Exosome-mediated propagation of pathogenic tau protein

https://neurodegenerationresearch.eu/survey/exosome-mediated-propagation-of-pathogenic-tau-protein/

Principal Investigators

IKEZU, TSUNEYA

Institution

BOSTON UNIVERSITY MEDICAL CAMPUS

Contact information of lead PI
Country

USA

Title of project or programme

Exosome-mediated propagation of pathogenic tau protein

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,633,968.81

Start date of award

30/09/2016

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract
Alzheimer’s disease (AD) is the most common cause of dementia, currently affecting over 5.3

million Americans, yet lacks an effective therapy. Neurofibrillary tangles are a hallmark of AD and primarily consist of phosphorylated tau protein aggregates. Suppressing the spread of tau during the pre-symptomatic stage will potentially provide a novel preventive therapeutic approach to AD. However, the molecular and cellular mechanism of the synaptic propagation of tau is largely unknown. Exosomes are thought to be important vehicles for the spread of tau; the presence of tau proteins in the exosome fraction of cerebrospinal fluid in AD patients provides strong evidence that this mechanism is an important aspect of the pathophysiology of AD in humans. We hypothesize that microglia apposed to synapses facilitate the spread of tau via phagocytosis and secretion of tau in exosomes, and that amyloid deposition as seen in the AD brain enhances the propagation of tau through microglial activation and co-secretion of inflammatory cytokines and tau protein. Our recent studycogently demonstrate that microglia efficiently phagocytize tau aggregates and then transfer them to neurons via exosomes (Asai H et al, Nat Neurosci 2015). Our work will be powered by novel mouse models that recapitulates tau propagation: The stereotactic injection of an adeno-associated viral vector expressing neuron-specific P301L tau into the medial entorhinal cortex shows that inhibition of exosome synthesis or depletion of microglia dramatically reduces tau propagation to the dentate gyrus in vivo. To support this evidence, we showed that stereotactic injection of tau-containing exosomes from microglia successfully spread tau into dentate granular cells of dentate gyrus in wild type mice. This approach will enable us to model tau propagation using exosomes isolated from human brain tissues and non-transgenic mice. This project will focus on characterizing the role of exosomal secretion in the propagation of tau along anatomically connected neural networks using these novel mouse models with three specific aims: 1) To characterize the composition and propagation property of exosomal tau isolated from human AD brain and its potential for the propagation, 2) To determine microglia or other cell types account for exosome secretion for tau propagation, and 3) To determine how exosomal tau propagation induces neurophysiological and morphological abnormality in novel tau propagation mouse models in vivo. We anticipate that the results obtained from this proposal will lead to an entirely novel paradigm for delaying the progression of disease in AD and other tauopathies, such as frontotemporal dementia and chronic traumatic encephalopathy. Additionally, the proposed mouse models will have a wider application, including synucleinopathies (Parkinson’s disease and Lewy body dementia) and prion diseases, since ?-synuclein and prion also spreads via exosomes.

Lay Summary

This proposal is designed to characterize the molecular mechanism of tau propagation, known as neurofibrillary tangle formation in Alzheimer’s disease and frontotemporal dementia. We will determine if exosomes mediate propagation of tau protein, and if exosome pathway is the novel therapeutic target. This study is critically relevant to understand the progression of devastating diseases and will elucidate a potential therapeutic target.

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