Role of phosphoinositides in neuronal membrane traffic and neurodegeneration

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Principal Investigators

LIEM, RONALD K.

Institution

COLUMBIA UNIVERSITY HEALTH SCIENCES

Contact information of lead PI
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USA

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Role of phosphoinositides in neuronal membrane traffic and neurodegeneration

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Alzheimer's disease & other dementias

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phosphatidylinositol 3-phosphate, Membrane Protein Traffic, Phosphatidylinositols, Amyloid beta-Protein Precursor, Nerve Degeneration

Research Abstract
DESCRIPTION (provided by applicant): Intracellular signaling lipids control a large variety of

cellular processes, including membrane trafficking, cytoskeletal dynamics, transport across membranes and signal transduction. Not surprisingly, lipid signaling and alterations thereof are increasingly linked to human disease. Alzheimer’s disease (AD) is one such disorder in which lipid dyshomeostasis and membrane trafficking defects are believed to play a critical role. This concept is easily reconciled with the fact that the main molecular players in AD, including amyloid precursor protein (APP) and the ?-, ß- and ?-secretases, are all transmembrane proteins (or protein complexes) that traffic in cells and exert their functions at or within cellulr membranes. Our working hypothesis is that specific lipid changes may drive or mediate fundamental aspects of AD pathogenesis. Systems-based approaches, such as “”lipidomics””, are emerging as a powerful tool to profile cells, tissues or organisms in a diseased state, providing both an unbiased and comprehensive picture of lipid alterations potentially linked to pathogenicity. To better understand the link between lipid signaling defects and AD pathogenesis, we have recently conducted a lipidomic analysis of brain samples derived from three transgenic animal models of familial AD as well as three independent brain regions from patients with late-onset AD. We found that out of 330 lipid species analyzed, only one lipid species was significantly reduced in AD-affected brain regions in mice (forebrain) and men (entorhinal and prefrontal cortex): phosphatidylinositol-3-phosphate (PI3P). PI3P is a phosphoinositide primarily synthesized by lipid kinase Vps34 and acts as a master regulator of the endosomal and autophagy pathways. PI3P controls the recruitment of a variety of compartment-specific effectors harboring PI3P binding modules, such as FYVE or PX domains. We found that knocking down/out Vps34 recapitulates salient features linked to AD pathogenesis, namely (i) enlarged endosomes; (ii) aberrant endosomal trafficking and processing of the amyloid precursor protein (APP); and (iii) accumulation of autophagy substrates. Additionally, work from others shows that chronic lack of Vps34 in neurons produces neurodegeneration. Altogether, our results have identified PI3P deficiency as a key factor in AD pathogenesis. This proposal focuses on addressing the consequences of disrupting PI3P signaling on two processes that emerge as critical in AD pathogenesis, namely the endosomal trafficking and processing of APP (Aim 1) and neuronal autophagy (Aim 2). It will also assess the impact of PI3P deficiency on the Aß and Tau pathologies in vivo (Aim 3). We anticipate that our studies will provide key insights into the biology of APP and Tau as well as a better understanding of the role of lipid dysregulation in AD pathogenesis.

Lay Summary

Lipid dysregulation is believed to play an important role in the pathogenesis of Alzheimer’s disease (AD). Our lipidomic analyses of brain tissue derived from mouse models of AD and AD-affected individuals have identified phosphatidylinositol-3-phosphate (PI3P) deficiency as a candidate lipid alteration involved in AD pathogenesis. The goal of the proposed studies is to test the role of PI3P and a key enzyme mediating its synthesis, Vps34, in the traffic of amyloid precursor protein and the clearance of tau aggregates.

Further information available at:

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