Endoplasmic Reticulum Stress and the Unfolded Protein Response

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KEYWORDS

- Non-alcoholic fatty liver disease • Non-alcoholic steatohepatitis
- Fatty liver • Unfolded protein response • ER stress
- Eukaryotic initiation factor • Inflammation
- Metabolic syndrome

The endoplasmic reticulum (ER) is a key cellular organelle that is involved in protein homeostasis. Following synthesis, proteins are exported from the ER to various subcellular locations for use or export. This process involves recognition of specific motifs by the molecular transporters required to take the synthesized proteins to their destination. The primary structure of the protein determines both the specific motifs for binding to targets and its' folding, which determines the availability of the motifs for binding to its targets. Therefore, a key function of the ER is to ensure the fidelity of protein synthesis and processing so that they are folded appropriately, which allows them to be transported to their cellular destination. This is accomplished by several energy-requiring steps within the ER which have been reviewed in depth elsewhere.[1]

When the ability of the ER to ensure fidelity of protein synthesis is overwhelmed by increased protein synthetic drive, primary dysfunction of the ER, or lack of ATP, unfolded proteins accumulates within the ER. The unfolded protein response (UPR) is a fundamental cellular process that is triggered by the accumulation of unfolded proteins within the ER, a phenomenon also referred to as the ER stress response.[2] The goal of the UPR is to restore homeostasis and allow the cell to adapt to the stressor event. If homeostasis is not restored, alternate pathways leading to apoptosis are triggered. The UPR has been shown to be involved in both normal physiologic functions and the cellular response to a host of pathologic states. In this article, we

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will review the pathways by which the UPR unfolds and its potential role in the development and progression of non-alcoholic fatty liver disease (NAFLD).

PATHWAYS OF THE UPR

When the normal mechanisms within the ER that ensure fidelity of protein folding are disturbed, unfolded proteins accumulates in the ER. Many known triggers for ER dysfunction lead to disturbances in protein folding in the ER. These include viral infections, glucose deprivation, changes in redox state, increased cholesterol to phospholipid ratio in the ER membrane, and decreased ATP stores.[3–7] The initial response is to correct this by inhibition of protein synthesis and increased degradation of unfolded protein by way of proteasomes. Simultaneously, adaptive genes are activated which improve protein folding and help the cell adapt to the trigger for UPR. Glucose regulated protein 78/BiP is considered the master regulator of the UPR and is a chaperone protein that is resident within the ER. BiP binds intraluminal proteins on one hand and a number of transmembrane mediators of the UPR on the other, thereby anchoring the latter to the ER (**Fig. 1**). When unfolded proteins accumulate within the ER, BiP is preferentially bound to these proteins, which release the previously bound transmembrane mediators from the ER membrane—thereby activating the UPR.[8]

The PKR-like ER Kinase Pathway

The PKR-like ER kinase (PERK) pathway is designed to produce translational arrest of protein synthesis and help further accumulation of unfolded proteins in the ER. PERK is a Ser/Thr transmembrane kinase that is located on the ER membrane.[8] It is anchored to the ER by interaction with another protein BiP, which resides in the lumen of the ER. Upon accumulation of unfolded proteins in the ER, BiP binds to the unfolded proteins, thus releasing PERK in to the cytoplasm and activating PERK in the process.[9]

Upon activation, PERK oligomerizes and phosphorylates its targets. One target is the eukaryotic initiation factor-2α (eIF-2α).[10,11] eIF-2α Phosphorylation produces a general translational arrest of protein synthesis.[10,11] Normally, during initiation of protein synthesis, GTP-eIF 2α binds to the 40 S ribosome and methionine initiator tRNA forming a ternary complex. After initiation, GDP-eIF 2α is released. For GDP-eIF 2α to be recycled, eIF 2B is required. Phosphorylated eIF 2α at serine 51 binds

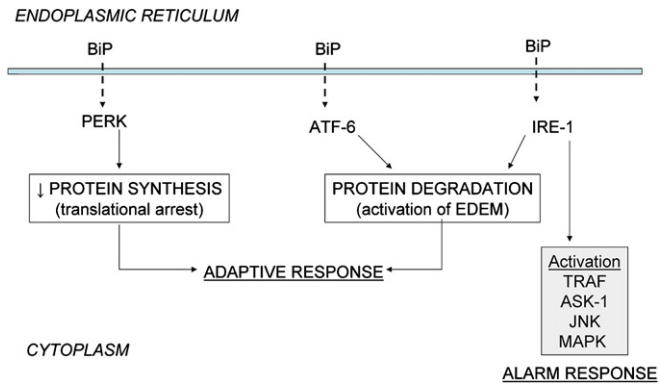

Fig. 1. UPR.