Loss of a cohort of axonal mRNAs as a result of reduced SMN levels.

https://neurodegenerationresearch.eu/survey/loss-of-a-cohort-of-axonal-mrnas-as-a-result-of-reduced-smn-levels-2/

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Research Abstract

Project Summary/Abstract There is a fundamental gap in our understanding of why motor neurons are selectively vulnerable to loss of a protein that has critical housekeeping functions within all cells. Spinal muscular atrophy (SMA) is an autosomal disease characterized by spinal motor neuron death and skeletal muscle paralysis, and is caused by deletion or mutation(s) of the survival motor neuron 1 (SMN1) gene. SMN has been proposed to exert neuron-specific role(s) to account for the selective motor neuron death. Of particular interest is the fact that

SMN is transported into distal neuronal processes and co-localizes with mRNAs within granules, suggesting a role in axonal RNA transport. This is further supported by the prior identification of several mRNAs that show significant reduction in their axonal levels as a result of deficits in SMN protein. Our long-term goal is to determine the role for SMN in subcellular mRNA localization and/or localized translational control in motor neurons. The overall objective of this proposal is to determine the extent to which SMN deficiency results in loss of axonal mRNAs and the mechanism(s) that drive this loss of axonal localization. Our central hypothesis is that deficiency in the levels of SMN protein causes the axonal loss of specific mRNAs and subsequent reduction in axonal protein synthesis, contributing to the pathophysiology of SMA. Building on our laboratory's long-standing interest in the role that axonal translation plays in neuronal health and using the tools we have developed to study axonal RNA localization, we will test this hypothesis with three specific aims: 1) Establish that the loss of SMN protein directly reduces the axonal levels of a cohort of mRNAs; 2) Identify the components required for axonal transport of SMN-regulated mRNAs; and 3) Show that SMN-regulated axonal mRNAs are necessary for neuromuscular junction integrity. In our opinion, this proposed research is innovative because few labs are currently focused on the role of axonal mRNA transport and local translation in axonal maintenance, repair and pathophysiology. Our lab has developed innovative and novel methods to identify and modify the axonal population of mRNAs in order to understand the role that local translation plays in axonal biology. Successful completion of this work would be significant because it will answer fundamental questions about how axonal transport of mRNAs is altered in SMA and, ultimately, point to new approaches to protect motor neurons.

Further information available at:

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