The Role of Appoptosin in Alzheimers Disease and Other Tauopathies

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Country

USA

Title of project or programme

The Role of Appoptosin in Alzheimers Disease and Other Tauopathies

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NIH (NIA)

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6

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)... Genetics... Neurodegenerative... Neurosciences... Pick's Disease... Rare Diseases

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is defined by two major pathological hallmarks, specifically senile plaques consisting of ?-amyloid (A?) and neurofibrillary tangles composed of abnormally phosphorylated and cleaved tau. A? is neurotoxic and can trigger a cascade of neurodegenerative events in AD. Tau abnormalities also contribute to AD progression. In addition, abnormal tau phosphorylation, cleavage, and mutations in the tau gene, MAPT can induce tau aggregation and consequent toxicity in neurons, leading to several other neurodegenerative tauopathic disorders which include progressive supranuclear palsy (PSP), Pick’s disease, corticobasal degeneration, frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17). Hence, identification of new factors mediating neurotoxicity caused by A? and/or tau is important for disease intervention. We recently identified a novel pro-apoptotic protein, appoptosin, and demonstrated that overexpression of appoptosion results in caspase-dependent apoptosis. Importantly, we found that appoptosin levels are elevated in neurons exposed to A? and [excitotoxic] glutamate stimulation, with increased levels in brain samples from AD and PSP patients. Increased appoptosin expression leads to caspase-mediated tau cleavage and concomitant tau aggregation and synaptic dysfunction in neurons. Appoptosin transduction impairs motor function and exacerbates neuropathology in tau Tg mice; whereas reduced expression of appoptosin inhibits tau cleavage and aggregation, and abrogates mitochondrial fragmentation, caspase activation and neuronal death caused by A? insults. Appoptosin+/- mice have normal learning/memory and LTP, but show reduced LTD and slowed memory decay, thereby implicating its involvement in synaptic plasticity. Moreover, a single nucleotide polymorphism (SNP) rs1768208(C/T) near the appoptosin gene was reported as a risk factor for PSP, AD, CBD and frontotemporal dementia and we demonstrate that the T-allele variant occurs much more frequently in PSP and correlates tightly with increased appoptosin expression. Therefore, we hypothesize that an upregulation of appoptosin expression induced by A? in AD, or controlled by the SNP rs1768208 in various tauopathies, plays a central role in inducing neurodegeneration, and that downregulation of appoptosin provides a novel strategy for disease intervention. In this proposal, we will further ascertain that appoptosin SNP and expression are associated with tauopathic diseases, and determine that the SNP rs1768208(C/T) variant regulates appoptosin expression. We will then determine whether caspases, tau and glutamate receptor dynamics are involved in appoptosin-mediated synaptic plasticity. Finally, we will corroborate the role of appoptosin in AD and other tauopathies in vivo by studying whether upregulation of appoptosin leads to tauopathy-related neuropathologies and behavior, and whether a decrease of appoptosin can ameliorate disease-related phenotypes in APP/tau bigenic mice. Results from these studies will establish appoptosin as a novel and important player and therapeutic target in AD and other tauopathies.

Lay Summary

PUBLIC HEALTH RELEVANCE: Tauopathic neurodegenerative disorders such as Alzheimer’s disease (AD), progressive supranuclear palsy (PSP), Pick’s disease, corticobasal degeneration, and frontotemporal dementia and Parkinsonism linked to chromosome 17 (FTDP-17) are characterized by the deposition of abnormal tau protein in the brain. Although mechanisms driving tauopathies are currently unclear, we have recently identified a novel pro-apoptotic protein, appoptosin that may be crucial for the regulation of tau cleavage/aggregation in tauopathy. This study will further elucidate the role of appoptosin in tauopathic pathologies, thereby providing a pathological mechanism for these poorly characterized disorders, which may eventually to the formulation of effective treatment strategies.

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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N/A

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