Tau-Spliceosome Interactions in Alzheimers Disease

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Country

USA

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Tau-Spliceosome Interactions in Alzheimers Disease

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NIH (NIA)

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1

The project/programme is most relevant to:

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)... Biotechnology... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract

The fidelity of messenger RNA precursor (pre-mRNA) splicing is critical for safeguarding the

neuronal transcriptional program, and splicing factors have been linked to both nervous system development and degeneration. Pre-mRNA splicing is mediated by the spliceosome, a dynamic and complex ribonucleoprotein machine including approximately 200 core proteins, 5 small nuclear RNAs, and an array of accessory factors. In compelling preliminary studies, we implicate spliceosomal disruptions in Alzheimer's disease (AD) pathogenesis through integrative analyses of human clinicopathologic cohorts and experimentation in the fruit fly, Drosophila melanogaster. In human brains with AD neuropathology, numerous components of the spliceosomal U1 small nuclear ribonucleoprotein particle (snRNP) are abnormally enriched within insoluble cortical fractions. We further demonstrate widespread intron retention within mRNA transcripts consistent with spliceosome dysfunction resulting in global splicing failure. Immunohistochemistry in postmortem brain tissue reveals cytoplasmic mislocalization of U1 snRNP proteins in neurons as well as co-aggregation with Tau neurofibrillary tangles, one of the defining pathologies of AD. In Drosophila, transgenic expression of human Tau induces age-dependent aberrant localization and sharply reduced U1 snRNP component levels, concomitant with increased intron retention of candidate transcripts encoding essential synaptic proteins. Loss- or gain-of-function in spliceosomal genes enhance and suppress Tau-induced neurodegeneration, and mutation of SmB, encoding a core spliceosomal protein, causes progressive neurodegenerative changes independent of Tau. We hypothesize that disruptions in the splicing machinery and resulting derangements of the neuronal transcriptome mediate Tau-induced neurodegeneration in AD. We will first (AIM 1) quantify U1, other spliceosomal snRNPs, and related factors in the insoluble proteome of 500 human brain autopsy samples, and in a subset, we will additionally characterize potential neuronal nuclear depletion. The most promising results will be confirmed by immunohistochemistry and immunofluorescence studies of postmortem tissue. Next (AIM 2), leveraging the rapid and powerful genetics available in Drosophila, we will elucidate Tau-spliceosome interactions and their impact on neurodegeneration. A combination of biochemistry and confocal microscopy will be utilized to examine for altered solubility and aggregation of spliceosomal factors. Lastly (AIM 3), we will integrate available human cortical transcriptomic data with a new reference transcriptome generated from the brains of Tau transgenic flies in order to pinpoint splicing errors with causal roles in neurodegeneration. IMPACT: By integrating proteomic and transcriptomic studies in human brains with targeted functional studies in Drosophila we will elucidate how Tau neuropathologic burden leads to disruptions in spliceosomal proteins and dissect the resulting causal chain leading to neurodegeneration.

Lay Summary

Alzheimer's disease is a devastating and incurable neurodegenerative disorder projected to affect 13 million individuals in the US by 2050. We have discovered that a fundamental cellular machine responsible for synthesizing proteins, "the Spliceosome", may be sensitive to disruption by one of the primary brain lesions of Alzheimer's disease, "Tau tangles". Integrating innovative studies of protein abnormalities detected in human brains with animal model experiments, we will further elucidate this novel mechanism of Tau-Spliceosome interactions, with potential application for breakthrough therapies in Alzheimer's disease

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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