Neuroregulatory Mechanisms of PIAS1 and Implications for Huntingtons Disease

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USA

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Neuroregulatory Mechanisms of PIAS1 and Implications for Huntingtons Disease

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3

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington Disease, Ligase, CAG repeat, Huntington gene, mutant

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is an inherited neurodegenerative disease that strikes in the prime of life and has no disease-modifying

treatment. HD is caused by CAG repeat expansion in the HD gene, causing complex and extensive cellular dysfunction. The identification of cellular targets that impact disease onset and progression and enlighten further mechanistic understanding of these targets are critical for development of new treatments. Mutant HTT (mHTT) and toxic fragments derived from the mutant protein are in a dynamic equilibrium poised to shift the homeostatic network from the appropriate balance of protein folding, misfolding, oligomerization and degradation to one in which that balance is disrupted. Upon network disruption, cellular proteins accumulate and degradation pathways become impaired. Our studies suggest that the E3 SUMO ligase, PIAS1, may be an important regulatory switch in this dynamic equilibrium. In published findings, we identified PIAS1 as a novel modulator of both SUMO-1 and SUMO-2 modification and accumulation of mHTT protein in cultured cells and that reduction of PIAS in Drosophila delays phenotypes caused by repeat expanded HTT. In recent preliminary data, we find that reduction of PIAS1 expression in R6/2 mice confers robust neuroprotection, suggesting PIAS may provide a selective therapeutic target. The communication and involvement between E3 SUMO ligases and protein clearance pathways are not well understood with respect to misfolded and accumulated proteins. In addition to functioning as a SUMO E3 ligase, PIAS is implicated in regulating transcription of proinflammatory cytokine signaling and innate immune response pathways. Therefore, clarifying the PIAS1 network in HD systems will provide a crucial understanding as to its role in HD pathology. We hypothesize that PIAS1 is a key regulator of HTT SUMOylation and accumulation, that it can modulate HD pathogenesis and that it may be a novel target for development of HD therapies. We propose to use cell based assays and in vivo studies to advance our mechanistic understanding of PIAS1-mediated networks, and validate PIAS1 as a molecular target for HD drug development. Specifically we will carry out the following proposed aims: Aim 1: PIAS1 modulation in HD mouse models. Aim 2: PIAS1 network in mHTT expressing neural cells. Aim 3: In vivo effects of mHTT expression in heterozygous PIAS1-null mice. Aim 4: Functional significance of PIAS1 domains in disease modifying pathways.

Lay Summary
PUBLIC HEALTH RELEVANCE: Huntington’s disease (HD) is a devastating, inherited neurological disorder that causes psychiatric, cognitive and movement deficits. Protein modifications of the mutated protein (mutant Huntingtin) that causes HD may alter progression of disease and understanding the mechanisms involved is crucial to the development of effective therapeutic intervention. This proposal will use an innovative approach to understand the relationship between a specific Huntingtin modification system, involving the E3 SUMO ligase PIAS1, and HD pathology.

Further information available at:

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Investments > €500k

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United States of America

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Huntington's disease

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