Molecular Regulation of AEP during Ageing

https://www.neurodegenerationresearch.eu/survey/molecular-regulation-of-aep-during-ageing/

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Country

USA

Title of project or programme

Molecular Regulation of AEP during Ageing

Source of funding information

NIH (NIA)

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01/08/2016

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... Neurodegenerative... Neurosciences

Research Abstract

Abstract The objectives of this proposal are to characterize the pathological roles of AEP-cleaved APP and AEP-cleaved Tau fragments in Alzheimer’s disease (AD) onset and progression and how AEP is molecularly regulated during ageing. AEP is an acidosis-activated

protease with a high level of specificity for cleavage of protein substrates after an asparagine residue. AD is characterized by the accumulation of the ?-amyloid peptide (A?) within the brain along with hyperphosphorylated and cleaved forms of the microtubule-associated protein Tau. Endogenous AEP is inhibited by Cystatin E/M, an A?-associated protein, preventing neurodegeneration in AD. Most recently, we show that AEP is activated by A? and cleaves APP and Tau in human AD brains and mediates AD pathology. Notably, AEP is expressed in brain and spinal cord in an age-dependent manner. We found that AEP upregulation and activation tightly correlate with APP and Tau fragmentation during ageing. Strikingly, we found that C/EBP?, an age-dependent transcription factor, plays a critical role in regulating AEP expression during ageing. Hence, we hypothesize that AEP may play a critical role in mediating AD pathogenesis, which is mediated by C/EBP?. Successful completion of the proposed studies will lead to the identification of a novel drug target for treatment of neurodegenerative diseases including AD.

Lay Summary
Project Narrative Asparagine endopeptidase (AEP) is upregulated and activated in brain during ageing, leading to degradation of APP and Tau in an age-dependent manner. AEP is selectively activated in human AD brains versus healthy controls, indicating that AEP is a novel proteinase distinguished from the well-known secretases or caspases. Successful completion of the proposed studies will lead to the identification of a novel drug target for treatment of neurodegenerative diseases including AD.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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