Pathogenic role for formin mediated microtubule stabilization pathways in Alzheimers disease

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Pathogenic role for formin mediated microtubule stabilization pathways in Alzheimers disease

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1

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Alzheimer's disease & other dementias

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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
Compelling evidence suggests that oligomeric A? plays a crucial neurotoxic and synaptotoxic role in Alzheimer's disease (AD), and that hyperphosphorylation of the microtubule associated protein (MAP) tau mediates or facilitates A? toxicity. The nature of the link between A? and tau in causing AD has however remained largely unexplained, casting doubt on the amyloid hypothesis itself. In neurons, control of microtubule dynamics and tubulin modifications that accumulate on stable microtubules is necessary for multiple homeostatic and regulated functions, including long--distance transport and synaptic activity. Thus, regulation of the ratio between stable and dynamic microtubules is crucial to avoid disease. To date, almost nothing is known about whether induction of hyperstable and modified microtubules is a primary activity of A? that contributes to tau hyperphosphorylation and synaptotoxicity. We have preliminary data that detyrosinated tubulin is enriched in hippocampal tissue of AD patients and animal models of AD, and that accumulation of detyrosinated tubulin may induce tau hyperphosphorylation in primary neurons. In addition, we found that acute incubation of primary neurons with oligomeric A?1--42 generated detyrosinated MTs by transient microtubule hyperstabilization. Inhibition of the formin mDia1, a positive regulator of microtubule stability, suppressed this activity, affected tau hyperphosphorylation and rescued synaptotoxicity induced by A? in vitro. The overall objective of this proposal is to test the paradigm-- shifting hypothesis that oligomeric A? acutely induces hyperstable detyrosinated microtubules through the activation of mDia1, and that tubulin detyrosination contributes to tau hyperphosphorylation as part of a negative feedback loop to maintain appropriate levels of dynamic and unmodified microtubules. In this proposal, we will characterize the nature of this microtubule hyperstabilization in neurites and at synaptic sites, and investigate whether APP and integrin signaling pathways are required for this A?--driven microtubule activity. In addition, we will test the role of mDia1 in mediating A?--synaptotoxicity in vivo, and examine the molecular mechanisms by which mDia1--synaptotoxicity occurs. Our proposal relies on a multidisciplinary effort to test a pathogenic role for formin--mediated regulation of microtubule stability by A? and the involvement of tubulin detyrosination in the induction of tau hyperphosphorylation and neuronal injury. Our studies will test a unifying theory for the pathogenesis of AD and examine the role for mDia1 and possibly other formins as potential targets in drug therapies aimed at rescuing A? and phospho--tau toxicity in AD.

Lay Summary
Alzheimer's disease is associated with altered handling of a peptide known as A? and a microtubule binding protein, tau. The relationship between the disease protein conformations and the microtubule cytoskeleton, and how this may cause Alzheimer's disease is unknown, but of fundamental importance for developing effective new therapies. We recently discovered that an important missing link in toxic mechanisms that lead to Alzheimer's disease might be mediated by acute A? induction of selective microtubule hyperstabilization through activation of a class of proteins known as formins, particularly the formin mDia1, which acts as a positive regulator of microtubule stability. Our

proposal is a multidisciplinary effort to test a synaptotoxic role for mDia1--mediated regulation of microtubule stability by A? and the involvement of tubulin post--translational modifications associated with stable microtubules in the induction of tau hyperphosphorylation and the neuronal injury of Alzheimer’s disease. Our studies will test a unifying theory for the pathogenesis of Alzheimer’s disease and examine the role for formins as potential targets in drug therapies aimed at rescuing A? and phospho--tau toxicity in Alzheimer’s disease.

Further information available at:

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United States of America

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