Cerebrovascular beta-Amyloidosis: A-beta CNS Transport Pathways

https://neurodegenerationresearch.eu/survey/cerebrovascular-beta-amyloidosis-a-beta-cns-transport-pathways/

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Country

USA

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Cerebrovascular beta-Amyloidosis: A-beta CNS Transport Pathways

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NIH (NIA)

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01/12/2003

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12

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... Cerebrovascular... Dementia... Neurodegenerative... Neurosciences... Rare Diseases... Stem Cell Research... Stem Cell Research - Induced Pluripotent Stem Cell... Stem Cell Research - Induced Pluripotent Stem Cell - Human

Research Abstract

DESCRIPTION (provided by applicant): In this competing renewal, we propose to continue our studies aimed at understanding the role of amyloid ?- peptide (A?) trans-vascular clearance in the development and prevention of cerebral ?-amyloidosis, neuronal dysfunction and neurodegeneration. Previous work on this project has identified that A? binds directly to the ectodomain of LRP1 (low density lipoprotein receptor related protein 1), and that endocytotic LRP1 receptor is a key receptor for A? clearance at the blood-brain barrier (BBB), by vascular cells and neurons, as shown by us and others. These findings contributed to development of A? clearance approaches for Alzheimer's disease (AD). Here, we focus on PICALM, the gene encoding phosphatidylinositol binding clathrin assembly protein that plays a key role in controlling endocytosis and the function of cell receptors. PICALM is a significant risk factor for AD, but its role in disease pathogenesis remains elusive. AD-associated SNPs in PICALM (~20) are all located upstream to the coding region of the gene. Our preliminary data show that PICALM could have a central role in A? trans-vascular clearance, development of cerebral ?-amyloidosis, neuronal dysfunction and neurodegeneration. Based on our pilot data, we hypothesize that i) PICALM deficiency in endothelium and neurons results in A? accumulation and increased neuronal vulnerability to A? species causing neuronal dysfunction and neurodegeneration, respectively; ii) PICALM regulates endocytosis of A?-LRP1 complex and A? transcytosis leading to clearance of A? across the BBB; and iii) PICALM allelic variants (rs3851179, rs541458) affect A? BBB clearance and neuronal toxicity by influencing PICALM expression. To test our hypothesis we will cross our novel Picalmlox/lox mouse line with Tie2-Cre mice and Camk2a-Cre mice for endothelium-specific (AIM1) and neuron-specific (AIM2) PICALM deletions, respectively, and will cross these mice with APPsw/0 mice. We will use intrahippocampal microdialysis to study clearance of soluble A?, voltage- sensitive dye imaging to study neuronal function, confocal and light microscopy to study A?, BBB and neuronal pathology, MRI to study microstructural and connectivity changes and BBB permeability changes, and behavioral tests. We will use an in vitro model of human BBB to identify the role of PICALM in A? endocytosis and transcytosis (AIM3); and, CRISPR genome editing to generate human iPSCs with rs3851179 (protective) and rs541458 (pathogenic) allelic variants in PICALM followed by direct lineage conversion to generate human endothelial cells and cortical neurons for studies on PICALM expression, A? BBB clearance and neuronal toxicity (AIM4). To achieve our goals, we propose interdisciplinary studies by a team of Investigators with expertise in A? transport and pathology, BBB, neurodegeneration, behavior, vascular biology, cellular reprogramming and stem cell technology, small rodent neuroimaging and high-resolution connectivity brain mapping. We expect to provide unique novel insights into PICALM biology that will have important implications for our understanding of the disease pathogenesis and may guide the development of new therapies for AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: The annual health care costs for neurodegenerative disorders range in excess of a hundred billion dollars. Sadly, we do not have cure yet for any of these diseases. This application is focused on PICALM that is a highly validated genetic risk factor for Alzheimer’s disease. We expect to generate unique new insights into PICALM biology, particularly in regards to its roles in regulating clearance of Alzheimer’s toxin A? and neurodegenerative process in Alzheimer’s disease that will have important implications for our understanding of the disease pathogenesis and may guide the development of new therapies for Alzheimer’s disease.

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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2016

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