RNA Processing Defects in SMA and Their Contribution to the Disease Phenotype

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Principal Investigators

ROSSOLL, WILFRIED

Institution

EMORY UNIVERSITY

Contact information of lead PI
Country

USA

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RNA Processing Defects in SMA and Their Contribution to the Disease Phenotype

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NIH (NINDS)

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4

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)

Keywords

Spinal Muscular Atrophy, RNA Processing, Motor Neurons, disease phenotype, SMN protein

Research Abstract
? DESCRIPTION (provided by applicant): Spinal muscular atrophy (SMA) is a devastating neurodegenerative disease that represents the most common genetic cause of infant death.

SMA is caused by reduced levels of functional survival of motor neuron (SMN) protein, leading to cell autonomous defects at the neuromuscular junctions, axon degeneration, and loss of motor neurons in the spinal cord. The ubiquitously expressed SMN protein has a well characterized essential function in the assembly of spliceosomal small nuclear ribonucleoproteins (snRNPs) in all tissues, but it is still unclear to what extent pre-mRNA splicing defects contribute to SMA. It is a central question in the field why spinal motor neurons are more severely affected by low SMN protein levels than other cell types. We and others have shown that SMN is also present in highly mobile multi-protein complexes that are actively transported along microtubules and actin filaments in axons of cultured neurons. More recently, we have discovered that axons of cultured SMN-deficient motor neurons have impaired localization of specific mRNA binding proteins (mRBPs) and mRNAs in axons that are known to play roles in axon growth. These findings have led us to hypothesize that SMN plays a critical role in the assembly and trafficking of messenger ribonucleoproteins (mRNPs) in neuronal processes that serve axonal growth and maintenance. However, how defects in these SMN-dependent processes may contribute to the SMA pathomechanism is still unknown. With the goal to reveal mRNA processing defects in SMA and their contribution to the disease phenotype, we propose two specific aims: in Aim 1, we will uncover disease-specific molecular axonal defects by a de- tailed and comprehensive analysis of differences in the axonal transcriptome and proteome. The use of novel SMA patient stem cell-derived motor neurons and compartmentalized cultures will allow us for the first time to comprehensively catalogue SMA-specific defects in mRNA processing and their consequences on axon development, and identify ways to rescue these defects. These studies will provide insight into mRNA processing defects in SMA patient stem cell-derived motor neurons and how they contribute to axonal defects in vitro. In Aim 2, we will use cell type-specific tagging of ribosomes with the RiboTag system to thoroughly characterize differences in the ribosome-associated transcriptome in spinal cord motor neurons of SMA mouse models. We will characterize axonal localization of known SMN targets, and rescue these axonal defects in SMA mice via AAV9-based viral transduction of genes that enhance axonal mRNP localization. These experiments will allow for the first time the assessment of the spectrum of mRNA processing defects in spinal motor neurons from an SMA mouse model and how they contribute to the disease phenotype in vivo. This proposal is expected to both increase our understanding of human pathology in the neuromuscular sys- tem, and to facilitate the development of therapies that are specifically targeted at mRNA processing defects in motor neurons in SMA and related neuromuscular diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: The proposed research is relevant to public health, since it is focused on a better understanding of the cellular and molecular biology of neurodegeneration in spinal muscular atrophy (SMA), the most common genetic cause of infant death. Reduced levels of the survival of motor neuron (SMN) protein in SMA cause the disruption of chaperone-mediated ribonucleoprotein (RNP) assembly, but the extent of SMA-specific mRNA processing defects and their contribution to the disease phenotype are unknown. The aim of this project is to utilize vertebrate animal models and SMA patient stem cell-derived motor neurons to determine which SMN- dependent mRNA processing defects contribute to the neurodegenerative disease phenotype, and how they may be amenable to rescue and treatment.

Further information available at:

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Investments > €500k

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United States of America

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