Role of TFEB in Tauopathy

https://www.neurodegenerationresearch.eu/survey/role-of-tfeb-in-tauopathy/

Principal Investigators

ZHENG, HUI

Institution

BAYLOR COLLEGE OF MEDICINE

Contact information of lead PI
Country

USA

Title of project or programme

Role of TFEB in Tauopathy

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,909,160.55

Start date of award

01/07/2015

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Tauopathies, tau Proteins, transcription factor, Neurofibrillary Tangles, Exocytosis

Research Abstract
? DESCRIPTION (provided by applicant): Tauopathies consist of a group of diseases, including frontotemporal dementias and the most common form Alzheimer’s disease, and are characterized by the accumulation of intracellular neurofibrillary tangles (NFTs) composed of aggregates of hyperphosphorylated Tau protein and extensive neurodegeneration. Tau is normally localized to the neuronal axons where it binds and stabilizes the microtubules.

Aberrant Tau phosphorylation leads to its dissociation from the microtubules followed by aggregation and redistribution to cell bodies and dendrites. In addition, Tau has been shown to be secreted, and this mechanism has been implicated in the prion-like transfer of Tau pathology. Accumulating evidence has implicated impaired autophagy-lysosome pathway in neurodegenerative diseases including Alzheimer’s disease. Recently, the Transcription Factor EB (TFEB) was discovered as a master regulator of cellular clearance through coordinated expression of autophagy and lysosomal target genes. We found that TFEB is highly efficacious in ameliorating phospho-Tau/NFT pathology, neurodegeneration, and behavioral deficits in rTg4510 Tau transgenic mice while exhibiting no adverse effect on wild-type mice; TFEB is effective when introduced both before and after the onset of neuropathology. Besides the autophagy-lysosome pathway, substantial evidence also supports a non-cell-autonomous role of TFEB in cellular clearance through neuronal exocytosis and astroglial-mediated endocytosis. Therefore, we hypothesize in this proposal that TFEB promotes lysosomal exocytosis and subsequent astroglial uptake of Tau, and that TFEB-mediated glial uptake of extracellular Tau prevents cell-to-cell transfer of the NFT-like pathology. We are equipped with sophisticated mouse models and innovative approaches that allow us to address these questions in vitro and in vivo at the subcellular, cellular, and network levels. At the completion of the proposal, we wil have gained mechanistic and functional insights into the poorly defined role of astrocytes in Tau clearance and the interplay between neurons and astrocytes in mediating Tau pathogenesis.

Lay Summary
PUBLIC HEALTH RELEVANCE: Accumulation of misfolded Tau and neurofibrillary tangles play critical roles in AD and other neurodegenerative diseases. We have shown that TFEB potently clears the toxic Tau proteins and NFT pathology without exerting untoward adverse effects on wild-type animals. The goal of the application is to decipher the cellular mechanisms and investigate the role of astrocytes and neuron-glia interaction in diseases of tauopathy, including AD. It will establish a new mechanistic framework for addressing AD pathogenesis and reveal cellular targets that are critical in the prevention and treatment of AD and other diseases of tauopathy.

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