Translational regulation by DJ-1

https://neurodegenerationresearch.eu/survey/translational-regulation-by-dj-1-2/

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USA

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Translational regulation by DJ-1

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Research Abstract
Project summary Eukaryotic cells have adopted several tactics to cope with a battery of stresses for their survival. One way is to pause the translation of most mRNAs to conserve their energy and to reduce the accumulation of damaged proteins. Such changes are mediated by the phosphorylation of eukaryotic translation initiation factor-2? (eIF- 2?) on serine 51, and subsequent gathering of non-translating mRNAs and RNA binding proteins into discrete cytoplasmic foci, called stress granules (SGs). SGs are stalled translational complexes that function to protect cells under stress. Dysregulation of eIF-2? phosphorylation and SG formation

plays an important role in the pathogenesis of several neurodegenerative disorders. DJ-1 is a small and multi-functional oxidative stress response protein. As loss-of-function mutations in DJ-1 are linked to recessively inherited Parkinson’s disease (PD), investigation of DJ-1’s function and the pathways in which DJ-1 is involved has been an active field of research. Diverse functions including chaperone, cysteine protease, transcriptional coactivator and transnitrosylase are suggested, but its role(s) in contributing to the pathogenesis of PD remains to be fully elucidated. Here, we propose to investigate a hitherto unexplored function of DJ-1, and elucidate the link of this function to neuronal survival. Our preliminary data show that silencing DJ-1 expression in neuronal cells leads to decreased phosphorylation of eIF-2?, subsequently impairs SG formation and fails to inhibit global protein synthesis in response to sodium arsenite. Among reactive oxygen species produced by arsenite challenge, we showed that intracellular nitric oxide (NO) is responsible for stimulating eIF-2? phosphorylation. NO is of particular interest as it is involved in the pathogenic processes resulting in dopaminergic neuronal death in PD. Therefore, we hypothesize that DJ-1 represses protein translation in response to NO by activating the eIF-2?? pathway and subsequent SG formation. Loss-of-function mutations in the DJ-1 gene impair the eIF-2?? pathway and compromise this cell survival response, and thereby contributes to PD pathogenesis. Further, characterizing this pathway in its molecular and cellular detail will lead to important insights into the pathogenic mechanism of sporadic PD as well. To test our hypothesis, we propose two specific aims. First, we will investigate the functional consequences and mechanism of DJ-1 on the activation of eIF-? pathway in response to NO. Second, we will investigate the molecular pathway of eIF-2? in a mouse model of PD. Successful completion of the proposed studies will further advance the knowledge about DJ-1’s biology and define the molecular mechanism by which DJ-1 regulates eIF-2? pathway and SG formation. Identified pathway and a molecular target of DJ-1 might be exploited as novel therapeutic targets for the treatment of PD.

Further information available at:

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