Endoplasmic Reticulum Stress Sensor IRE1α

Subjects: Cell Biology
Contributor: Thoufiqul Alam Riaz

Inositol-requiring transmembrane kinase endoribonuclease-1α (IRE1α) is the most prominent and evolutionarily conserved unfolded protein response (UPR) signal transducer during endoplasmic reticulum functional upset (ER stress). A IRE1α signal pathway arbitrates yin and yang of cellular fate in objectionable conditions. It plays several roles in fundamental cellular physiology as well as in several pathological conditions such as diabetes, obesity, inflammation, cancer, neurodegeneration, and in many other diseases.

Keywords: IRE1α ; ER stress

1. Introduction

IRE1/ERN1 (Inositol-Requiring Enzyme 1/Endoplasmic Reticulum to Nucleus 1) is the most evolutionarily conserved endoplasmic reticulum membrane resident protein. It is involved in multiple cellular processes and regulates both cell survival and cell death. IRE1, a transmembrane protein kinase gene, was first detected in yeasts while exploring genes involved in the metabolism of inositol phospholipids to complement exogenous inositol for the growth of yeast mutants in which the disruption of the IRE1 locus triggered myo-inositol auxotrophy [1]. Following Peter Walter and Mori K's benchmark study, IRE1 was identified as a UPR molecule on the screen of yeast genes involved in signal transduction from the endoplasmic reticulum (ER) to nucleus during misfolded protein accumulation/ER stress [2,3]. In yeasts, IRE1 is the sole UPR sensor which governs the response to ER stress [4]. In metazoans, IRE1 is one of the three distinct UPR sensors, and it exists in two isoforms IRE1α/ERN1 and IRE1β/ERN2. IRE1α is ubiquitously present, whereas IRE1β's presence is restricted to intestinal epithelial cells [5] and airway mucous cells [6]. IRE1α and IRE1β differ in luminal domain amino acid sequences that are not conserved, especially in association with binding immunoglobulin protein (BiP) [7]. Both are functionally different in substrate specificity by their RNase domain [8]. Therefore, this clearly indicates that sensing and activation of IRE1α and IRE1β are different from each other. Moreover, unlike IRE1α, the IRE1β activity is more similar to yeast IRE1 homologue. The amino acid sequence of the human IRE1α and IRE1β sensor, kinase, and RNase domains has 48%, 80%, and 61% identity, respectively [9]. IRE1α activates the X-box binding protein 1 (XBP1) transcription factor through an unconventional splicing event while IRE1β partially reduces the site-specific 28sRNA cleavage translation [9] and also cleaves XBP1 [10].

2. Related

This difference in the nature of activity would contribute to their different downstream effects. However, the question is how this functional difference is relevant in physiological conditions and why these sensors act differently. The answer could be the tissue environment, intrinsic molecular factors, or the nature of stress. Another point is that, in tissues like the gastrointestinal tract and airway mucous layer, where both isoforms are expressed, the physiological requirement of both the isoforms in these tissues needs to be understood. Both isoforms might function competitively or complimentarily to each other during the UPR induction. It would be interesting to understand the x-factor, which influences the IRE1β expression or repression.

IRE1 functional dimensions are very diverse; however, it has been majorly implicated in ER stress. The tissue, pathological attributes, stress intensity, and the UProsome molecules association/dissociation decide the nature of IRE1 activity. This versatile ER membrane molecule controls various cellular functions, including cell morphogenesis, signal transduction, secretion, and regulation of many chronic diseases. IRE1 expression in cells must be stringently regulated because overexpression and prolonged activation of mammalian IRE1α and IRE1β induce apoptosis [11]. Therefore, during adaptable disturbances, it gets transiently activated and then gets inactivated, whereas in severe stress, its activity is for longer periods, which triggers the apoptosis inducing molecule and results in cell death. The mechanisms of differential regulation of IRE1α in physiological conditions and in different stress levels are still vague. However, this

diverse activity is coordinated by a number of molecules from the ER lumen, cytoplasm, and ER membrane, which form the UPRosome. Orchestrating this molecule, cells can be directed towards survival or death. This difference in the nature of activity contributes to their different downstream effects.

ER performs various cellular functions, such as protein folding, post- translational modifications, fatty acid and sterol biosynthesis, xenobiotic detoxification, and intracellular calcium storage [12]. The rough endoplasmic reticulum on its external surface is lined with ribosomes and is involved in processing and sorting of proteins. If the ribosomes translate the mRNA, a synthesized peptide is inserted into the ER according to the signal sequence. Then, the signal sequence is cleaved, and the protein is released into the lumen of the ER. The protein released into the ER may stay in the ER or move through the Golgi to the lysosome or plasma membrane or may be secreted. However, regardless of its final destination, the protein can undergo different processes in the ER lumen. These involve folding, assembling into multisubunit complexes, formation of disulfide bonds, glycosylation, and glycolipid additions. About one-third of total cellular proteins contains secretory proteins, and transmembrane proteins are matured in the ER. Its functions require the environment in the ER to be oxidative and rich in calcium and other protein folding machinery. The protein folding requirement and amount of secretory protein synthesis vary depending on the cell types. Cells which are meant for the secretory functions are rich in ER to meet the demand. Secretory proteins, helped by chaperones and other movements, fold precisely to their native configuration as they pass through the ER. However, cells can encounter conditions in which demand for ER protein folding activities exceeds the efficiency. Subsequently, ER protein folding functions will get a hit by different perturbations like viral infections, cancers, neurodegenerative diseases, diabetes, inflammation, protein-folding diseases, and other aberrations at a cellular level. This results in the accumulation of unfolded proteins in the endoplasmic reticulum, referred to as ER stress. However, the cell has evolved a mechanism to detect these changes and to restore homeostasis by activating signal transducing pathways, known as the UPR, and this process is conserved from yeast to human. Initially, the UPR system attempts to restore homeostasis by inducing transcription of folding enzymes, chaperones, oxidoreductases, and decreasing protein translation, autophagy, lipid biogenesis, vesicular trafficking, and also by degrading ER-associated mRNA, which helps to minimize translation in the initial adaptive phase. However, in the event of failure of this adaptive process due to prolonged stress, UPR triggers cellular apoptotic pathways to remove ER-stressed cells as a physiological process, but unrestricted apoptosis becomes pathological, which in turn leads to loss of cells in essential organs [13]. Thus, the UPR is an essential fundamental process in the quality control of proteins not only during ER stress, but also in normal growth conditions [14].
