Involvement of myelin integrity in Alzheimers disease pathogenesis

https://neurodegenerationresearch.eu/survey/involvement-of-myelin-integrity-in-alzheimers-disease-pathogenesis/

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Country

USA

Title of project or programme

Involvement of myelin integrity in Alzheimers disease pathogenesis

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 832,319.27

Start date of award

01/05/2016

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... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): This K99/R00 application provides career development

training and a research plan to further the understanding of glial responses in white matter in the context of Alzheimer's disease (AD). The hypothesis to be tested is that a progressive loss of myelin integrity occurs in AD, activating microglia towards a proinflammatory feed-forward loop, which mediates hyperphosphorylation of the microtubule-associated protein tau and traditional AD pathology: neuritic plaques (NP) and neurofibrillary tangles (NFTs). Conventionally considered a disease of the CNS gray matter, AD also has pronounced and progressive deterioration of cerebral white matter. Recent evidence suggests that changes in myelin integrity could be an early factor driving AD pathology, through stimulation of inflammatory microglia activation and subsequent axonal damage. Extensive work has been done to understand the glial response in AD gray matter yet very little is known about microglia activation in AD white matter, despite the fact that we and others have found a more robust activation of microglia and inflammatory response in AD white matter compared to gray matter. No studies have systematically and quantitatively examined myelin changes and inflammatory profiles as a function of disease progression. Our project will fill this gap by using human autopsy tissue and a mouse model that exhibits loss of myelin integrity to test our hypothesis. Our specific aims are: 1) Quantify the relationship between myelin integrity, microglia activation, proinflammatory cytokine levels, and traditional measures of AD burden (NPs and NFTs) in the white matter of autopsy samples; 2) Determine if loss of myelin integrity, induced by mutation in PLP, in hTau mice will accelerate hyper-phosphorylated tau pathology, and if this pathology can be rescued by suppressing the chronic neuroinflammation using a glia cytokine inhibitor. This project takes advantage of a strong scientific environment and extensive resources at the University of Kentucky, including the Alzheimer's Disease Center, clinically well-characterized autopsy cases that span the disease pathology continuum, and renowned scientific expertise of an enthusiastic and committed mentoring team. A comprehensive training and career development plan has been developed for the K99 phase that includes further scientific training in oligodendrocyte/myelin biology and human neuropathology; formal coursework and participation in local, national and international scientific meetings; evaluative meetings with th mentoring team; and activities designed to improve communication, writing, teaching, and management skills. Overall, there is an outstanding intellectual environment and access to relevant expertise in the applicant's project area, multiple opportunities for career growth, and substantial institutional commitment. This rich and supportive environment will enable a highly promising young scientist to further develop his research expertise, pursue his structured training and career development plan, and launch his career as an independent academic investigator.

Lay Summary

PUBLIC HEALTH RELEVANCE: This research project will provide fundamental insights regarding the role of microglia, dysregulated neuroinflammation, and white matter integrity in the temporal onset of Alzheimer's disease. Recent data suggest white matter involvement in a variety of neurodegenerative and psychiatric disease. Therefore, the understanding of oligodendrocyte – microglia – neuron interaction in Alzheimer's disease could have a broad impact on our understanding of cognitive health and disease.

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