In vivo models of small RNP biogenesis and Spinal Muscular Atrophy

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Country

USA

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In vivo models of small RNP biogenesis and Spinal Muscular Atrophy

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01/04/2016

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4

The project/programme is most relevant to:

Spinal muscular atrophy (SMA)

Keywords

Spinal Muscular Atrophy, Ribonucleoproteins, Motor Neurons, Biogenesis, Small Nuclear Ribonucleoproteins

Research Abstract

? DESCRIPTION (provided by applicant): Small ribonucleoproteins (RNPs) are essential cellular components in all three kingdoms of life. Indeed, eukaryotic gene expression requires a

veritable constellation of small non-coding RNPs that participate in multiple aspects of organismal function. The long-term goal is to understand the molecular mechanisms that govern the biogenesis and function of small RNPs. As key elements of the spliceosome, the Sm-class small nuclear (sn)RNPs are essential for post-transcriptional gene regulation. Assembly of Sm-class RNP particles is thought to be mediated by the Survival Motor Neuron (SMN) protein complex, which loads Sm proteins onto snRNAs, forming the core RNP. Understanding this process is important for human health, as mutations in human SMN1 result in a genetic disorder called Spinal Muscular Atrophy (SMA). One in fifty unrelated individuals is a carrier for SMA, making this disease a serious health concern. Unfortunately, most people with SMA typically die in early childhood. SMA is caused by reduced levels of SMN protein, whereas complete loss of SMN expression results in prenatal lethality. Although SMN1 has been identified as the mutant gene in SMA, the downstream trigger of the disease remains a mystery. Emerging evidence suggests that SMN has additional tissue-specific functions, especially in muscles and neurons. However, a molecular understanding of how SMN carries out its various functions is missing. Hence, detailed knowledge of the roles played by the SMN complex in small RNP metabolism and neuromuscular development is essential. Therefore, the major objective of this application is to determine the consequences of mutations in SMN and other snRNP biogenesis factors to animal viability and development in vivo. To address this objective we have developed Drosophila as a model system. We generated an allelic series of flies expressing SMN missense mutations derived from human SMA patients. Using this genetic platform, we expect to identify separation-of-function mutations that uncouple the putative housekeeping and tissue-specific functions of SMN, enabling us to study them independently. We will employ genome-wide techniques together with molecular genetics and biochemistry to identify cellular pathways and protein binding partners that are disrupted by SMA-causing point mutations. Because mutations in other genes known to be involved in snRNP biogenesis may phenocopy aspects of SMN dysfunction, experiments are also proposed to identify snRNP-dependent versus snRNP-independent changes in splicing and gene expression that result from loss of SMN. The combined data will elucidate the molecular, cellular and developmental consequences of hypomorphic SMN mutations, and lead to a better understanding of Spinal Muscular Atrophy.

Lay Summary

PUBLIC HEALTH RELEVANCE: Spinal Muscular Atrophy (SMA) is a common genetic disease that strikes one in 6,000-8,000 young children, most of whom die before reaching the age of two years. The responsible gene (SMN) has been identified, but the precise role of its protein product in disease pathology is not known. To understand the underlying basis of SMA and to aid development of effective treatments, this proposal seeks to uncover fundamental information on SMN function.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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