The integrated stress response directs cell fate decisions in response to perturbations in protein homeostasis

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Teske, Brian Frederick

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Abstract:

Disruptions of the endoplasmic reticulum (ER) cause perturbations in protein folding and result in a cellular condition known as ER stress. ER stress and the accumulation of unfolded protein activate the unfolded protein response (UPR) which is a cellular attempt to remedy the toxic accumulation of unfolded proteins. The UPR is implemented through three ER stress sensors PERK, ATF6, and IRE1. Phosphorylation of the α-subunit of eIF2 by PERK during ER stress represses protein synthesis and also induces preferential translation of ATF4, a transcriptional activator of stress response genes. Early

UPR signaling involves translational and transcriptional changes in gene expression that is geared toward stress remedy. However, prolonged ER stress that is not alleviated can trigger apoptosis. This dual signaling nature of the UPR is proposed to mimic a 'binary switch' and the regulation of this switch is a key topic of this thesis. Adaptive gene expression aimed at balancing protein homeostasis encompasses the first phase of the UPR. In this study we show that the PERK/eIF2~P/ATF4 pathway facilitates both the synthesis of ATF6 and trafficking of ATF6 from the ER to the Golgi where ATF6 is activated. Liver-specific depletion of PERK significantly lowers expression of survival genes, leading to reduced expression of protein chaperones. As a consequence, loss of PERK in the liver sensitizes cells to stress which ultimately leads to apoptosis. Despite important roles in survival, PERK signaling is often extended to the vii activation of other downstream transcription factors such as CHOP, a direct target of ATF4-mediated transcription. Accumulation of CHOP is a hallmark of the second phase in the binary switch model where CHOP is shown to be required for full activation of apoptosis. Here the transcription factor ATF5 is found to be induced by CHOP and that loss of ATF5 improves the survival of cells following changes in protein homeostasis. Taken together this study highlights the importance of UPR signaling in determining the balance between cell survival and cell death. A topic that is important for understanding the more complex pathological conditions of diseases such as diabetes, cancer, and neurodegeneration.

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