Etiological Linkage of DNA Damage/Repair Deficiency in Neurodegenerative Diseases

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Country

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Title of project or programme

Etiological Linkage of DNA Damage/Repair Deficiency in Neurodegenerative Diseases

Source of funding information

NIH (NINDS)

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€ 1,608,000.00

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01/07/2015

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

DNA-Binding Proteins, DNA Repair, Neurodegenerative Disorders, Double Strand Break Repair, Amyotrophic Lateral Sclerosis

Research Abstract

? DESCRIPTION (provided by applicant): The transactive response DNA-binding protein-43

(TDP-43), is an hnRNP family protein, whose intracellular aggregation has been etiologically implicated in Amyotrophic Lateral Sclerosis (ALS), a motor neuron degenerative disease (affecting two per 100,000 people worldwide) and about 40% of other common neurodegenerative diseases including Alzheimer's (AD) and Parkinson's disease (PD). Primarily involved in RNA processing, TDP-43 also binds to DNA; but its DNA binding functions are not investigated. While hereditary mutations in TDP-43 have been linked to ALS, the molecular mechanism(s) of its pathology contributing to neuronal death are still unclear. The unique feature of TDP-43 pathogenesis in ALS is its nuclear clearance and simultaneous cytoplasmic aggregation in affected motor/cortical neurons. Furthermore, significant accumulation of genomic damage is observed in TDP-43-linked diseases and previous studies identified a key DNA repair protein `Ku' in TDP-43 immunocomplex from human cells; which raises the possibility of TDP-43's involvement in DNA damage repair, which has not been investigated. In support of this, our preliminary data demonstrate: (1) involvement of nuclear TDP-43 for efficient DNA double-strand break repair (DSBR) in neurons; (2) TDP-43's recruitment at the DSB sites and stable interaction with DSBR proteins; (3) marked increase in DSB accumulation, and delayed DSB repair in TDP-43-depleted neurons and their sensitization to DSB-inducing agents; and (4) strong correlation of TDP-43 nuclear clearance/functional loss with accumulation of DSBs in ALS-affected human post-mortem spinal cord tissue. Based on these, which warrant a detailed investigation into the role of TDP-43 in neuronal genome damage response, we propose that the loss of nuclear TDP-43 causes deficient repair of DSBs in neuronal genomes, leading to persistent accumulation of lethal DSBs, which promote cell death. Thus the central goal of this project is to test this novel hypothesis to establish that TDP-43 pathology-induced DNA repair deficiency is a key etiological factor in ALS/other neurodegenerative diseases. Using state-of-the-art approaches and multiple model systems, we will comprehensively test this hypothesis by pursuing the following Specific Aims: Aim 1: To characterize TDP-43's involvement in DSBR in neuronal genomes, and confirm that persistent genomic damage due to TDP-43 depletion causes cell death. Aim 2: To establish the molecular mechanism of TDP-43's function in DSBR using our novel in vitro reconstituted DSBR assay and test the impact of ALS-linked TDP-43 mutants in repair. Aim 3: To unravel the linkage of TDP-43 pathology (nuclear clearance) and neurodegeneration, with the genomic damage in tissues from TDP-43 (WT/mutant) transgenic mice and human ALS postmortem brains. This grant application with many innovative aspects and based on strong preliminary data represent previously unexplored area of ALS research and understanding this phenomenon could open up new avenues of therapeutic interventions.

Lay Summary

PUBLIC HEALTH RELEVANCE: Amyotrophic lateral sclerosis (ALS) is a rapidly progressing, fatal motor neuron degenerative disease, for which no effective treatment is available even for slowing down the disease progression. Multiple, complex pathologies have been implicated, including the RNA/DNA binding protein TDP-43's nucleus cytoplasm redistribution in a majority of both sporadic and inherited cases; however the molecular mechanisms of its pathology and/or physiological consequence(s) leading to neuronal death/dysfunction are still unknown. The project will establish that TDP-43 is a key component of DNA double strand break (DSB) machinery in neurons of healthy individuals and its loss of nuclear functions in ALS and other TDP-43-associated neurodegenerative diseases which include about 40% of Alzheimer's and Parkinson's disease affected patients, leads to deficient DSB repair. The resulting accumulation of lethal DSBs promotes neuronal toxicity and death. Thus this innovative grant proposal, based

on strong preliminary data, will examine previously unexplored area of ALS research that would lead to a major paradigm shift in our understanding of the molecular pathogenesis of not only ALS, but also other TDP-43-associated neurodegenerative diseases; and could open up new avenues of therapeutic interventions.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Motor neurone diseases

Years:
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