

Identification of Potential Small Molecule Regulators of PERK Kinase

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Abstract : PKR-like ER kinase (PERK) is serine/threonine endoplasmic reticulum (ER) transmembrane kinase activated during ER-stress. PERK can activate signaling pathways known as unfolded protein response (UPR). Attenuation of translation is mediated by PERK via phosphorylation of eukaryotic initiation factor 2 α (eIF2 α), which is necessary for translation initiation. PERK activation also directly contributes to activation of Nrf2 which regulates expression of anti-oxidant enzymes. An increased phosphorylation of eIF2 α has been reported in Alzheimer disease (AD) patient hippocampus, indicating that PERK is activated in this disease. Recent data have revealed activation of PERK signaling in non-Hodgkins lymphomas. Results also revealed that loss of PERK limits mammary tumor cell growth in vitro and in vivo. Consistent with these observations, activation of UPR in vitro increases levels of the amyloid precursor protein (APP), the peptide from which beta-amyloid plaques (AB) fragments are derived. Finally, proteolytic processing of APP, including the cleavages that produce AB, largely occurs in the ER, and localization coincident with PERK activity. Thus, we expect that PERK-dependent signaling is critical for progression of many types of diseases (human cancer, neurodegenerative disease and other). Therefore, modulation of PERK activity may be a useful therapeutic target in the treatment of different diseases that fail to respond to traditional chemotherapeutic strategies, including Alzheimer's disease. Our goal will be to developed therapeutic modalities targeting PERK activity.

Keywords : PERK kinase, small molecule inhibitor, neurodegenerative disease, Alzheimer's disease

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