Mechanisms of Apolipoprotein E Isoform Conferred Susceptibility and Resistance to Alzheimers Disease

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Principal Investigators

SADOWSKI, MARTIN JOSEPH

Institution

NEW YORK UNIVERSITY SCHOOL OF MEDICINE

Contact information of lead PI
Country

USA

Title of project or programme

Mechanisms of Apolipoprotein E Isoform Conferred Susceptibility and Resistance to Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,954,319.27

Start date of award

15/07/2016

Total duration of award in years

1

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

Research Abstract

Susceptibility to sporadic Alzheimer's disease (AD) is foremost modulated by APOE genotype. A single copy of the APOE ?4 allele endows a ~3 fold increase in AD risk, and 2 ?4 copies effect a ~15 fold increase, while an ?2 allele halves AD risk compared to ?3 homozygotes. Neither etiology of ?4 deleterious effect nor ?2 conferred protection is fully explained. Past work primarily focused on the role of apoE in A? deposition showed thatapoE in isoform-dependent fashion binds A? peptides, facilitates assembly of A? into amyloid fibrils and promotes formation of parenchymal plaques and vascular deposits in the rank order of E4>>E3>E2, while the Apoe gene knockout in APP transgenic mice precludes formation of fibrillar A? deposits. In addition to the well-studied catalytic effect on fibrillization and deposition of A?, there is evidence of apoE isoform-specific effect on the clearance of A? from the brain extracellular (or interstitial) space, modulation of microglia inflammatory response, and regulation of synaptic plasticity and neuronal network function, which all may contribute to the differential effect of APOE genotype on AD susceptibility. Though relationship between APOE genotype and variable rate of A? clearance from the brain interstitial space is well recognized, how apoE isoforms differentially engage this process and whether it depends on direct apoE/A? binding remains disputed. Our preliminary microdialysis experiments indicate substantial degree of binding between apoE and A? in the brain interstitial fluid (ISF) of Tg2576 and PDAPP mice while application of specific apoE/A? antagonist, dramatically increases unbound A? level. Based on these data we hypothesize that apoE isoforms differentially bind A? in the ISF and that pharmacological targeting of the apoE/A? interaction may enhance A? clearance and prevent A? oligomerization. This hypothesis will be explored in Specific Aim I using APPSW/PS1dE9/apoE-TR mice (APP/E-TR) with targeted replacement (TR) of the mouse Apoe gene for various human APOE alleles and APP/E-/- mice subjected to various in vivo microdialysis experiments. Specific Aim II will investigate how APOE genotype influences inflammatory microglia response. Our preliminary studies show greater microglia activation in APP/E4 mice in response to A? deposition and anti-A? passive immunization than in APP/E2 and APP/E3 mice. We thus hypothesize that ineffective A? phagocytosis and deleterious microglia activation can be an independent mechanism of ?4 allele conferred susceptibility to AD. This hypothesis will be explored by functional phagocytosis and transcriptomics studies of primary CNS microglia isolated from apoE-TR and apoE-/- mice of various ages and from APP/E-TR and APP/E-/- mice. Transcriptome assessment will include RT-qPCR of pro- and anti-inflammatory cytokines and unbiased RNA-Seq to identify signaling pathways differentially activated by apoE isoforms in microglia. Specific Aim III, using aged apoE-TR mice and APP/E-TR mice, will investigate how apoE isoforms in A?-independent and A?-dependent way modulate Reelin-Apoer2/Vldlr signaling, which regulates synaptic plasticity and neuronal network integrity.

Lay Summary

This project investigates how APOE genotype differentially modulates risk of sporadic Alzheimer's disease. Investigated mechanisms include effects of apoE isoforms on A? brain clearance, modulation of microglia inflammatory response, and regulation of synaptic plasticity and neuronal network function.

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