Tyrosine phosphorylation in Alzheimers disease

https://neurodegenerationresearch.eu/survey/tyrosine-phosphorylation-in-alzheimers-disease-2/

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Country

USA

Title of project or programme

Tyrosine phosphorylation in Alzheimers disease

Source of funding information

NIH (NIA)

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Start date of award

01/05/1999

Total duration of award in years

15

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

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

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer's disease (AD) affects 20% of those over the age of 75 and 50% over the age of 85. It is difficult to identify early stages of AD and there are no methods to quantitatively follow disease progression. Therapies to slow AD or to cure AD are also absent. One of the neuropathological features of AD is the neurofibrillary tangles made of abnormally phosphorylated tau protein. The discovery of mutations in the tau gene that cause age-related neurodegenerative diseases, such as frontotemporal dementia, has led to research showing that (1) abnormally phosphorylated tau is sufficient to cause disease and (2) neuronal death is caused by abnormal tau. Moreover, AD is now considered a ""tauopathy"". To discover new biomarkers and therapeutics for AD and other tauopathies, it is critical to determine how tau causes disease. While many investigators have focused in the well-known property of tau as a microtubule-associated protein, we have focused on identifying new properties for tau, as there are many microtubule-associated proteins that have no connection to AD. We have found that tau associates with Src-family non-receptor tyrosine kinases and is tyrosine phosphorylated. We have also found that tau can up-regulate kinase activity and that both abnormally phosphorylated and mutated forms of tau can associate more strongly with Fyn, a Src-family kinase. In fact, other investigators have shown that deleting Fyn is neuroprotective for AD in mouse models. Because tau is tyrosine phosphorylated, we investigated the possibility that tau might function as a signal transduction protein. We found that tau potentiated NGF-induced MAPK and AP1 activation in neuronal cells and that phosphorylation of tau at thr231 and tyr18/tyr29 were critical for this new property. Microtubule binding was not involved. In addition, we found that tau associated with the protein tyrosine phosphatase SHP2 in an NGF-dependent manner. In this application, we propose to investigate the tyrosine phosphorylation of tau using two approaches. In Specific Aim I, we will determine if deletion of Fyn from a tauopathy mouse model alters the tau pathology and neuronal viability in the model. We will also determine if the behavior of the mouse is altered. In Specific Aim II, we will investigate the function of abnormally phosphorylated tau. Specifically, we will investigate the role of phosphorylation in the interaction between tau and SHP2 as well as the functional significance of the interaction. In Specific Aim III, we will determine if SHP2 is activated in AD. SHP2 and MAPK activation will also be investigated in a mouse tauopathy model. These aims will (1) advance our knowledge of the mechanisms undertaken by abnormally phosphorylated tau and (2) determine if these mechanisms are taking place during neurodegeneration. Abnormally phosphorylated tau is the earliest sign of neurodegenerative disease and our investigation aims to identify the earliest steps taken towards the neuropathogenic process. Our data will aid in the identification of new targets for disease therapeutics and new biomarkers for tracking disease progress.

Lay Summary

Alzheimer's disease is the sixth leading cause of death in the United States and caring for Alzheimer's disease patients costs close to $200 billion per year. Our laboratory is investigating tau protein, a critical component in Alzheimer's disease neuropathology. Our goal is to identify mechanisms activated by tau that lead to cell death. The data will suggest new targets for disease therapeutics and new biomarkers for tracking disease progress.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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