Multiple Roles for eIF2alpha Phosphatases in the Unfolded Stress Response

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Abstract

Transient repression of mRNA translation is a universal response of all eukaryotic cells to perturbations in their metabolic or growth environment. This “integrated stress response” temporarily slows general protein synthesis and allows cells to redirect their efforts towards translating mRNAs encoding stress response proteins that are required to overcome the “stress”. Failure to execute this complex translational and transcriptional response triggers cell death and likely contributes to a wide variety of chronic human diseases. The repression of global mRNA translation is mediated via the phosphorylation of a single serine-51 on the eukaryotic initiation factor, eIF2α. Subsequently, the transcriptional and translational upregulation of GADD34 (Growth Arrest- and DNA Damage-induced transcript 34), a regulator of protein phosphatase-1 (PP1), assembles an eIF2α phosphatase that restores general protein synthesis. Cells also express another eIF2α phosphatase, containing the regulatory subunit, CReP (constitutive repressor of eIF2α phosphorylation). This presentation will review our current understanding of the distinct roles of GADD34- and CReP-containing eIF2α phosphatases in the control of transcritome and translatome in unstressed cells and in stressed cells experiencing the unfolded protein response. The data highlight some of the challenges and opportunities in therapeutic targeting of eIF2α phosphatases with small molecules to treat diabetes, cancer and neurodegenerative disorders.