Role of Oligodendroglia in the Pathogenesis of ALS

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Country

USA

Title of project or programme

Role of Oligodendroglia in the Pathogenesis of ALS

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,560,110.09

Start date of award

01/09/2016

Total duration of award in years

5

The project/programme is most relevant to:

Motor neurone diseases

Keywords
Research Abstract

Project Summary Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive degeneration of motor neurons and the eventual failure of upper and lower motor systems. Numerous genetic mutations have been linked to ALS, but the disease mechanism remains elusive. A large body of evidence from past studies suggests that ALS-linked, mutant- expressing glial cells form a neurotoxic environment, and thereby play a

critical role in motor neuron degeneration and disease progression. Whereas astrocytes and microglia have been the focus of extensive investigation as potential sources of the neurotoxicity, other glial cells have not been given adequate consideration until recently. Oligodendrocytes, the myelinating CNS glia, provide metabolic and nutritional support to neurons, and they undergo massive degeneration near motor neuron cell bodies during the course of this disease. This oligodendroglial pathology must be significant, because selective inactivation of the mutant expression of oligodendroglia reduces disease symptoms and progression markedly more than when the same manipulation is applied to other neural cell populations. This proposal will focus on the cellular mechanisms of oligodendroglial dysfunction in vivo, and their detrimental impact on motor neuron survival in mouse models of ALS. First, we will identify the relative timing and causal relationship between oligodendrocyte degeneration and motor neuron death by controlling the natural oligodendrocyte regeneration. Second, using newly developed, cell specific Sod1 (G93A) expressing mice, we will define cell-intrinsic, molecular abnormalities of oligodendrocytes and the course of disease progression after oligodendroglia-specific Sod1 (G93A) expression. Third, we will determine whether promoted oligodendrocyte regeneration and remyelination can serve as a novel therapeutic strategy for ALS. Through these experiments, we will investigate an important supporting glial population that previous ALS studies have long ignored. The outcomes will determine whether the CNS myelinating glia are a key player or a modifier in ALS, illustrate oligodendrocyte-specific molecular pathways contributing to ALS pathophysiology, and evaluate oligodendrocyte-directed regenerative approaches as possible ALS treatments. Through this project we will also add a novel mouse genetic tool for cell-type specific, in vivo studies of the disease mechanisms of ALS.

Lay Summary
Project Narrative Although long-neglected as a critical contributor to ALS, oligodendrocytes now appear to play important roles in the proper functioning and survival of motor neurons. Understanding how these cells become dysfunctional in ALS, and how their function can be recovered, will provide clues toward better treatment of this disease. This study has the potential to develop a new therapeutic strategy for ALS by defining cellular mechanism of these glial abnormalities, and by promoting glial regeneration for a better disease outcome.

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