Mechanisms and Consequences of Heterochromatin Loss in Tauopathies

https://neurodegenerationresearch.eu/survey/mechanisms-and-consequences-of-heterochromatin-loss-in-tauopathies/

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Contact information of lead PI
Country

USA

Title of project or programme

Mechanisms and Consequences of Heterochromatin Loss in Tauopathies

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 855,743.12

Start date of award

15/12/2015

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Tauopathies, Heterochromatin, tau Proteins, Lamins, Nuclear Lamin

Research Abstract

DESCRIPTION (provided by applicant): Tauopathies, including Alzheimer’s disease (AD) and frontotemporal dementia, are degenerative disorders characterized by accumulation of

aggregated tau protein in the brains of affected individuals. AD affects an estimated 5.2 million Americans, and is the only cause of death among the top ten in the US that lacks a disease-modifying therapy or method of prevention. It has become increasingly recognized that tau-based therapies may be effective in treating AD, with the added benefit of potentially being used to treat other tauopathies. Unfortunately, major gaps in our understanding of tau-induced neurodegeneration remain a barrier to therapeutic intervention. Using a simple genetic model of tauopathy in Drosophila melanogaster that recapitulates many key features of these diseases, as well as tau transgenic mice and human AD brain tissue, we have identified heterochromatin loss as a mechanism of tau-induced neurodegeneration. The overall goal of the proposed project is to determine the upstream mediators and downstream consequences of heterochromatin loss in tauopathies. The K99 phase of this award will be conducted at Brigham and Women's Hospital and Harvard Medical School under the mentorship of Dr. Mel Feany and co-mentorship of Dr. David Pellman, where super-resolution microscopy, cell biological, biochemical, and genetic approaches will be used to identify the mechanisms leading to heterochromatin loss in tauopathies (Aim I). In the independent phase of this award, small RNA sequencing and other biochemical and genetic approaches will be used to identify the consequences of tau-induced heterochromatin loss (Aim II). The combination of classical and highly innovative techniques with novel hypotheses and targets in a well described model of tauopathy will lead to key advances in our understanding of tau-induced neurodegeneration and the development of disease-modifying therapies. Formal and informal interactions between Dr. Frost and her mentors, Drs. Feany and Pellman, will provide training and career guidance throughout this award. During the mentored phase of this award, Dr. Frost will gain professional skills that are vital to her long-term success as an academic through courses offered through Brigham and Women's Office of Research Careers and Harvard Catalyst. The proposed studies and career development plan are central to her scientific growth and advancement to independent investigator.

Lay Summary

PUBLIC HEALTH RELEVANCE: There are currently no effective treatments for tauopathies, including Alzheimer's disease, the sixth leading cause of death in the United States. The objective of the proposed research is to identify the upstream causes and downstream consequences of widespread heterochromatin loss in tauopathies. The research plan utilizes a multisystem approach to understand mechanisms involved in tauopathy, and will identify novel targets for therapeutic intervention.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A