Mechanisms of Neurodegeneration in ALS

https://neurodegenerationresearch.eu/survey/mechanisms-of-neurodegeneration-in-als/

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Country

USA

Title of project or programme

Mechanisms of Neurodegeneration in ALS

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,501,063.30

Start date of award

01/05/2013

Total duration of award in years

1

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Amyotrophic Lateral Sclerosis, Astrocytes, protein TDP-43, Nerve Degeneration, LCN2 gene

Research Abstract

DESCRIPTION (provided by applicant): Amyotrophic lateral sclerosis (ALS) results from the progressive degeneration of motor neurons. Astrocytes are important for neuronal function and survival, but exactly how astrocytes contribute to ALS pathogenesis is not known. Compared to neurons, astrocytes can be replaced much more easily and thus are the focus of regenerative medicine. Familial ALS is caused by pathogenic mutation in individual genes, including TDP-43.

A critical need in ALS research is determining how astrocytes contribute to the initiation and progression of motor neuron degeneration in the presence and absence of the disease gene in astrocytes. Using a tetracycline- inducible gene expression system, we have created transgenic rats that restrictedly and reversibly express mutant TDP-43 in astrocytes. By microarray assays, we have determined the expression profiles of astrocytic genes. Many secretory genes are induced in astrocytes expressing mutant TDP-43. Functional analyses of astrocytic genes suggest a loss of neuroprotective functions and a gain of neurotoxic properties in astrocytes expressing mutant TDP-43. Here we will further determine how mutant TDP-43 in astrocytes causes non-cell- autonomous motor neuron death in transgenic rats. In response to neurodegeneration, astrocytes become reactive and may play important roles in disease pathogenesis. Increasing evidence strongly suggests that reactive astrocytes gain neurotoxic properties, but how reactive astrocytes execute neurotoxicity remains to be determined. Using various approaches, we have identified an inducible gene that is secreted by reactivate astrocytes. We will further define the route by which reactive astrocytes use to promote neurodegeneration. This proposal will determine how astrocytes contribute to the initiation and progression of motor neuron death in the presence and absence of mutant TDP-43 in astrocytes, advancing our understanding of ALS disease mechanisms.

Lay Summary
PUBLIC HEALTH RELEVANCE: Using various approaches and complementary model systems, this proposal will dissect disease mechanisms underlying neurodegeneration in amyotrophic lateral sclerosis and thus will guide the development of therapies for this devastating disease.

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:
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