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Review

The endoplasmic reticulum and the unfolded protein response

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Abstract

The endoplasmic reticulum (ER) is the site where proteins enter the secretory pathway. Proteins are translocated into the ER lumen in an unfolded state and require protein chaperones and catalysts of protein folding to attain their final appropriate conformation. A sensitive surveillance mechanism exists to prevent misfolded proteins from transiting the secretory pathway and ensures that persistently misfolded proteins are directed towards a degradative pathway. In addition, those processes that prevent accumulation of unfolded proteins in the ER lumen are highly regulated by an intracellular signaling pathway known as the unfolded protein response (UPR). The UPR provides a mechanism by which cells can rapidly adapt to alterations in client protein-folding load in the ER lumen by expanding the capacity for protein folding. In addition, a variety of insults that disrupt protein folding in the ER lumen also activate the UPR. These include changes in intralumenal calcium, altered glycosylation, nutrient deprivation, pathogen infection, expression of folding-defective proteins, and changes in redox status. Persistent protein misfolding initiates apoptotic cascades that are now known to play fundamental roles in the pathogenesis of multiple human diseases including diabetes, atherosclerosis and neurodegenerative diseases.

Keywords: Endoplasmic reticulum; Unfolded protein response; ER; Secretory pathway; Apoptosis

Contents

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1. Introduction

Protein folding is an essential process for protein function in all organisms. As a consequence, all cells have evolved sophisticated mechanisms to ensure proper protein folding occurs and to dispose of irreversibly misfolded proteins. All proteins that transit the secretory pathway in eukaryotic cells first enter the endoplasmic reticulum (ER) where they fold and assemble into multi-subunit complexes prior to transit to the Golgi compartment [1]. 'Quality control' is a surveillance mechanism that permits only properly folded proteins to exit the ER *en route* to other intracellular organelles and the cell surface. Misfolded proteins are either retained within the ER lumen in complex with molecular chaperones or are directed toward degradation through the 26S proteasome in a process called ER-associated degradation (ERAD) or through autophagy.

The efficiency of protein-folding reactions depends on appropriate environmental, genetic and metabolic conditions. Conditions that disrupt protein folding present a threat to cell viability. The ER provides a unique environment that challenges proper protein folding as nascent polypeptide chains enter the ER lumen. A high concentration of partially folded and unfolded proteins predisposes protein-folding intermediates to aggregation. Polypeptide binding proteins, such as BiP and GRP94, act to slow protein-folding reactions and prevent aberrant interactions and aggregation. The ER lumen is an oxidizing environment so disulfide bond formation occurs. As a consequence, cells have evolved sophisticated machinery composed of multiple protein disulfide isomerases (PDIs) that are required to ensure proper disulfide bond formation and prevent formation of illegitimate disulfide bonds. The ER is also the primary Ca^{2+} storage organelle in the cell. Both protein-folding reactions and protein chaperone functions require high levels of ER intralumenal calcium. Protein folding in the ER requires extensive amounts of energy and depletion of energy stores prevents proper protein folding. ATP is required for chaperone function, to maintain Ca^{2+} stores and redox homeostasis, and for ERAD. Finally, proteins that enter the ER lumen are subject to numerous post-translational modifications including N-linked glycosylation, amino acid modifications such as proline and aspartic acid hydroxylation and γ-carboxylation of glutamic acid residues, and addition of glycosylphosphatidylinositol anchors. All these processes are highly sensitive to alterations in the ER luminal environment. As a consequence, innumerable environmental insults alter protein-folding reactions in the ER through mechanisms that include depletion of ER calcium, alteration in the redox status, and energy (sugar/glucose) deprivation. In addition, gene mutations, elevated protein traffic through the ER compartment, and altered post-translational modification all contribute the accumulation of unfolded proteins in the ER lumen.

Accumulation of unfolded protein initiates activation of an adaptive signaling cascade known as the unfolded protein response (UPR). Appropriate adaptation to misfolded protein accumulation in the ER lumen requires regulation at all levels of gene expression including transcription, translation, translocation into the ER lumen, and ERAD. Coordinate regulation of all these processes is required to restore proper protein folding and ER homeostasis [1–6]. Conversely, if the protein folding defect is not resolved, chronic activation of UPR signaling occurs which eventually induces an apoptotic (programmed cell death) response.

In this review we summarize the signaling pathways that mediate the UPR, mechanisms that signal cell death, the role of the UPR in mammalian physiology, and the clinical implications of the UPR in health and disease.

2. Protein folding and quality control in the ER

Protein folding and maturation *in vivo* is a highly assisted process. The ER lumen contains molecular chaperones, folding enzymes and quality control factors that assist in folding and trafficking of newly synthesized polypeptides. Nascent polypeptide chains enter the ER lumen through a proteinaceous channel, the Sec 61 translocon complex. The nascent chains of most translocated polypeptides are subject to addition of a preassembled oligosaccharide core (*N*-acetylglucosamine$_2$-mannose$_9$-glucose$_3$), i.e., $Glc_3Man_9GlcNac_2$ to selective asparagine (*N*) residues. *N*-Glycosylation is catalyzed by the oligosaccharyltransferase (OST), a multisubunit enzyme associated with the translocon complex. Subsequently, sequential action by the ER α-glucosidases I and II removes the two outermost glucose residues to produce a mono-glucosylated core glycan. The mono-glucosylated glycoprotein can then interact with two homologous ER lectins calnexin (CNX) and calreticulin (CRT) that associate with Erp57, an oxidoreductase that catalyzes disulfide bond formation. Upon release of folding substrates from CNX and/or CRT, the innermost glucose residue is rapidly removed by glucosidase II. Two potential mechanisms by which chaperones may monitor protein folding are through exposed hydrophobic patches or through excessive surface dynamics associated with the non-compact partially folded state. The protein chaperone BiP binds to the hydrophobic patches exposed on protein folding intermediates. Highly dynamic, non-native deglucosylated glycoproteins are recognized by the ER folding sensor UDP-glucose:glycoprotein glucosyltransferase (UGT1). UGT1 specifically re-glucosylates folding intermediates released from CNX/CRT cycle. Reglucosylation mediates ER retention of immaturely folded glycoproteins so they enter