The role of TREM1 signaling in the development of Alzheimer’s disease

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Principal Investigators

ANDREASSON, KATRIN I.

Institution

STANFORD UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

The role of TREM1 signaling in the development of Alzheimer’s disease

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NIH (NIA)

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1

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Alzheimer's disease & other dementias

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Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Immune System... Neurodegenerative... Neurosciences

Research Abstract

Title and Abstract The role of TREM1 signaling in the development of Alzheimer’s disease Abstract Recent systems biology studies and GWAS have confirmed a dominant role of microglial immune responses in increasing risk of late onset Alzheimer’s disease (LOAD). In parallel, studies in AD model mice demonstrate that healthy microglial function is lost with advancing amyloid pathology, and suggest that disease-modifying components of the innate immune response could be targeted to slow or halt disease progression. In recent transcriptome studies of AD model mice, we identified TREM1 as a gene highly induced in microglia and highly correlated with microglial maladaptive responses. TREM1, and its anti-inflammatory relative TREM2, both signal through DAP12, an adapter signaling protein that was recently identified in gene regulatory network analyses as a top regulator of immune genes involved in increased risk of AD. Moreover, published data in peripheral models of inflammation demonstrate a pivotal role of TREM1 in amplifying toxic aspects of the innate immune response and worsening disease progression and outcome. Recent genetic studies of the TREM1 locus demonstrate an intronic variant in TREM1 that is associated with increased CERAD pathology and cognitive decline. In this proposal, we will test the role of TREM1 in worsening microglial immune responses in models of AD. TREM1 is an inflammatory membrane receptor that is expressed on myeloid lineage cells. TREM1 is unique in its function as a potent amplifier of inflammatory responses where it generates a severe pro-inflammatory response only in association with activation of classical pattern recognition receptors. Here, we will test the hypothesis that in the development of AD, TREM1 induces a maladaptive microglial immune response to accumulating Aß peptide assemblies that accelerates synaptic and neuronal injury and behavioral impairment. We will use a combination of in vitro pharmacologic and in vivo conditional knockout strategies in AD model mice to test this hypothesis. Our studies will determine whether TREM1 amplifies the maladaptive microglial response to accumulating Aß peptides, and whether TREM1 may represent a novel immune target to slow progression to AD at pre-clinical and early clinical stages.

Lay Summary
Project Narrative RO1 Disrupted function of microglia, the immune cells of the brain, contributes to the development of Alzheimer’s disease. Identification of key immune pathways mediated by microglia may lead to novel preventive and therapeutic approaches. The research objective of this proposal is to examine the role of microglial TREM1 signaling in models of AD.

Further information available at:

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Investments > €500k

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