PATHOBIOLOGICAL STUDIES OF VESSEL BACE1 IN CEREBROVASCULAR AMYLOID ANGIOPATHY

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Principal Investigators

SHEN, YONG

Institution

ROSKAMP INSTITUTE, INC.

Contact information of lead PI
Country

USA

Title of project or programme

PATHOBIOLOGICAL STUDIES OF VESSEL BACE1 IN CEREBROVASCULAR AMYLOID ANGIOPATHY

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,651,376.15

Start date of award

30/09/2016

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

cerebrovascular amyloid, Cerebral Amyloid Angiopathy, beta-site APP cleaving enzyme 1, cerebrovascular, Vascular Smooth Muscle

Research Abstract

Abstract The incidence of Alzheimer disease (AD) with vascular degeneration is greatly increased following cerebral hemorrhagic stroke in which cerebral amyloid angiopathy (CAA) occurs in affected brain areas. The most common form of CAA is of the amyloid beta-peptide (A?) type. A?, which is derived from the beta-amyloid precursor protein (APP) by sequential proteolytic cleavages from ?-secretase (BACE1) and ?-secretase, is widely believed to trigger a cascade of pathological events culminating in AD including accompanied by degeneration of vascular cells: vascular smooth muscle cells (VSMCs), vascular endothelial cells (VENCs) and pericytes. While extensive studies on pericytes in CAA have been performed, multiple studies demonstrated that an increasing accumulation of A? in the vessel basement membrane is associated with the degeneration of adjacent VSMCs and VENCs. Importantly, our recent preliminary data showed that cerebral vascular cells from human CAA brains express high levels of ?-secretase (BACE1). However, what causes vascular degeneration or death in CAA remains unclear. We recently reported that a cell death receptor, TNFRI, is required for A?-induced cell death and depletion of TNFRI reduced BACE1. In this application, we will study whether and how BACE1 can be up-regulated in vascular cells and what molecular mechanisms of BACE1 elevation causes cerebral vascular cell death in our new mouse models of AD related CAA. The ultimate goal of this proposal will not only advance our understanding the mechanisms of CAA- induced hemorrhage but, also to, in principle, identify novel therapeutic targets and offer novel alert for potential side effects of BACE1 inhibitors in patients with Alzheimer’s disease accompanying vascular degeneration. Key words: BACE1, TNF? inflammation, animal models, neurodegeneration

Lay Summary

Narrative The molecular roles of BACE1 in cerebral vascular degeneration in Alzheimer’s disease are not clear. In this application, we proposed, by using two new animal models, to study how cerebral amyloid angiopathy (CAA)/BACE1 enhances cerebral vascular degeneration, which contributes to Alzheimer’s disease. Completion of this project will help not only advance our understanding of normal physiological roles of BACE1 in cerebral vascular cells and pathological mechanisms of hemorrhage but, also will identify novel therapeutic targets and offer a novel alert of potential side effects of BACE1 inhibitors in the clinic.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:

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