TDP-43 acetylation as a pathogenic modification in ALS & related proteinopathies

https://neurodegenerationresearch.eu/survey/tdp-43-acetylation-as-a-pathogenic-modification-in-als-related-proteinopathies/

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USA

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TDP-43 acetylation as a pathogenic modification in ALS & related proteinopathies

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NIH (NIA)

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Start date of award

15/06/2014

Total duration of award in years

3

The project/programme is most relevant to:

Motor neurone diseases|Alzheimer's disease & other dementias

Keywords

protein TDP-43, DNA-Binding Proteins, Amyotrophic Lateral Sclerosis, Acetylation, Frontotemporal Lobar Degenerations

Research Abstract

7 Project Summary/Abstract Amyotrophic Lateral Sclerosis (ALS) is a devastating motor neuron

disease with a 35 year survival rate and no disease modifying therapies. TAR DNA binding protein of 43kD (TDP43) is a nuclear RNA and DNA binding protein that becomes abnormally aggregated in the brain and spinal cord of most ALS patients as well as a subset of dementia patients (frontotemporal lobar degeneration with TDP43 pathology, or FTLDTDP), placing ALS and FTLDTDP within a spectrum of diseases known as TDP43 proteinopathies. Although TDP43 pathology has been implicated in disease onset and progression, little is known about how TDP43 becomes aggregated leading to progressive neurodegeneration.My long term goal is to uncover the pathogenic mechanisms that promote TDP43 aggregation, which will provide insights for future therapies against these debilitating diseases. Post translational modifications have been implicated in the progression of neurodegenerative diseases.Using my background in acetylation biology, I previously demonstrated that acetylation of the tau protein promotes tangle formation in Alzheimer?s disease and related tauopathies (Nat Commun.2011~2:252).I have now?demonstrated?that?TDP?43?is?subject?to?acetylation,?thus?highlighting?a?new? TDP?43? modification? that? is? potentially? linked? to? ALS? and? related? proteinopathies.? ? The? central? hypothesis? of? this? proposal? is? to? determine? whether? acetylation? of? TDP?43? promotes? aggregation? and? neurodegeneration.? To? accomplish? this? goal,? I? will? acquire? expertise? in? neuropathology? from? the? mentoring? laboratory? and? analyze? TDP?43? acetylation? in? ALS? and? FTLD?TDP? post?mortem? brain? and? spinal? cord? as? well? as? TDP?43? transgenic? mice? characterized? by? TDP?43? pathology? and? neurodegeneration.? To? directly? determine? whether? acetylated? TDP?43? promotes? disease,? primary? neuronal?cultures?and?transgenic?mice?expressing?acetylated?TDP?43?will?be?evaluated?for hallmarks,? toxicity,? and? neurodegeneration? that? recapitulate? human? TDP?43? proteinopathies.? Having? established?the?disease?relevance?of?TDP?43?acetylation,?the?independent?phase?will?utiliz cell?based?approaches?to?investigate?the?biological?significance?of?acetylation?in?causing?ir 43?binding?to?target?genes?and?RNAs,?leading?to?a?TDP?43?loss?of?function.??Finally,?as investigator,?I?will?utilize?K99?phase?training?in?neurodegenerative?disease?to?generate?a?r of? hyper?acetylated? TDP?43? and? determine? the? ALS? phenotype? in? both? brain? and? skeletal? muscle.?? These? innovative? studies? will? highlight? TDP?43? acetylation? as? a? critical? modification? linked? to? the? progression?of?ALS?and?related?TDP?43?proteinopathies.?

Lay Summary
Project narrative Amyotrophic Lateral Sclerosis (ALS) and frontotemporal lobar degeneration (FTLD-TDP) represent two major TDP43 proteinopathies with no effective treatment strategies. The proposed studies will provide insights into the underlying mechanism of TDP 43 aggregation and highlight acetylated TDP 43 as a therapeutic target and potential biomarker for patients with ALS and related TDP43 proteinopathies.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias, Motor neurone diseases

Years:
2016

Database Categories:
N/A

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