Mechanisms of age-related tauopathy

https://neurodegenerationresearch.eu/survey/mechanisms-of-age-related-tauopathy/

Principal Investigators

CRARY, JOHN FONDA

Institution

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI

Contact information of lead PI
Country

USA

Title of project or programme

Mechanisms of age-related tauopathy

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,694,444.95

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15/09/2015

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Tauopathies, age related, Neurofibrillary Tangles, Amyloid beta-Protein, Alzheimer's Disease

Research Abstract

? DESCRIPTION (provided by applicant): Recent consensus criteria have been put forth by a large group of prominent neuropathologists and neuroscientists to define a new category of Alzheimer’s disease (AD) neuropathologic changes. Individuals with this disorder, now termed primary age-related tauopathy (PART), develop AD-type neurofibrillary tangles (NFT) in the absence of amyloid beta peptide (A?) containing-plaques. Patients with PART may have normal

cognition, amnestic mild cognitive impairment (aMCI), or an amnestic dementia. The prevalence of PART dementia is unclear, with estimates ranging from 1-7%, but PART is likely more pervasive. Recent studies have found a common neuroimaging and cerebrospinal fluid biomarker profile, termed suspected non-amyloid pathophysiol- ogy (SNAP), in ~25% of non-demented elderly individuals and patients with aMCI which shows remarkable similarities to PART. The objective of this application is to perform a focused histopathological, molecular and rigorous genetic study of PART. Our central hypothesis is that subjects with PART have distinct characteristics that underlie their NFT+/A?- phenotype. Understanding the molecular changes of, and genetic risk factors for, PART will reveal mechanistic insights into its pathogenesis and in turn advance our understanding of the re- gional vulnerability of the temporal lobe to neurodegeneration and the pathogenesis of tauopathies in general. In aim 1, we will validate the new neuropathologic criteria for PART and lay the groundwork for clinical and mechanistic studies that will elucidate disease burden, pathogenesis and progression. This will be performed in a large dementia autopsy series using stereology-based semiquantitative and quantitative measurements of NFT burden. In aim 2, we will test the hypothesis that PART has a molecular signature consisting of AD-type tau pathology alongside non-amyloidogenic APP metabolites. This will be accomplished by comparing the levels and distribution of toxic tau species and APP metabolites using quantitative immunoblot, ELISA, brightfield immunohistochemistry and immunofluorescence confocal microscopy in autopsy brain tissue from PART, AD, and control cases. Finally, in aim 3 we will test the hypothesis that PART has a genetic risk profile that over laps with some aspects of AD genetics (e.g., MAPT haplotypes) but diverges with respect to others (e.g., APOE genotype). This aim will be accomplished by performing a series of association analyses comparing the frequency of known AD risk alleles in PART, AD and controls. We will also perform a genome-wide quantitative trait analysis of NFT burden using a large cohort of PART subjects to discover new candidate risk alleles. This project will establish that a group of individuals with AD tauopathic changes have a distinct constellation of clinical features, molecular changes and genetic risk factors. The proposed research is innovative because considering PART as an A?-independent process represents a paradigm shift in terms of how we conceptual- ize the tauopathic component of AD neuropathologic changes.

Lay Summary
PUBLIC HEALTH RELEVANCE This research is relevant to public health because we will transform the way clinicians and scientists classify individuals with Alzheimer’s disease neuropathologic change. Validating the neuropathological criteria for primary age-related tauopathy will lay the groundwork for clinical and mechanistic studies that will elucidate disease burden, pathogenesis and progression.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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