Molecular mechanisms and cellular implications of tau dysfunction

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USA

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Molecular mechanisms and cellular implications of tau dysfunction

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1

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Alzheimer's disease & other dementias

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Research Abstract

Tau is a microtubule-associated protein that is the primary component of the neurofibrillary tangles that are a hallmark of Alzheimer's disease. Tau modulates the stability of neuronal microtubules and it is generally thought that modifications to tau associated with disease disrupt tau-microtubule interactions, which can in turn affect proper motor-based cargo trafficking in axons. Despite intensive study, a detailed understanding of the biophysical basis of tau's interaction with and influence on microtubule assembly dynamics is lacking. Therefore, our goal is to develop a molecular level understanding of this mechanism and determine how tau aggregation and microtubule assembly dynamics are altered by disease-associated tau variants. We have developed the hypothesis that disease-associated modifications to tau primarily affect its interactions with tubulin, manifested in vivo as altered microtubule assembly dynamics and loss of microtubule stability. To investigate this hypothesis, we have developed two specific aims with the following goals: assessing the impact of disease-associated variants of tau on interactions with tubulin and microtubules (Aim 1); determining the impact of tau variants on microtubule assembly and dynamics (Aim 2). In order to achieve these goals, we will use in vitro experimental analysis of purified proteins, live cell imaging of tau interaction with single microtubules, and computational modeling at the molecular and cellular levels to create a more detailed biophysical picture of tau function. Through this research, we expect to develop a cellular systems-level understanding of the molecular factors that alter native tau-tubulin/microtubule interactions to result in neurofibrillary tangle formation and loss of normal microtubule assembly dynamics. We expect that our studies will lead to biophysics-based prediction of cellular-level phenotypes from tau genetic sequence information, which will then serve to rationally guide therapy development toward target(s) that restore normal tau-microtubule dynamics and self-assembly.

Lay Summary

Loss of function of the microtubule associated protein tau leads to microtubule destabilization, consequent disruption of normal trafficking of cellular components, and is one of the major hallmarks of Alzheimer's disease. Here, we seek to develop a detailed molecular model of tau-mediated polymerization of tubulin and to understand of how these normal interactions are altered by mutations to tau found in disease. As one rational approach to drug design would be to alter tau-tubulin or tau-microtubule interactions, our work may provide a framework for understanding the structural features of tau to be targeted for therapeutic purposes.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
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