Role of LDLR in regulating metabolism of Apolipoprotein E and Amyloid-beta

https://neurodegenerationresearch.eu/survey/role-of-ldlr-in-regulating-metabolism-of-apolipoprotein-e-and-amyloid-beta/

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Country

USA

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Role of LDLR in regulating metabolism of Apolipoprotein E and Amyloid-beta

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NIH (NIA)

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15/09/2016

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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

PROJECT SUMMARY/ABSTRACT Apolipoprotein E (ApoE) genotype is the strongest genetic risk factor for Alzheimer’s disease (AD). Prevailing evidence suggests that ApoE isoforms affect amyloid ? (A?), tau, neuroinflammation, and synaptic plasticity. In addition to isoforms, alteration in ApoE protein levels has been shown to influence neuroinflammation and A? clearance. Previously, we reported the critical roles of ApoE receptor, low density lipoprotein receptor (LDLR), in regulating ApoE clearance and A? levels in the brain. Overexpression of LDLR in the brain dramatically inhibits amyloid formation by decreasing ApoE level and increasing A? clearance. These beneficial effects were seen with as little as just 2-fold over-expression of LDLR. However, translating these observations into therapy has been hampered by a poor understanding of cellular and molecular mechanism and a paucity of effective approach to regulate the levels of LDLR in the brain. To overcome this critical barrier, we propose to investigate cellular mechanism by which Inducible Degrader Of LDLR (IDOL) regulates LDLR, ApoE, A?, and tau. In collaboration with Dr. Tontonoz (HHMI, UCLA), we found that global deletion of IDOL gene dramatically increases LDLR levels and decreases apoE levels in the brain. IDOL is an E3 ubiquitin ligase that ubiquitinates LDLR and targets it for degradation. Importantly, loss of IDOL expression significantly reduced amyloid plaque burden and ameliorated neuroinflammation in an AD mouse model. Based on these strong preliminary data, we now propose to determine the cellular and molecular mechanism by which IDOL affects ApoE and A? using primary cells isolated from global and conditional knockout IDOL mouse model. We hypothesize that the beneficial effect of IDOL deletion is mediated through LDLR-mediated ApoE level reduction and ApoER2- mediated Reelin signaling. To test hour hypothesis, we will apply innovative methods, such as molecular dynamics simulation, in vivo stable isotope pulse chase mass spectrometry, and in vivo A? and cytokines microdialysis. Deciphering IDOL pathway in cellular details may help better understanding ApoE signaling in basic biology and AD.

Lay Summary

PROJECT NARRATIVE Alzheimer’s disease is clinically characterized by progressive memory loss and pathologically characterized by the accumulation of toxic protein. In this project, we propose to study role of a lipid regulating protein in cognition and toxic protein aggregation. Our study may offer novel mechanistic insights into Alzheimer’s disease pathogenesis.

Further information available at:

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Investments > €500k

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