Molecular phenotyping of cortical cell types in multiple rodent models of ALS

https://neurodegenerationresearch.eu/survey/molecular-phenotyping-of-cortical-cell-types-in-multiple-rodent-models-of-als/

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Country

USA

Title of project or programme

Molecular phenotyping of cortical cell types in multiple rodent models of ALS

Source of funding information

NIH (NINDS)

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€ 1,700,830.28

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01/05/2016

Total duration of award in years

5

The project/programme is most relevant to:

Motor neurone diseases

Keywords

molecular phenotype, Amyotrophic Lateral Sclerosis, Rodent Model, Motor Neurons, cell type

Research Abstract

? DESCRIPTION (provided by applicant): Over 30,000 Americans currently suffer from amyotrophic lateral sclerosis (ALS) which is characterized by progressive paralysis due to the

degeneration of nerve cells in the brain and spinal cord that control muscles. Almost all cases of ALS are eventually fatal and the rapid progression of the disease makes it particularly terrible, with over 80% of patients dying within five years of diagnosis. No cure exists for ALS and the only available treatment slows disease progression by merely a few months. Therefore a great need exists for more effective and specific therapies that can stop or even reverse neurodegeneration. Innovation for such therapies will only arise from a better understanding of the molecular mechanisms underlying the pathological process. The proposed study aims to identify molecules and pathways dysregulated during disease progression in specific cell populations in the cerebral cortex, including the vulnerable “”upper”” motor neurons (UMNs). Such an analysis has never been done before due to the complexity of cortical architecture hampering the ability to distinguish between cell populations. Genetic studies have linked a number of genes to ALS pathology, including SOD1, TDP43, and FUS, yet all of these genes are widely expressed in many cell types throughout the body while ALS afflicts only certain cells in the CNS. This project will utilize the novel translating ribosome affinity purification (TRAP) methodology to overcome these limitations by allowing for the examination of protein translation from genetically defined cell types. Engineered mice harboring the TRAP transgene (bacTRAP mice) in four cortical cell types (two populations of vulnerable UMNs, a non-vulnerable neuronal population, and astrocytes) will be crossed to three mouse models of ALS that utilize disease-linked mutations in the SOD1 (G93A), TDP43 (M337V), and FUS (P525L) genes. These models recapitulate the neurodegeneration seen in human patients and will enable a comprehensive assessment of cell-type specific molecular changes during ALS pathology. Changes in gene expression during disease progression will be determined by analyzing TRAP translational profiles at three time points (early, pre-symptomatic, and late) within each model. While this is a pre-clinical basic research project, efforts will be focused on identifying candidate genes that wil have the strongest and most immediate clinical impact. Particular emphasis will be placed on changes that occur at early and pre-symptomatic stages since earlier intervention will likely have an increased rate of success. These studies aim to improve upon the success rate of therapies arising from animal models by probing genes altered specifically in vulnerable cells across multiple models. Results from the proposed study will provide the field with a valuable resource of novel genes and signaling pathways to serve as candidate targets for more specific and innovative therapeutics to treat ALS.

Lay Summary

PUBLIC HEALTH RELEVANCE: Over 30,000 Americans currently suffer from amyotrophic lateral sclerosis (ALS) which is a devastating disease characterized by progressive paralysis due to the degeneration of nerve cells within the brain and spinal cord that control muscles, and for which there is no cure. The proposed research will utilize cutting edge molecular and genetic techniques to capture a “”snapshot”” of genes being expressed at different time points in the vulnerable cell populations in the brain during disease progression in three animal models of ALS. The results obtained from these experiments will allow us to better understand the molecular changes that occur in vulnerable cells as they get sick and to identify candidate genes that may serve as novel therapeutic targets for early intervention.

Further information available at:

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Investments > €500k

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United States of America

Diseases:
Motor neurone diseases

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