Mechanism of DNA strand-break repair deficiency in Huntingtons disease

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Principal Investigators

SARKAR, PARTHA S

Institution

UNIVERSITY OF TEXAS MEDICAL BR GALVESTON

Contact information of lead PI
Country

USA

Title of project or programme

Mechanism of DNA strand-break repair deficiency in Huntingtons disease

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NIH (NINDS)

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01/02/2016

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5

The project/programme is most relevant to:

Huntington's disease

Keywords

Polynucleotide 5'-Hydroxyl-Kinase, DNA strand break, Huntington Disease, Huntington gene, Phosphoric Monoester Hydrolases

Research Abstract
? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is an incurable autosomal

dominant neurodegenerative disease that is caused by an expansion of CAG triplet repeats in the huntingtin (HTT) gene. The expanded CAG repeats in the mutant HTT gene are translated into a polyglutamine (polyQ) tract that confers a deleterious gain of function on the mutant protein. The structurally altered mutant (m)HTT interacts with and inactivates critical factors; loss of function of these factors disrupts transcription of specific genes, synaptic function, calcium homeostasis and mitochondrial dynamics and energetics in HD. Additionally, accumulation of DNA damage and aberrant activation of DNA damage-response (DDR) ataxia telangiectasia-mutated (ATM) signaling is also implicated in the HD pathomechanism. Notwithstanding these discoveries defining the underlying disease mechanisms, the early instigating processes by which mHTT induces these pathological changes and drives functional decline and neuronal loss remain unknown. This knowledge gap is a major rate-limiting step in developing a targeted therapeutic strategy to prevent neurological decline in HD; due to this limitation this degenerative illness remains untreatable and invariably fatal. In an important step forward, we have discovered that the normal HTT recruits polynucleotide kinase 3? phosphatase (PNKP), a major DNA strand break repair enzyme; ataxin-3 (ATXN3), a deubiquitinating enzyme; and RNA polymerase II (RNAPII) to form a transcription-dependent multi- protein DNA repair complex likely to be involved in the repair of actively transcribing genes. In contrast, mHTT disrupts the functional integrity of this repair complex and abrogates PNKP activity, resulting in DNA strand break accumulation to stimulate a pathogenic surge of DNA damage-response signaling in HD. The overall objective of this project is to characterize the molecular interactions by which mHTT impairs the enzymatic activities of PNKP and ATXN3, perturbs repair of the actively transcribed genes, and contributes to HD pathomechanism so that we can ultimately develop a preventive therapy for this terminal disease. These studies are designed to provide a mechanistic basis for neurodegeneration in HD and uncover the critical role of DNA repair therein. Aim 1 should confirm that mHTT alters the functional integrity of the transcription coupled repair complex, and inactivates PNKP to induce DNA strand breaks in the actively transcribing genes in HD. These studies should thus provide important insights into how polyQ expansion interferes with a specific DNA repair machinery to induce nuclear and mtDNA damage in HD. Aim 2 will provide critical mechanistic insights into how mHTT triggers pro-apoptotic stimuli to cause neurotoxicity in HD. Aim 3 will test the effectiveness of PNKP overexpression in the mutant cells and in HD transgenic mouse model in decreasing DNA lesions, preventing or slowing down DDR pathway activation in HD. These studies should confirm that mutant HTT-mediated impairment of neuronal DNA repair contributes to neurotoxicity in HD, and identify proximal molecular targets to develop mechanism-based therapeutic strategies for HD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Huntington’s disease (HD) is an incurable, fatal neurodegenerative disease, and caused by the expansion of a CAG tri-nucleotide repeat in the coding regions in huntingtin (HTT) gene. We have discovered that mutant HTT carrying expanded polyglutamine sequences binds and inactivates PNKP polynucleotide kinase 3?-phosphatase), an essential DNA strand break repair enzyme disrupting efficacy of neuronal DNA strand break repair. The proposed research will investigate how mutant HTT-mediated inactivation of PNKP causes neurotoxicity in HD, and help to develop mechanism-based therapeutic strategies for HD.

Further information available at:

Types:

Investments > €500k

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United States of America

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Huntington's disease

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