The COPA vesicle protein and pathogenesis of spinal muscular atrophy

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Country

USA

Title of project or programme

The COPA vesicle protein and pathogenesis of spinal muscular atrophy

Source of funding information

NIH (NINDS)

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15/08/2013

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2

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)

Keywords

Coat Protein Complex I, Spinal Muscular Atrophy, Vesicle, Neurites, Motor Neurons

Research Abstract

DESCRIPTION (provided by applicant): We discovered that the SMN protein binds to alpha-COP, the largest constituent of the heptameric COPI vesicle. The hypothesis to be investigated

in this project is that pathogenesis of SMA results from inability of this cargo transport complex to sustain the functional integrity of motor neurons. We explore the role of the SMN protein's interaction with alpha-COP in neurite development and maintenance. Importantly, we observed that over-expression of alpha-COP restores neurite development in SMN depleted NSC34 cells. New data reveal that low levels of SMN alter the functionality of endoplasmic reticulum-Golgi trafficking, suggesting a previously unrecognized effect on this protein processing pathway. We recently reported that the alpha-COP complex incorporates ~800 specific RNAs from the total transcriptome of differentiated NSC-34 cells. A high fraction of these mRNAs contain in their 3? untranslated regions a G-quadruplex motif, which has been assigned a role in neurite localization. Our goal is to identify the mRNAs that depend on SMN for association with the COPI complex, enabling studies of the roles of alpha-COP and SMN in the trafficking of these RNAs into the axon and characterization of their requirement for neuronal development. To examine the biological physiologic significance of the interaction of SMN with alpha-COP and subsequent mechanistic studies, we generated novel transgenic mice with reduced levels of alpha-COP protein, with the prediction this will result in motor unit dysfunction. We also have created a transgenic strain that over-expresses tagged human alpha- COP. These mice will be crossed with SMA model mice with low levels of SMN to test the hypothesis that increased levels of alpha-COP and COPI vesicles promote SMN dependent cargo delivery to the axon and restore motor skills and increase lifespan. These experimental mouse models will be important resources to study the mechanism of neurodegeneration and the transport of proteins and specific RNAs to and within the axon. Pharmacologic induction of the COPI pathway may represent a novel means to treat SMA.

Lay Summary
PUBLIC HEALTH RELEVANCE: The SMN protein that is deficient in spinal muscular atrophy (SMA) binds to and moves with a known intracellular transport factor. We will undertake detailed investigations of the ability of this pathway and its relationship to SMN to deliver vital cargoes throughout the nerve cell, which will provide novel insights into the what goes wrong in SMA. In this project, we will generate novel mouse models that will have broad implications for SMA and other diseases of the motor neuron.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Spinal muscular atrophy (SMA)

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