Epigenetic pathology and therapy in Huntingtons disease

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Country

USA

Title of project or programme

Epigenetic pathology and therapy in Huntingtons disease

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NIH (NINDS)

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01/04/2015

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4

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington Disease, Epigenetic Process, Huntington gene, Pathology, chromatin modification

Research Abstract

? DESCRIPTION (provided by applicant): Transcriptional dysregulation is a pathognomonic feature of Huntington’s disease (HD). Analysis of human brain at autopsy, PET ligand binding in pre-manifest HD patient brain and gene expression studies in numerous cell and animal HD

models as well as human HD brain tissue all support the view that transcriptional dysregulation is an important feature of this disease. Several key questions arise in assessing the role of transcriptional dysregulation in HD. One important question is the mechanistic basis by which the presence of pathological Huntingtin (HTT) protein in HD brain leads to transcriptional dysfunction. An equally important question is the extent to which reversal or blockage of the transcriptional dysregulation program in HD can lead to a therapeutic benefit in this disease. While there have been many significant contributions towards understanding these questions, this proposal is focused on an extension of recent studies that we have carried out which implicate the epigenetic machinery of the cells of the basal ganglia and the cortex in the mechanistic basis of transcriptional dysregulation. Our recent observations on the specific patterns of histone marks and DNA methylation patterns altered at or near the promoters of downregulated genes provide very strong new support for a key role for epigenetic modulation in HD transcriptional dysregulation and pathology. Our findings provide further support for the concept that therapeutic intervention directed towards modulating the epigenetic machinery of the cell can be beneficial in impeding the pathology in HD. We propose here to extend these studies in depth to gain a deeper and more complete understanding of the programmatic and potentially causative changes caused by the expression of the pathological form of HTT. We will expand our analysis to examine additional models of HD and to examine individual cell types. We will also explore the role of mutant huntingtin in establishing the epigenetic patterns. Finally we will test methods for modifying the epigenetic patterns using cell based and whole organism studies, and we will determine the impact of these changes on HD transcriptional dysregulation and pathology. Our specific aims are therefore to: Aim 1: Establish baseline genome wide analyses of chromatin structure marks and transcription and Aim 2: Evaluate targets for potential therapeutic intervention through modulation of the pathological epigenetic program in HD. The development of a comprehensive and detailed analysis of chromatin modification in HD will provide a unique framework for understanding the role of epigenetic modification in nervous system function. The evaluation of potential efficacy of therapeutic interventions which operate through modulating chromatin modification pathways has the potential to have a decisive impact on the development of effective HD therapeutics by identifying the best potential targets for intervention and the extent to which HD pathology can be limited or perhaps reversed.

Lay Summary

PUBLIC HEALTH RELEVANCE: Huntington’s disease (HD) is a devastating degenerative brain disease for which no disease-modifying treatments are available and inevitably leads to death. Based on recent findings that link changes in the epigenetic machinery in the brain to how transcriptional patterns are altered in HD, we propose an in depth analysis of how changes in chromatin structure relate to these transcriptional changes. The information will be used to select enzymes involved in regulating these processes for preclinical testing in cell and whole organism studies.

Further information available at:

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Investments > €500k

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United States of America

Diseases:
Huntington's disease

Years:
2016

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