Mechanistic analysis of axonal transport defects in neurodegenerative disease

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Country

USA

Title of project or programme

Mechanistic analysis of axonal transport defects in neurodegenerative disease

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NIH (NINDS)

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01/12/2007

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2

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Dynein ATPase, Axonal Transport, Autophagosome, Amyotrophic Lateral Sclerosis, Charcot-Marie-Tooth Disease

Research Abstract
DESCRIPTION (provided by applicant): Mutations in cytoplasmic dynein or its activator dynactin

are causative for neuronal diseases including heritable forms of motor neuron degeneration and Charcot-Marie-Tooth disease. More broadly, we know that defects in dynein-driven functions such as retrograde axonal transport are involved in the pathogenic mechanisms of neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Huntington's, and Alzheimer's. However, the specific mechanisms involved remain unclear. Dynein is a pleiotropic cellular motor with multiple distinct roles in the neuron. Here we will focus on the hypothesis tha defects in the dynein-driven retrograde transport of degradative organelles including lysosomes and autophagosomes are major contributors to the axonal degeneration that characterize these diseases. The goal of this proposal is to understand the specific mechanisms linking defects in dynein function to neurodegeneration, focusing on the following three aims: (1) How is retrograde axonal transport altered during neurodegeneration? We hypothesize that pathological alterations in the JNK and Cdk5 pathways lead to the dysregulation of opposing microtubule motors during axonal transport. We will test this hypothesis using quantitative live cell imaging of vesicular transport in primary neurons from multiple models of ALS. Then, we will mechanistically dissect how kinase mis-regulation affects motor function using in vitro reconstitution approaches with single molecule resolution. These studies will test the model that a disruption in the coordination of oppositely-oriented motors is the primary defect leading to altered transport along the axon. (2) What are the pathways for autophagosome biogenesis and cargo-loading in the neuron? We hypothesize that autophagy in the neuron follows a stereotypical and spatially regulated pathway that is required to maintain cellular homeostasis. We will examine autophagosome biogenesis and cargo-loading in primary sensory and motor neurons using quantitative live cell imaging, focusing on the roles of dynein and optineurin. Then we will determine how this pathway responds to cellula, to address the hypothesis that this pathway has a limited ability to up-regulate in response to cellular stress. (3) How do defects in dynein-driven autophagy lead to degeneration of the axon? We hypothesize that the active, dynein-driven transport of autophagosomes is tightly linked to function, and that defects in transport will lead to defective degradation of aging organelles and aggregated proteins. We will use live imaging and biochemical and cellular assays to determine how defects in autophagosome transport along the axon contribute to neurodegeneration and how distinct dynein mutations differentially perturb cellular functions, leading to disparate clinical manifestations. Mutations in cytoplasmic dynein are sufficient to cause human neurodegenerative diseases including spinal muscular atrophy (SMA-LED) and Charcot-Marie-Tooth disease (Type 2O), but the mechanisms involved remain to be determined. Progress on these aims should offer new opportunities for therapeutic approaches or clinical intervention.

Lay Summary
PUBLIC HEALTH RELEVANCE: The active movement of proteins, vesicles, and organelles along the extended axons of neurons is called axonal transport. This transport is essential to maintain healthy motor and sensory neurons, which have axons that can extend for a meter. Defects in axonal transport cause neurodegeneration, and occur in diseases such as Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease). Here, we propose to investigate the mechanisms by which defects in axonal transport lead to degenerative disease.

Further information available at:

Types:
Investments > €500k

Member States:

United States of America

Diseases:
Motor neurone diseases

Years:
2016

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