Mechanism of modulation of huntingtin exon 1 aggregation by profilin

https://neurodegenerationresearch.eu/survey/mechanism-of-modulation-of-huntingtin-exon-1-aggregation-by-profilin/

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Country

USA

Title of project or programme

Mechanism of modulation of huntingtin exon 1 aggregation by profilin

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NIH (NINDS)

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5

The project/programme is most relevant to:

Huntington's disease

Keywords

profilin, Huntington gene, Exons, polyproline, polyglutamine

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is a devastating neurodegenerative disease caused by CAG codon expansion in exon 1 of the huntingtin (htt)

gene. Exon 1 spanning protein products, referred to as Httex1 are the major components of neuronal intranuclear inclusions that are the hallmarks of HD. Y-27632, a small molecule inhibitor of the rho-associated kinase (ROCK), was shown by the Diamond lab to reduce Httex1 aggregation in cells and ameliorate Httex1-mediated toxicity in Drosophila and mouse models. Serine-137 of profilin was established as the direct target of ROCK. Phospho-profilin does not reduce Httex1 aggregation whereas unphosphorylated profilin modulates Httex1 aggregation through direct interactions thus explaining the effect of Y-27632. We envisage a direct therapeutic approach that involves the design of molecules to mimic the effects of profilin. Such an approach requires a comprehensive understanding of the mechanisms by which profilin suppresses Httex1 aggregation, and this is the focus of our proposal. Our goal is to understand how profilin modulates the aggregation of exon 1 of huntingtin through interactions with its polyproline regions. Our approaches will include intracellular assays of aggregation and in vitro biophysical studies that combine fluorescence spectroscopies, electron paramagnetic resonance spectroscopy, and electron microscopy. The relevant entity for modulation of Httex1 aggregation by profilin is the 38-residue proline-rich stretch (C38) that is C-terminal to polyglutamine in Httex1. This stretch encompasses two polyproline modules that are connected via a 17-residue flexible linker. Profilin binds to the polyproline modules in C38. Our preliminary data show that in the presence of profilin, a higher total concentration of Htt-NTFs is required to form large spherical and fibrillar aggregates because profilin binds preferentially to smaller oligomeric species. Our preliminary data also establish that the apparent affinity of profilin for Httex1 constructs is higher when compared to C38 alone. This appears to be due to increased avidity that derives from oligomerization of Htt-NTFs in the M-phase. Avidity refers to the increased local concentration of C38 modules within oligomers. We will build on our preliminary data to uncover the mechanisms by which profilin binding impacts the phase behavior of disease- relevant N-terminal fragments of Httex1.

Lay Summary
PUBLIC HEALTH RELEVANCE: Huntington’s disease is a devastating neurodegenerative disease that is caused by polyglutamine expansions in the exon 1 encoded region of the huntingtin protein. Building on recent advances that identified profilin as a modulator of huntingtin exon 1 aggregation and toxicity this project is focused on developing a mechanistic understanding of this modulation. The insights afforded by this work, if successful, should lead directly to the identification of targets for therapeutic intervention

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

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