

RNA splicing dysfunction in Alzheimers disease

<https://www.neurodegenerationresearch.eu/survey/rna-splicing-dysfunction-in-alzheimers-disease/>

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Country

USA

Title of project or programme

RNA splicing dysfunction in Alzheimers disease

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NIH (NIA)

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01/05/2015

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

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer's disease (AD), the most common form of

dementia, is the sixth-leading cause of death in the US. The disease affects ~5 million Americans, and had a care cost of ~\$200 billion in 2012. Despite extensive investigation of AD pathogenesis and tremendous investment in developing therapeutics for AD, no cure is available for the disease. Thus, there is an urgent need to accelerate research to develop effective treatments for AD. Deposition of protein aggregates is a common feature of AD pathology. Identification of the aggregated proteins, together with genetic studies, can provide crucial insights into the molecular pathogenesis of AD. The resulting amyloid cascade and tau hypotheses dominate AD studies, but their interpretation has been evolving and soluble protein oligomers emerge as toxic species. However, AD etiology remains to be fully illustrated. We previously performed a comprehensive study of the human brain aggregated proteome by mass spectrometry and identified 4,216 proteins, among which 36 proteins accumulate in AD, including U1-70K and other U1 small nuclear ribonucleoprotein (U1 snRNP) spliceosome components. Multiple U1 snRNP subunits form cytoplasmic tangle-like structures in AD but not in other neurodegenerative disorders [e.g., Parkinson's disease, frontotemporal lobar degeneration, and corticobasal degeneration (with tauopathy)], indicating that U1 snRNP pathology is AD specific and cannot be induced by tauopathy alone. Deep RNA sequencing revealed global dysregulation of RNA processing in AD brain. Importantly, U1-70K aggregation was found in mild cognitive impairment and early Braak stages of AD, indicating that U1 snRNP alteration occurs early in AD development. U1 snRNP components also aggregate in early onset genetic forms of AD cases with PS1 and APP mutations as well as trisomy 21, suggesting that abnormal amyloid cascade may cause U1 snRNP dysfunction in human. Interestingly, U1-70K knockdown or antisense oligonucleotide inhibition of U1 snRNP increased the level of amyloid precursor protein (APP) and A β production in cellular models and possibly in a mouse model, suggesting a vicious cycle of A β production and U1 snRNP abnormality. Thus, our hypothesis is that U1 snRNP dysfunction can mediate neurodegeneration and modulate A β production, contributing to AD pathogenesis. We will test this hypothesis in three specific aims: (i) investigate whether U1 snRNP dysfunction leads to neurotoxicity in cellular models; (ii) examine whether U1 snRNP dysfunction leads to neurodegeneration in a mouse model; and (iii) determine how U1 snRNP dysfunction causes aberrant A β production. Our results will illustrate the potential role of RNA splicing dysfunction in AD pathogenesis, which may lead to the development of novel strategies to effectively diagnose and treat this disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease is the sixth leading cause of death in the United States, affecting ~5.4 million Americans, but there is no cure for the disease. We propose to investigate the role of RNA splicing dysfunction in the development of Alzheimer's disease. The study will provide important insights into molecular mechanisms of pathogenesis, which may offer new strategies for therapeutic intervention.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Alzheimer's disease & other dementias

Years:

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Database Categories:

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