Tau Conformation in Tauopathies and Neuronal Function

https://neurodegenerationresearch.eu/survey/tau-conformation-in-tauopathies-and-neuronal-function/

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Country

USA

Title of project or programme

Tau Conformation in Tauopathies and Neuronal Function

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NIH (NIA)

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15/04/2014

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1

The project/programme is most relevant to:

Neurodegenerative disease in general

Keywords

tau conformation, Tauopathies, tau Proteins, corticobasal degeneration, Phosphoric Monoester Hydrolases

Research Abstract

DESCRIPTION (provided by applicant): Taupathology is a prominent feature of multiple neurological diseases known collectively as tauopathies. These include Alzheimer’s disease

(AD), Progressive Supranuclear Palsy (PSP), Cortical Basal Degeneration (CBD), Pick's disease, and Frontotemporal Dementia with Parkinsonism linked to chromosome 17. Some of these diseases are hereditary, associated with mutations in the tau gene, but normal tau may also be pathological. Although each tauopathy has a disease specific phenotype, histological presentation, morphology, and neurological presentation, all of them are associated with misfolded tau and altered phosphorylation of tau. The search for a common pathogenic mechanism has been hindered by this clinical diversity. Two recent findings provide new insight into tau pathology. The first is identification of conformation specific tau antibodies that recognize some, but not all, pathological forms of tau, suggesting conformational diversity within the tauopathies. Second, our recent demonstration of a biologically active motif in the tau amino terminus that activates a signaling pathway involving protein phosphatase 1 (PP1) and glycogen synthase kinase 3b (GSK3b): 17 amino acids comprising a Phosphatase Activation Domain (PAD) provides a molecular basis for altered kinase activities in tauopathies. The central hypothesis of this application is that pathogenic forms of tau represent a misregulation of a normal biological function for tau as a scaffold for localization and regulation of microtubule based kinases and phosphatases. This PAD region is aberrantly displayed in all pathological forms of tau examined to date and is a necessary component of at least two forms of tau toxicity: inhibition of fast axonal transport and cell toxicity in culture. We propose that pathological forms of tau in different tauopathies are structurally distinct with variable degrees f toxicity. Experiments in this application will characterize the conformations of tau from different tauopathies and evaluate their relative toxicity in affecting the PP1/GSK3b pathway and axonal transport using authentic and synthetic aggregates. We further hypothesize that toxicity of different tau conformers may be modulated by disease specific patterns of tau phosphorylation and conformation. Disease specific patterns of these alterations will be determined for AD, PSP and CBD. Normal and pathological functions of tau will be analyzed to test the hypothesis that tau serves as a scaffold for localizing and regulating specific kinases and phosphatases to microtubules. We will focus on the role of tau in the normal regulation of PP1 and GSK3b in microtubule rich domains of the axon and identify interaction domains with tau for these phosphotransferases. The localization of the PP1/GSK3b pathway by tau allows for spatial and temporal control of these activities and we propose that presentation of PAD is restricted to specific subcellular compartments in normal neurons and deregulated in pathological states. Consistent with this model, tau, PP1 and GSK3b have all been implicated in neuronal development. Developmental regulation of tau isoforms, conformation, and phosphorylation may play critical roles in neuronal development. We suggest that the regulated presentation of PAD is important for neurite outgrowth and targeting of axonal proteins during normal neuronal development and function, allowing us to understand the relationship between the toxicity of misfolded tau and normal tau function.

Lay Summary

PUBLIC HEALTH RELEVANCE: The tauopathies, which include Progressive Supranuclear Palsy, Cortical Basal Degeneration, Frontotemporal Dementia with Parkinsonism linked to chromosome 17, Pick’s disease and Alzheimer’s disease, are all associated with misfolded tau protein, but differ in the neuronal population affected as well as the isoform composition and structure of tau aggregates involved. Misfolding of tau may lead to misregulation of a normal biological function of tau. Studies in this application characterize the toxicity of disease-specifc conformations for pathological tau and evaluate the possibility that tau acts as a scaffold for signaling pathways in the neuron which can affect axonal transport and other neuronal functions.

Further information available at:

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Investments > €500k

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United States of America

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Neurodegenerative disease in general

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N/A

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