Cellular and Molecular Mechanisms of FUS-related Amyotrophic Lateral Sclerosis

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Country

USA

Title of project or programme

Cellular and Molecular Mechanisms of FUS-related Amyotrophic Lateral Sclerosis

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,583,967.89

Start date of award

01/03/2014

Total duration of award in years

2

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Amyotrophic Lateral Sclerosis, RNA Binding, protein TDP-43, fly, Drosophila genus

Research Abstract

DESCRIPTION (provided by applicant): Abstract Amyotrophic lateral sclerosis (ALS) is a late onset neurodegenerative disorder characterized by the loss of upper and lower motor neurons.

FUS and TDP-43 are DNA/RNA binding proteins found to be mutated in both sporadic and familial forms of ALS. To investigate the pathogenesis of ALS caused by FUS/TLS mutations, we established a series of transgenic Drosophila lines that ectopically express human wild type and mutant FUS/TLS. Targeted expression of mutant, but not wild type FUS, in Drosophila eyes causes the formation of ubiquitinated aggregates and an external eye degenerative phenotype. Interestingly, ectopic expression of mutant FUS in motor neurons resulted in larval paralysis, pupal lethality, whereas wild type FUS expression had minimal effect. Mutant FUS localized to both the cytoplasm and nucleus, whereas wild type FUS localized only to the nucleus, suggesting that the cytoplasmic localization of FUS/TLS is required for toxicity. Furthermore, we found that deletion of the nuclear export signal strongly suppressed toxicity, suggesting that cytoplasmic localization is necessary for neurodegeneration. We found that expression of mutant FUS in the fly muscles leads to held-up wing phenotype, muscle degeneration and mitochondrial degeneration. We also found that mutating RNA binding residues of FUS strongly suppress mutant FUS toxicity in vivo. While doing an unbiased genetic screening, we discovered muscleblind as a novel modifier of mutant FUS toxicity. In our proposed studies, we will determine the role of mitochondrial functions in mediating FUS- related ALS and which functions of mitochondria are disrupted by the ALS causing mutations. We will systematically determine the role of RNA binding ability of FUS in causing ALS pathogenesis. We will also investigate if muscleblind regulates alternative splicing and sub- cellular distribution of FUS and contributes to the onset and progression of FUS-related ALS. Our proposed studies are expected to provide novel insights into the molecular mechanism of FUS-related ALS that would help in developing a therapeutic interventions for ALS for which currently no cure available.

Lay Summary

PUBLIC HEALTH RELEVANCE: Determining factors responsible for causing accumulation of misfolded and toxic proteins will contribute to our understanding of molecular mechanisms of Lou Gehrig’s disease and will help in developing an effective therapy since currently no treatment available. We developed a novel Drosophila model of FUS-related amyotrophic lateral sclerosis that recapitulates several key pathological features of human disease but molecular mechanism responsible of ALS is not well understood and our proposed research would increase our understanding of FUS and its interacting partners. Because there is considerable overlap between several neurodegenerative diseases at clinical and molecular level we expect that our findings will be relevant to the mission of the NIH and be broadly applicable to researchers studying molecular mechanisms of neurodegeneration.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A