Retromer deficiency and Alzheimers disease pathology

https://neurodegenerationresearch.eu/survey/retromer-deficiency-and-alzheimers-disease-pathology/

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Country

USA

Title of project or programme

Retromer deficiency and Alzheimers disease pathology

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,418,283.49

Start date of award

01/05/2014

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences... Prevention

Research Abstract

DESCRIPTION (provided by applicant): VPS35 is a major component of retromer that is

essential for selective endosome-to-Golgi retrieval of membrane proteins. Dysfunction of VPS35/retromer is implicated in the pathogenesis of Alzheimer’s disease (AD) as well as Parkinson’s disease (PD), because mutations in Vps35 and SorLA (a cargo of retromer) genes have been identified in the late-onset PD and AD patients, respectively. Thus, it is of considerable interest to investigate how VPS35/retromer deficiency contributes to neurodegeneration. Three hypotheses will be tested in this proposal. The first hypothesis is that VPS35/retromer expression in pyramidal neurons is critical to prevent AD-relevant neuropathology. The second hypothesis is that VPS35/retromer deficient neurons are impaired in BACE1 retrograde trafficking, thus increasing BACE1 activity and promoting dendritic and axonal degeneration. The third hypothesis is that VPS35/retromer deficient microglial cells are hypersensitive to TNF¿ family cytokines, releasing excessive proinflammatory cytokines and promoting brain inflammation and neurodegeneration. Both hypotheses are supported by our publications and recent preliminary studies. We hope that the proposed studies will not only establish novel cellular functions of VPS35/retromer in preventing hyper-activation of BACE1 and microglia, but also shed new lights into pathogenesis of neurodegenerative disorders, such as AD and PD. We also hope that this research may point to new therapeutic strategies for the treatment of these disorders.

Lay Summary
PUBLIC HEALTH RELEVANCE: This proposal will investigate mechanisms by which VPS35, a major component of retromer, prevents neurodegeneration.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A