REGULATION OF CHOP TRANSLATION IN RESPONSE TO eIF2 PHOSPHORYLATION AND ITS ROLE IN CELL FATE

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Abstract:

In response to different environmental stresses, phosphorylation of eukaryotic initiation factor-2 (eIF2) rapidly reduces protein synthesis, which lowers energy expenditure and facilitates reprogramming of gene expression to remediate stress damage. Central to the changes in gene expression, eIF2 phosphorylation also enhances translation of ATF4, a transcriptional activator of genes subject to the Integrated Stress Response (ISR). The ISR increases the expression of genes important for alleviating stress, or alternatively triggering apoptosis. One ISR target gene encodes the transcriptional regulator CHOP whose accumulation is critical for stress-induced apoptosis. In this dissertation research, I show that eIF2 phosphorylation induces preferential translation of

CHOP by a mechanism involving a single upstream ORF (uORF) located in the 5'-leader of the CHOP mRNA. In the absence of stress and low eIF2 phosphorylation, translation of the uORF serves as a barrier that prevents translation of the downstream CHOP coding region. Enhanced eIF2 phosphorylation during stress facilitates ribosome bypass of the uORF, and instead results in the translation of CHOP. Stable cell lines were also constructed that express CHOP transcript containing the wild type uORF or deleted for the uORF and each were analyzed for expression changes in response to the different stress conditions. Increased CHOP levels due to the absence of inhibitory uORF sensitized the cells to stress-induced apoptosis when compared to the cells that express CHOP mRNA containing the wild type uORF. This new mechanism of translational control explains how expression of CHOP and the fate of cells are tightly linked to the levels of phosphorylated eIF2 and stress damage.

Description:

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