Validation of Novel Pathogenic Htt Post-Translational Modifications (PTMs)

https://www.neurodegenerationresearch.eu/survey/validation-of-novel-pathogenic-htt-post-translational-modifications-ptms/

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Country

USA

Title of project or programme

Validation of Novel Pathogenic Htt Post-Translational Modifications (PTMs)

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NIH (NINDS)

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€ 2,795,216.51

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01/04/2014

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3

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington gene, Post-Translational Protein Processing, Post-Translational Modification Site, Validation, induced pluripotent stem cell

Research Abstract

DESCRIPTION (provided by applicant): The best validated therapeutic target in HD remains Htt

itself. Previously identified PTMs of expanded Htt (e.g. S13/16 and S421) are important modulators of HD pathogenesis. We previously studied proteolytic cleavage of Htt (Ratovitski et al., 2007, 2009, 2011), and more recently have been studying covalent PTMs of Htt, especially phosphorylation. Htt is very likely to have many other sites of PTM besides the currently known ones (described in the Significance section). We plan to characterize Htt PTMs systematically and quantitatively. Furthermore, our experiments include the use of human HD iPS cells for our continuing discovery studies, and a staged program beginning with mass spectrometry for discovery and progressing through in vitro and then in vivo confirmation and functional validation. Phosphorylation which enhances toxicity will be especially promising as a therapeutic target, if relevant kinases can be identified and inhibited. In Aim 1, we will define Htt PTMs usin Htt-N586-82Q mice, HD “”knock-in”” mice and human HD iPS cells, and will determine whether the polyQ expansion in Htt leads to changes in PTMs. In Aim 2, we will conduct in vitro functional studies of the effects of Htt PTMs on mutant Htt conformation and cellular toxicity. In Aim 3, we will test the effects of PTMs on mutant Htt toxicity in vivo, using our N-586-82Q transgenic mouse model or stereotactic injection of viral expression vectors encoding Htt with altered PTMs into the striatum of wild-type mice. These studies taken together will identify novel sites of PTM in mutant Htt, and functionally validate their role in pathogenesis in vitro and in vivo. The sites will then be candidate targets for therapeutic development.

Lay Summary
PUBLIC HEALTH RELEVANCE: The best validated therapeutic target in HD remains the Huntingtin protein (Htt) itself. Previously identified post-translational modifications of mutant Ht are important modulators of HD pathogenesis. We will identify novel sites of post-translational modification, and, using biochemical, cell culture, and transgenic mouse model techniques, we will validate them as therapeutic targets.

Further information available at:

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Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
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