THE EIF2 KINASE PERK AND THE INTEGRATED STRESS RESPONSE FACILITATE ACTIVATION OF ATF6 DURING ENDOPLASMIC RETICULUM STRESS

Brian F. Teske[1] (Ronald C. Wek), Sheree A. Wek[1], Piyawan Bunpo[2], Judy K. Cundiff[2], Jeanette N. McClintick[1], Tracy G. Anthony[2], and Ronald C. Wek[1]

[1]Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana 46202; USA
[2]Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Evansville, IN 47712; USA

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Disruptions of the endoplasmic reticulum (ER) that perturb protein folding cause ER stress and elicit an unfolded protein response (UPR) that involves changes in gene expression aimed at expanding the ER protein processing capacity and alleviating cellular injury. Three ER stress sensors PERK, ATF6, and IRE1 implement the UPR. Mutations of these ER stress sensors have been linked to diabetes, cancer and neurodegenerative diseases. Consequently, understanding the regulation of these three pathways has substantial therapeutic potential for development of biomarkers and pharmaceuticals for management of these conditions. PERK phosphorylation of eIF2 during ER stress represses protein synthesis, which prevents further influx of ER client proteins. PERK phosphorylation of eIF2 (eIF2~P) also induces preferential translation of ATF4, a transcription activator of the UPR. In this study we show that the PERK/eIF2~P/ATF4 pathway is required not only for translational control, but also activation of ATF6 and its target genes. The PERK pathway facilitates both the synthesis of ATF6 and trafficking of ATF6 from the ER to the Golgi for intramembrane proteolysis and activation of ATF6. As a consequence, liver-specific depletion of *PERK* significantly reduces both the translational and transcriptional phases of the UPR, leading to reduced protein chaperone expression, disruptions of lipid metabolism, and enhanced apoptosis. These findings show that the regulatory networks of the UPR are fully integrated, and helps explain the diverse biological defects associated with loss of *PERK*.