthesis and folding. The UPR is primarily aimed at restoring ER homeostasis by increasing the folding capacity of the ER, reducing the load of incoming proteins, and triggering the degradation of misfolded proteins.

When proteins are synthesized in the ER, they undergo a process of folding to achieve their functional three-dimensional structures. Various factors, such as changes in cellular conditions or an increased demand for protein synthesis, can disrupt this folding process, leading to the accumulation of unfolded or misfolded proteins in the ER.

The UPR is activated to manage this stress, and it involves three main signaling pathways, each mediated by specific ER transmembrane proteins:

IRE1 (Inositol-Requiring Enzyme 1) Pathway: IRE1 becomes activated and splices a specific mRNA, leading to the production of a transcription factor called XBP1 (X-box binding protein 1). XBP1 then induces the expression of genes involved in ER protein folding and degradation.

PERK (Protein Kinase RNA-like ER Kinase) Pathway: PERK is activated and phosphorylates the eukaryotic initiation factor 2 alpha (eIF2α), which results in a global reduction in protein synthesis. Paradoxically, this selective translation inhibition allows cells to cope with ER stress by reducing the protein-folding load.

ATF6 (Activating Transcription Factor 6) Pathway: ATF6 is transported to the Golgi apparatus, where it undergoes proteolytic cleavage. The cleaved fragment then acts as a transcription factor to induce the expression of genes involved in protein folding and ER-associated degradation.

The overall goal of the UPR is to restore ER function and alleviate the stress caused by the accumulation of misfolded proteins. However, if the stress is severe or prolonged, the UPR may also

trigger programmed cell death (apoptosis) to eliminate damaged cells and prevent further harm to the organism. Dysregulation of the UPR has been implicated in various diseases, including neurodegenerative disorders and certain types of cancer.

The UPR is activated in response to an accumulation of unfolded or misfolded proteins in the lumen of the endoplasmic reticulum. In this scenario, the UPR has three aims: initially to restore the normal function of the cell by halting protein translation, degrading misfolded proteins, and activating the signaling pathways that lead to increasing the production of molecular chaperones involved in protein folding. If these objectives are not achieved within a certain period or the disruption is prolonged, the UPR aims towards apoptosis.

Sustained overactivation of the UPR has been implicated in prion diseases as well as several other neurodegenerative diseases, and inhibiting the UPR could become a treatment for those diseases.

Diseases amenable to UPR inhibition include Creutzfeldt–Jakob disease, Alzheimer's disease, Parkinson's disease, and Huntington's disease.