The role of Clusterin in cerebral amyloid angiopathy

https://neurodegenerationresearch.eu/survey/the-role-of-clusterin-in-cerebral-amyloid-angiopathy/

Principal Investigators

FRYER, JOHN DAVID

Institution

MAYO CLINIC JACKSONVILLE

Contact information of lead PI
Country

USA

Title of project or programme

The role of Clusterin in cerebral amyloid angiopathy

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,570,385.32

Start date of award

30/09/2015

Total duration of award in years

4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

sulfated glycoprotein 2, Cerebral Amyloid Angiopathy, plexin, APP-PS1, Cerebrovascular system

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer disease (AD) is the most common cause of dementia and is characterized by extracellular plaques formed by the deposition of amyloid-? (A?) peptide and intracellular tangles comprised of hyperphosphorylated forms of the tau

protein. Another common pathology in AD is cerebral amyloid angiopathy (CAA), caused by A? deposition in the walls of cerebral vessels leading to vascular dysfunction and hemorrhage. The strongest genetic risk factor for both AD and CAA is ?4 allele of the apolipoprotein E (APOE) gene, but multiple recent genome-wide association studies have proven that a similar apolipoprotein, Clusterin (CLU), also confers risk for AD. The role of CLU in CAA is unknown, but we have strong evidence that CLU is critically involved in the formation of CAA. While much is known about apoE receptor biology, the only known receptor for Clu, LRP2/Megalin, is very poorly expressed in the adult brain, suggesting other receptors are present but undiscovered. We have found that Plexin A4 (PLXNA4) is a novel receptor that regulates the levels of extracellular CLU in mice and in humans. PLXNA4 levels are significantly decreased in mouse models of AD as well as human AD brain tissue compared to controls. The objective of this proposal is to define how CLU regulates A? metabolism and deposition in brain parenchyma and cerebrovasculature. Using a combination of cell culture, biochemistry, mouse genetics, pharmacology, and pathologically defined human tissue, we will determine how the CLU and PLXNA4 affect AD by studying functional endpoints such as histopathology, vascular dysfunction, neuritic dystrophy, electrophysiology, and behavior. Deciphering this pathway could lead to new therapeutic targets not only for AD, but also for stroke and breast cancer, given the emerging role of CLU in those respective fields.

Lay Summary
PUBLIC HEALTH RELEVANCE: Alzheimer disease is characterized by the buildup of protein deposits in the brain termed “”amyloid plaques.”” These plaques can form around neurons or within the vessels and are extremely toxic to both. In this project, we will explore new molecular pathways that may explain exactly how these amyloid plaques form.

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