Neurofilaments, SOD1 and Motor Neuron Diseases

https://neurodegenerationresearch.eu/survey/neurofilaments-sod1-and-motor-neuron-diseases/

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Country

USA

Title of project or programme

Neurofilaments, SOD1 and Motor Neuron Diseases

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,239,072.48

Start date of award

01/04/1989

Total duration of award in years

1

The project/programme is most relevant to:

Motor neurone diseases

Keywords

neurofilament, Motor Neuron Disease, Amyotrophic Lateral Sclerosis, Motor Neurons, MIF gene

Research Abstract

DESCRIPTION (provided by applicant): A proportion of dominantly inherited ALS arises from mutation in superoxide dismutase (SOD1). Accumulation of misfolded SOD1 is widely recognized as a component of this toxicity, especially its aggregation onto mitochondria within

spinal cord. How mitochondrial composition is affected by mutant SOD1 will be determined using quantitative SILAM mass spectrometry. The mechanism(s) through which ALS-linked mutations aggregate and damage mitochondria only in affected tissues will be also be determined, focusing on our discovery of a chaperone that can block misfolded SOD1 accumulation in non-neuronal cells. Combining 1) Barres' discovery of a role for complement in synaptic pruning and 2) our discovery that components of the complement cascade are induced in motor neurons early in SOD1 mutant-mediated disease, gene disruption will now be used to test the role in disease pathogenesis of complement induction within motor neurons. We previously demonstrated that toxicity from SOD1 mutants is non-cell autonomous, with damage within motor neurons driving disease onset and damage within neighboring glial cells (both astrocytes and microglia) driving rapid disease progression. The contribution(s) of mutant SOD1 toxicity within additional cell types, especially oligodendrocytes and their precursors will be tested by deletion of the mutant encoding transgene using cell type specific expression of Cre recombinase. Mechanistically, how mutant SOD1 damages motor neurons, astrocytes and oligodendrocytes will be identified by high throughput sequencing of polysomal mRNAs recovered by ribosomal affinity tagging. This question is of especially high interest for astrocytes, which are known to generate one or more toxicities from their synthesis of ALS causing mutants in SOD1.

Lay Summary

Beginning with the discoveries of three genetic causes of the fatal motor neuron disease Amyotrophic Lateral Sclerosis (ALS), this effort seeks to uncover how mutation in these genes triggers the premature death of motor neurons that is the salient feature of this paralytic disease. Key questions to be tackled (whose solution may be central to devising successful therapies for ALS) will be determining the intracellular cascade of damaging events that the mutant proteins provoke and identifying which cell types are damaged by the disease causing mutants.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

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