RNA binding proteins as novel targets in Alzheimers disease

https://neurodegenerationresearch.eu/survey/rna-binding-proteins-as-novel-targets-in-alzheimers-disease/

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Country

USA

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RNA binding proteins as novel targets in Alzheimers disease

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NIH (NIA)

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15/09/2015

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2

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

Research Abstract

? DESCRIPTION (provided by applicant): This proposal investigates a novel mechanism for the

misfolding and aggregation of microtubule associated protein tau (MAPT), which we hypothesize provides an unrecognized but major aspect of the pathophysiology of tauopathies, such as Alzheimer’s disease (AD). We have recently identified a new type of molecular pathology in AD that derives from the aggregation of RNA binding proteins, forming RNA-protein complexes that include stress granules. These stress granules progressively accumulate in the brains of transgenic models of tauopathy, as well as massively accumulate in subjects with AD and FTDP-17. The genesis of this research comes from the simple observations that 1) RNA binding proteins form RNA granules through a striking property of reversible aggregation, which is under physiological regulation, and 2) MAPT binds to some RNA binding proteins, including TIA-1. RNA granules consolidate transcripts for transport, storage and/or degradation. Our results suggest that TIA-1 stimulates phosphorylation and misfolding of MAPT, and that MAPT stimulates formation of TIA-1 positive stress granules; the association of MAPT with stress granules reduces its degradation and appears to stabilize insoluble MAPT. The chronic nature of AD might lead to excessive formation of stress granules and aggregation of MAPT, contributing to neurodegeneration. We hypothesize that MAPT and RNA binding proteins exhibit bidirectional regulation. MAPT promotes the formation and stability of RNA granules, including stress granules. Conversely, RNA binding proteins and the translational signaling cascade stimulate the phosphorylation, and misfolding of MAPT. This hypothesis will be studied in the context of three aims: Aim 1 will determine the mechanisms by which TIA-1 interacts with MAPT. We will use structural studies, imaging and mass spectroscopy to highlight key changes in discover key binding proteins. Aim 2 will determine the role of MAPT in neuronal RNA granule biology, including stress granules. This aim will explore this biology using live cell imaging to explore RNA granule dynamics under basal and stress conditions and will examine whether MAPT modulates the types of transcripts associated with particular RNA granules/ stress granules (using iCLIP). Finally, Aim 3 will determine whether stress granule/RNA translation pathways regulate MAPT-mediated neurodegeneration in vivo. This aim will focus on the RNA binding proteins used in our preliminary studies (e.g., TIA-1) as well as the novel MAPT/ stress granule components identified by mass spectroscopy.

Lay Summary
PUBLIC HEALTH RELEVANCE: This proposal seeks to identify the role of RNA binding proteins in regulating the formation of tau pathology, and the process of neurodegeneration occurring 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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