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Abstract:

Phosphorylation of eukaryotic initiation factor 2 (eIF2) is an important mechanism regulating global and gene-specific translation during different environmental stresses. Repressed global translation by eIF2 phosphorylation allows for cells to conserve resources and elicit a program of gene expression to alleviate stress-induced injury. Central to this gene expression program is eIF2 phosphorylation induction of preferential translation of ATF4. ATF4 is a transcriptional activator of genes involved in stress remediation, a pathway referred to as the Integrated Stress Response (ISR). We investigated whether there are additional transcription factors whose translational expression is regulated by eIF2 kinases. We found

that the expression of the transcriptional regulator ATF5 is enhanced in response to many different stresses, including endoplasmic reticulum stress, arsenite exposure, and proteasome inhibition, by a mechanism requiring eIF2 phosphorylation. ATF5 is regulated by translational control as illustrated by the preferential association of ATF5 mRNA with large polyribosomes in response to stress. ATF5 translational control involves two upstream open reading frames (uORFs) located in the 5′-leader of the ATF5 mRNA, a feature shared with ATF4. Mutational analyses of the 5′-leader of ATF5 mRNA fused to a luciferase reporter suggests that the 5′-proximal uORF1 is positive-acting, allowing scanning ribosomes to reinitiate translation of a downstream ORF. During non-stressed conditions, when eIF2 phosphorylation is low, ribosomes reinitiate translation at the next ORF, the inhibitory uORF2. Phosphorylation of eIF2 during stress delays translation reinitiation, allowing scanning ribosomes to bypass uORF2, and instead translate the ATF5 coding region. In addition to translational control, ATF5 mRNA and protein levels are significantly reduced in mouse embryo fibroblasts deleted for ATF4, or its target gene, the transcriptional factor CHOP. This suggests that ISR transcriptional mechanisms also contribute to ATF5 expression. To address the function of ATF5 in the ISR, we employed a shRNA knock-down strategy and our analysis suggests that ATF5 promotes apoptosis under stress conditions via caspase-dependent mechanisms. Given the well-characterized role of CHOP in the promotion of apoptosis, this study suggests that there is an ATF4-CHOP-ATF5 signaling axis in the ISR that can determine cell survival during different environmental stresses.

Description:

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