Seeded transmission of SOD1 misfolding

https://neurodegenerationresearch.eu/survey/seeded-transmission-of-sod1-misfolding/

Principal Investigators

BORCHELT, DAVID R

Institution

UNIVERSITY OF FLORIDA

Contact information of lead PI
Country

USA

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Seeded transmission of SOD1 misfolding

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1

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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. To investigate this, we initiated studies and obtained tantalizing evidence that we can transmit ALS and that different ALS mutants may have “”strain-like”” attributes that modulate transmission. We have now been able to induce paralytic disease with aggregate SOD1 pathology in a strain of transgenic mice that express mutant SOD1 (G85R) fused to YFP. This strain of mice expresses at levels too low to induce disease on their own. Intraspinal injection of homogenates from a paralyzed G93A SOD1-overexpressing mouse transmits motor neuron disease to G85R-YFP mice in 6-11 months, and serial passage of spinal cord homogenates of these animals to naïve G85R-YFP mice produces disease in less than 3 months. This appearance of adaptation is typical of prion disease. In contrast, administration of homogenate from paralyzed G37R SOD1 mice failed to induce disease in the same recipient mice. The question this grant seeks to resolve is whether different SOD1 mutations produce conformations that produce strain-like properties that manifest as differing abilities to transmit motor neuron disease and if these abilities relate to rates of disese progression in patients. To establish whether mutations associated with slowly progressing ALS represent poorly transmissible strains of mutant SOD1, we will test 5 mutants that are found in slowly progressing SOD1-linked fALS and 5 found in rapidly progressing disease and compare these to WT SOD1 as well as negative controls. We will test both soluble and insoluble fractions of cell culture homogenates from cells transiently transfected with mutant SOD1 and recombinant hSOD1 fibrils created in a cell-free system as our inoculum, and test their potential to cause disease by direct spinal injection in G85R-YFP mice at postnatal day P0. Overall, our proposed studies could have an enormous impact in the field as they could lead to the development of an experimentally facile model of transmitted ALS and facilitate exploration of the causes for the heterogeneity of clinical symptoms observed in SOD1-linked fALS patients.

Further information available at:

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