Developing neuroprotective strategies for proteinopathy

https://www.neurodegenerationresearch.eu/survey/developing-neuroprotective-strategies-for-proteinopathy/

Principal Investigators

KRAEMER, BRIAN C

Institution

SEATTLE INST FOR BIOMEDICAL/CLINICAL RES

Contact information of lead PI
Country

USA

Title of project or programme

Developing neuroprotective strategies for proteinopathy

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,354,646.79

Start date of award

01/12/2008

Total duration of award in years

3

The project/programme is most relevant to:

Motor neurone diseases

Keywords

DNA-Binding Proteins, protein TDP-43, Amyotrophic Lateral Sclerosis, ubiquilin, neurotoxicity

Research Abstract

DESCRIPTION (provided by applicant): Developing neuroprotective strategies for proteinopathy. The lesions seen in the degenerating neurons of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with ubiquitin positive inclusions (FTLD-U) consist

primarily of abnormal TDP-43 protein. Pathological TDP-43 containing deposits associated with motor neuron neurodegeneration are the hallmark pathology in over 90% of ALS cases, including both familial and sporadic types. How aggregated, ubiquitinated and phosphorylated TDP-43 protein causes neuronal dysfunction and neurodegeneration remains incompletely understood. This work focuses on extending previous studies to complete the molecular dissection of the mechanisms causing neurodegeneration in ALS and FTLD. In the previous funding period we characterized a C. elegans model of ALS mutation driven TDP-43 proteinopathy and investigated the molecular, cellular, and genomic basis of TDP-43 neurotoxicity. We identified phosphorylation of TDP-43 at serines 409/410 as a critical molecular species driving neurotoxicity, and identified kinases modulating neurodegeneration by controlling the accumulation of phosphorylated TDP-43. The specific aims of this competitive renewal are: 1) Determine the relative toxicity of phosphorylated wild type TDP-43 and the role of kinase activation in the genesis of phosphorylated TDP-43; 2) Identify the cellular machinery responsible for detoxifying phosphorylated TDP-43 3) Dissect the mechanisms by which Ubiquilin mediates TDP-43 neuropathology and neurodegeneration. The development of neuroprotective strategies for TDP-43 related neuropathology in ALS and FTLD is the long term objective of this work. By completing the proposed experiments we will construct additional models of sporadic ALS/FTLD, address the critical question of whether or not pS409/410 TDP-43 is a neurotoxic species in mammals, dissect the molecular mechanism mediating TDP-43 toxicity and capitalize on this information to develop new translationally relevant neuroprotective strategies for targeting TDP-43 neurotoxicity.

Lay Summary
PUBLIC HEALTH RELEVANCE: Pathological TDP-43 in either cortical or motor neurons causes neurodegenerative changes in a group of disorders known as TDP-43 proteinopathies which include frontotemporal lobar degeneration and amyotrophic lateral sclerosis. The progressive dementia and/or motor dysfunction caused by TDP-43 proteinopathy disorders have no effective treatment, cause severe disability, and lead to premature death. By identifying new neuroprotective strategies targeting phosphorylatedTDP-43 we hope to advance the development of therapeutic options for both FTLD and ALS.

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