RNA dysregulation in neurodegeneration

https://neurodegenerationresearch.eu/survey/rna-dysregulation-in-neurodegeneration/

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Country

USA

Title of project or programme

RNA dysregulation in neurodegeneration

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NIH (NINDS)

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01/09/2015

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

protein TDP-43, Nerve Degeneration, Amyotrophic Lateral Sclerosis, RNA, Motor Neurons

Research Abstract

? DESCRIPTION (provided by applicant): In recent years, it has become increasingly clear that RNA dysregulation is a critical contributor to the pathophysiology of amyotrophic lateral sclerosis (ALS) and related neurodegenerative diseases. Indeed, several RNA binding proteins have been identified in pathologic aggregates and have also been shown to harbor mutations causative of ALS. Among these, TDP-43, which is linked to the vast majority of ALS cases, has

been implicated in several aspects of RNA metabolism including splicing, transport, storage in stress granules (SGs) and translation. These findings suggest an intimate link between TDP-43, RNA SGs, translation and disease. Although recent studies have provided insights into the relationship between TDP-43 and RNA stress granules in ALS, our current knowledge of TDP-43's role in translation, the identity of its mRNA translation targets and their contribution to disease remain poorly understood. The long-term goal of this research is to determine the mechanistic connections between TDP-43 and translation in the nervous system, and to establish the contribution of RNA dysregulation to the pathophysiology of neurodegenerative diseases. We have recently demonstrated that TDP-43 regulates the localization and translation of futsch/MAP1B in Drosophila and defects identified in fly motor neurons are remarkably similar to those found in ALS spinal cords. Using a Drosophila model of ALS based on TDP-43 we also found that FMRP, a well- established translational regulator is neuroprotective by reducing TDP-43 aggregation and restoring the translation of specific mRNA targets. Furthermore, we have identified several new candidate mRNA translation targets including hsc70-4 mRNA, a molecular chaperone that controls synaptic vesicle (SV) trafficking as well as additional candidates implicated in synaptic function. Notably, restoring Hsc70-4 levels in motor neurons by overexpression rescues synaptic vesicle endocytosis defects caused by ALS associated mutant TDP-43. Based on these findings we hypothesize that TDP-43 acts as a translational regulator in motor neurons and that dysregulation of protein synthesis contributes to the pathophysiology of ALS. Our hypothesis will be critically tested in three specific aims. First, we will determine physical and functional interactions between TDP-43 and the translation machinery. Second, we will identify mRNA translation targets of TDP-43 in motor neurons using tagged ribosome affinity purification (TRAP), then will use ribosome footprinting to determine what stage of translation is impacted by TDP-43. Third, we will establish the synaptic defects caused by TDP- 43 and will determine whether restoring candidate targets by overexpression in motor neurons rescues TDP-43 dependent toxicity. Our findings in the Drosophila model will be validated in ALS spinal cords. This research is expected to provide novel insights into TDP-43's function in translation, to identify physiologically significant and disease relevant protein partnrs and mRNA translation targets, which in turn may pinpoint much needed molecular targets and pathways with therapeutic potential for ALS and related neurodegenerative diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: Increasing evidence for RNA dysregulation in neurodegeneration has led to a paradigm shift and new hypotheses for the pathophysiology of disease. The proposed research is relevant to public health because elucidating the role of TDP-43, an RNA binding protein involved in the vast majority of ALS cases, in mRNA translation in motor neurons will provide much needed molecular targets and therapeutic strategies that may help reduce the burden of this devastating disease.

Further information available at:

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Investments > €500k

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United States of America

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