TDP-43, RNA Metabolism, and ALS/FTD Pathology

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Country

USA

Title of project or programme

TDP-43, RNA Metabolism, and ALS/FTD Pathology

Source of funding information

NIH (NINDS)

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01/04/2009

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4

The project/programme is most relevant to:

Motor neurone diseases

Keywords

protein TDP-43, Frontotemporal Dementia, C9orf72, Ribosomal RNA, Amyotrophic Lateral Sclerosis

Research Abstract

? DESCRIPTION (provided by applicant): Dramatic advances have been made in recent years in the identification of genes that cause familial amyotrophic lateral sclerosis (ALS) and

frontotemporal dementia (FTD), two closely related neurodegenerative diseases. This includes at least three RNA binding proteins (TDP-43, FUS and MATR3) and a hexanucleotide expansion in RNA transcripts of the C9orf72 gene. These findings have focused much attention on understanding how changes in RNA metabolism might underlie these diseases. Although most cases of ALS are sporadic (no obvious familial inheritance), in almost all cases the TDP-43 protein is found in cytoplasmic inclusions in affected motor neurons, suggesting the functions of this protein are broadly relevant to ALS. We have characterized the functions of TDP-43 in a model system (C. elegans) and cell culture, and discovered that loss of this protein results in accumulation of double-stranded RNA (dsRNA) and abnormal processing of ribosomal RNA. The goal of this proposal is to determine if these changes in the metabolism of RNA play a role in ALS/FTD pathology. We will investigate the molecular mechanisms by which TDP-43 limits dsRNA, and seek to determine if loss of FUS and MATR3, or expression of the C9orf72 hexanucleotide expansion, have similar effects on RNA metabolism. The disease-associated cytoplasmic redistribution of TDP-43 will also be investigated, particularly in response to expression of the C9orf72 hexanucleotide expansion and the associated production of aggregation-prone poly-dipeptides. These studies will employ RNA interference, genetic mutations, immunocytochemistry, in situ hybridization, and deep sequencing to globally characterize RNAs (the transcriptome), using both human cell culture and C. elegans models. We will test the disease relevance of our findings by extending these studies to patient cells (fibroblasts and reprogrammed neurons) as well as pathological samples. In particular, we will test the hypothesis that the RNA changes we have identified may play a role in the neuroinflammation and astroglial dysfunction that has been implicated in ALS pathology.

Lay Summary
PUBLIC HEALTH RELEVANCE: Amyotrophic Lateral Sclerosis and Frontotemporal Dementia are fatal, currently untreatable neurodegenerative diseases. Although specific genes have been identified that can mutate to cause the familial versions of these diseases, the specific molecular and cellular defects that lead to pathology are unknown. The proposed studies will test a specific hypothesis about the cellular defects that underlie these conditions.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

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2016

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