Mechanisms and functions of subcellular motility

https://neurodegenerationresearch.eu/survey/mechanisms-and-functions-of-subcellular-motility/

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Country

USA

Title of project or programme

Mechanisms and functions of subcellular motility

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,207,711.93

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01/08/1991

Total duration of award in years

1

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Kinesin, Motor Neuron Disease, axonal degeneration, cell motility, Dense Core Vesicle

Research Abstract

DESCRIPTION (provided by applicant): The objective of this project is to elucidate at the molecular level how force-generating microtubule motor proteins transport vesicles and mitochondria in neurons and how specific defects in those transport mechanisms cause the

length-dependent axon degeneration that underlies human motor neuron diseases. Tremendous progress has been made by in vitro studies of how microtubule motor proteins generate force, how they walk progressively along microtubules, and how they can be autoregulated by switching between two states of folding. In contrast, relatively little is known about how such in vitro capabilities are used to accomplish the many intricately controlled transport processes that are essential for the growth and specialized functions of living cells. We have developed a powerful in vivo experimental model system that will allow rigorous investigation at the molecular level of how motor proteins function specifically in the transport o single organelles in neurons of living animals. Our system enables us to study the influences of any desired change in a motor protein's sequence on the detailed transport behavior of mitochondria and other types of organelles in Drosophila. It was with Drosophila that we made the original discovery that defects in certain microtubule motors cause the length-dependent axon degeneration and progressive distal paralysis that in humans underlie motor neuron diseases. We have just completed development of a new approach that allows homologous gene replacement at the kinesin heavy chain (Khc) microtubule motor locus in Drosophila. Using that new approach, along with standard non-homologous gene insertion, time-lapse microscopy of fluorescently tagged organelles, genetics, and biochemistry, we will build on our past work to determine in vivo: 1) how the C-terminal tail of Khc contacts its N-terminal head for autoregulatory control of movement, and how that control contributes to axonal organelle transport; 2) how the functions of three different types of microtubule motors, including ones that transport cargoes in opposite directions, are highly interdependent (i.e., loss of any one type of motor inhibits the function of the others); and 3) how defective transport of mitochondria may specifically trigger the sort of length-dependent axon degeneration that causes motor neuron diseases. It is anticipated that the results of these studies will generate substantial advances fo understanding fundamental mechanisms of directed organelle transport, and will lead to the identification of targets within those mechanisms for the development of therapeutic treatment of neurodegenerative disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: This project will investigate molecular mechanisms of long-distance transport of vesicles and mitochondria in the axons of neurons and how defects in specific transport mechanisms cause human motor neuron disease. The experimental system used, Drosophila, is powerful and economical, and will allow studies of transport mechanisms at the molecular level in unperturbed axons in living animals. The expected results will advance the understanding of in vivo transport mechanisms and of the pathology of neurodegeneration.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:

N/A

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