Novel mechanisms of actin dynamics underlying cell motility, axon growth, and ALS

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axon growth, G Actin, Amyotrophic Lateral Sclerosis, Actins, cell motility

Research Abstract

Project Summary/Abstract Amyotrophic lateral sclerosis (ALS) is a fatal disease involving motor neuron degeneration. Death occurs 3-5 years after diagnosis, there is no cure, and what limited

treatments do exist only extend survival by a matter of months. The mechanism of ALS pathogenesis has remained elusive to researchers; scientists are still unsure exactly what causes the motor neurons to become toxic and die. In this proposal, we will investigate the mechanistic role that defects in the regulation of actin dynamics plays in ALS. This course of investigation was spurred by the discovery that mutations in Profilin1 (PFN1), a key regulator of cytoskeletal dynamics, that inhibit its ability to bind actin are responsible for about 1-2% of familial Amyotrophic lateral sclerosis (fALS). Motor neurons overexpressing these mutant PFN1 constructs displayed inhibited axon growth and had abnormal actin cytoskeletons. The identification of PFN1 mutations as causative agents in fALS presents an exciting new hypothesis that actin cytoskeletal dynamics play a fundamental role in maintaining the health of motor neurons and that impairment of actin dynamics could, over time, lead to neurodegeneration. Because Pfn1 is a G-actin binding protein, the processes that spatially localize G-actin to regulate filament polymerization and the G-/F-actin (G/F) ratio are of particular interest. We hypothesize that defects in actin cytoskeletal dynamics downstream of PFN1, such as G-actin localization, play a crucial role in ALS pathogenesis. To determine if impaired actin dynamics are a hallmark of ALS and to investigate the mechanism of how Pfn1 mutations induce fALS, we propose the following Specific Aims: (1) Determine the role that defects in the dynamic regulation of G-actin plays in ALS; (2) Determine the specific mechanism of how ALS-linked PFN1 mutants alter actin dynamics; and (3) Determine the specific cellular mechanism of dynamic G-actin localization and its function in regulating motor neuron growth and maintenance. We will investigate actin dynamics using high-resolution quantitative imaging in motor neurons and nerve- muscle explants from mouse models of ALS. We will also examine actin in functional motor neurons derived from induced pluripotent stem cells from human ALS patients. Recently, we discovered a novel pathway where G-actin was spatiotemporally localized to regulate cell motility and axon guidance. Thus, we have designed a number of unique assays to visualize G-actin localization, calculate the G/F actin ratio, and quantify actin mobility. The questions addressed in this proposal will yield a deeper understanding of the role that actin dynamics play in motor neuron development and maintenance of the presynaptic terminal of the neuromuscular junction, as well as identify ways that defects in actin regulation can cause ALS.

Lay Summary

Project Narrative Amyotrophic lateral sclerosis (ALS) is a fatal disease involving motor neuron death. Understanding the fundamental biology that underlies motor neuron degeneration in ALS will allow for the development of new diagnostic tools and treatments. In this proposal we will determine if defects in the dynamic regulation of the actin cytoskeleton can cause ALS.

Further information available at:

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Investments > €500k

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United States of America

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