

Modeling the progression of SOD1-linked motor neuron disease

<https://www.neurodegenerationresearch.eu/survey/modeling-the-progression-of-sod1-linked-motor-neuron-disease/>

Principal Investigators

BORCHELT, DAVID R

Institution

UNIVERSITY OF FLORIDA

Contact information of lead PI

Country

USA

Title of project or programme

Modeling the progression of SOD1-linked motor neuron disease

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,505,160.55

Start date of award

01/07/2015

Total duration of award in years

4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

superoxide dismutase 1, Motor Neuron Disease, Paralyzed, Prions, Amyotrophic Lateral Sclerosis

Research Abstract

? DESCRIPTION (provided by applicant): Cu-Zn superoxide dismutase 1 (SOD1)-linked familial amyotrophic lateral sclerosis (fALS) is an extremely heterogeneous disease phenotypically with

diverse clinical symptoms that can originate in upper or lower motor neurons and with a wide range of disease durations, from as short as a year to as long as 20 years. The duration of disease is largely a function of the speed with which symptoms spread along the neuraxis until motor neurons involved in respiration become affected. The question of how the disease seems to spread is one of the major unanswered questions in the study of ALS. Over the past few years, there has been increasing evidence that one mechanism by which the disease spreads may involve a prion-like propagation of a toxic misfolded protein from cell to cell along anatomically connected pathways of the CNS. Proteins that can transmit toxic conformations between cells often can also experimentally transmit disease between individual organisms. To survey the ease with which motor neuron disease (MND) can be transmitted, we injected spinal cord homogenates prepared from paralyzed mice expressing mutant superoxide dismutase 1 (SOD1-G93A and G37R) into the spinal cords of genetically vulnerable SOD1 transgenic mice. From the various models we tested, one emerged as showing high vulnerability. Tissue homogenates from paralyzed G93A mice induced MND in 6 of 10 mice expressing low levels of G85R-SOD1 fused to yellow fluorescent protein (G85R-YFP mice) by 3-11 months, and produced widespread spinal inclusion pathology. Importantly, second passage of homogenates from G93A;G85R-YFP mice back into newborn G85R-YFP mice, induced disease in 4 of 4 mice by 3 months of age. Homogenates from paralyzed mice expressing the G37R variant were among those that transmitted poorly, regardless of the strain of recipient transgenic animal injected, a finding suggestive of strain-like properties that manifest as differing abilities to transmit MND. Although these preliminary findings are very exciting, we recognize that our studies to date are underpowered and we cannot fully assess the ease with which SOD1-linked motor neuron disease (MND) can be transmitted between animals without a much larger effort. Aims 1 and 2 propose such an effort to better understand genotype/phenotype interactions in transmitting MND in these models. We also have very exciting evidence that we might be able to create a model in which we could initiate disease focally, by injecting the “infectious” tissue homogenates from paralyzed mice in to the sciatic nerves of vulnerable transgenic models. However, again, our preliminary data is limited and much larger effort is required. Aim 3 proposes such an effort. Collectively, our studies are designed to better establish the biological relevance of SOD1-MND transmissibility and to build model systems that would enable investigations into the mechanisms of disease progression.

Lay Summary

PUBLIC HEALTH RELEVANCE: The symptoms of amyotrophic lateral sclerosis (ALS) seem to spread along neuroanatomical pathways to engulf the motor nervous system, and the rate at which symptoms spread dictates how long patients live. In preliminary studies, we have provocative evidence that spinal cords of mice that model ALS caused by mutations in superoxide dismutase 1 (SOD1) contain entities that can mediate “transmission” of motor neuron disease to genetically vulnerable mice. Our planned studies will further develop these models and define the general transmissibility of SOD1-linked motor neuron 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:

N/A