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-2/

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Contact information of lead PI
Country

USA

Title of project or programme

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

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 806,967.89

Start date of award

15/06/2014

Total duration of award in years

1

The project/programme is most relevant to:

Motor neurone diseases

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? 3?5? year? survival? rate? and? no? disease?modifying? therapies.? TAR? DNA?binding? protein? of? 43kD? (TDP?43)? 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 with? TDP?43? pathology,? or? FTLD?TDP),? placing? ALS? and? FTLD?TDP? within? a? spectrum? of? diseases? known?as?TDP?43?proteinopathies.??Although?TDP?43?pathology?has?been?implicated?in?c and? progression,? little? is? known? about? how? TDP?43? becomes? aggregated? leading? to? progressive? neurodegeneration.??My?long?term?goal?is?to?uncover?the?pathogenic?mechanisms?that?pro aggregation,?which?will?provide?insights?for?future?therapies?against?these?debilitating?disea Post?translational? modifications? have? been? implicated? in? the? progression? of? neurodegenerative? diseases.??Using?my?background?in?acetylation?biology,?I?previously?demonstrated?that?ace 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?highli 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

8.??Project?narrative?? ? Amyotrophic?Lateral?Sclerosis?(ALS)?and?frontotemporal?lobar?degeneration?(FTLD?TDP)?re major?TDP?43?proteinopathies?with?no?effective?treatment?strategies.??The?proposed?studie insights?into?the?underlying?mechanism?of?TDP?43?aggregation?and?highlight?acetylated?TD therapeutic?target?and?potential?biomarker?for?patients?with?ALS?and?related?TDP?43?prote ?

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A