Nucleocytoplasmic transport and nuclear pore disruption in ALS/FTD

https://neurodegenerationresearch.eu/survey/nucleocytoplasmic-transport-and-nuclear-pore-disruption-in-als-ftd-2/

Principal Investigators

ROTHSTEIN, JEFFREY D

Institution

JOHNS HOPKINS UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Nucleocytoplasmic transport and nuclear pore disruption in ALS/FTD

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 3,043,445.87

Start date of award

15/06/2016

Total duration of award in years

5

The project/programme is most relevant to:

Motor neurone diseases|Alzheimer's disease & other dementias

Keywords

Nuclear Pore, nucleocytoplasmic transport, Frontotemporal Dementia, Amyotrophic Lateral Sclerosis, Nuclear Pore Complex

Research Abstract

PROJECT SUMMARY A GGGGCC hexanucleotide repeat expansion (HRE) in C9ORF72 is the most common genetic cause of familial amyotrophic lateral sclerosis (ALS) and frontotemporal

dementia (FTD), though the underlying disease mechanism is poorly defined. Multiple studies, including our own, support a gain-of-function mechanism of neurotoxicity mediated by the HRE. Expanded repeats may generate toxic RNAs that sequester RNA-binding proteins. They may also be translated via Repeat-Associated Non-ATG Translation (RANT) into toxic dipeptide repeat proteins (DPRs). Both HRE RNA and DPRs are hypothesized to mediate neurotoxicity in C9-ALS/FTD. Multiple recent studies from our lab and others suggest that disruption of the nuclear pore and/or nucleocytoplasmic transport is a primary cause of neurodegeneration in yeast, fly, and induced pluripotent cell (iPS) models of C9- ALS/FTD. In addition, our recent studies, using a C9-ALS/FTD Drosophila model, human iPS neurons derived from C9-ALS patients, and human C9-ALS CNS tissues, suggest that nucleocytoplasmic transport defects may be a fundamental pathway for ALS/FTD pathogenesis amenable to therapy. This proposal will comprehensively investigate the mechanism by which the C9ORf72 HRE disrupts nucleocytoplasmic transport and nuclear pores utilizing several complementary models including C9-ALS fly and mouse models and iPS neurons and brain tissue from C9 ALS/FTD patients, and investigate whether modulation of nucleocytoplasmic transport may be a therapeutic strategy for ALS/FTD. (1) We will determine the morphological and biochemical composition of the nuclear pore complex (NPC) in motor neurons and glia, and characterize NPC pathology in C9-ALS/FTD in fly, iPS, mouse models and human brain. Little is known about CNS NPCs including differences between cell types and ultimately how the NPC constituents, nucleoporins, are dysregulated in C9-ALS/FTD models. Therefore, understanding the basic characteristics of the NPC and nucleocytoplasmic transport in the CNS and in disease models is fundamentally important to dissecting the nature of pathology. (2) We will then investigate the mechanism of nucleocytoplasmic transport disruption in C9-ALS/FTD. We hypothesize that disrupted NPC and/or nucleocytoplasmic transport function causes neurodegeneration due to nuclear loss and/or cytoplasmic accumulation of nuclear export sequence (NES) containing cargo in fly, mouse, and iPS models of C9-ALS. (3) Therefore, we will determine the consequences of nucleocytoplasmic transport disruption in C9-ALS/FTD models. (4) Finally, we will determine if restoration of nucleocytoplasmic transport rescues neurodegeneration in C9-ALS/FTD by employing a series of novel compounds that may have human utility.

Lay Summary

PROJECT NARRATIVE: Relevance to Human Health Understanding the pathophysiology and development of new therapeutics for ALS, ALS/FTD and FTD has been an enormous challenge. Recently the development of human disease induced pluripotent cell lines representing the natural disease in the most relevant cell types, motor neurons and glia, and drosophila models, representing an in vivo system, provides unprecedented tools to 1) study the underlying disease process, 2) allow for identification of disease markers of pathology and of drug actions and 3) provide critical tools for future drug discovery and drug action validation. Eventually these ALS/FTD model systems will also be useful to compare common and uncommon pathways between ALS and other neurodegenerative models.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias, Motor neurone diseases

Years:
2016

Database Categories:
N/A

Database Tags:
N/A