Mechanism of IL-1 Dependent A-beta Plaque Clearance in Alzheimers Disease

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Country

USA

Title of project or programme

Mechanism of IL-1 Dependent A-beta Plaque Clearance in Alzheimers Disease

Source of funding information

NIH (NIA)

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01/04/2007

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8

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)... Biotechnology... Brain Disorders... Dementia... Immune System... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Neuroinflammation has long been recognized as a consistent component of Alzheimer's disease (AD) pathology. Our understanding of neuroinflammation's involvement in AD pathogenesis has evolved: for years it was believed to drive plaque and tangle pathology and contribute to neurodegeneration; however, recent evidence reveals a complex role for neuroinflammation. Indeed, our own findings suggest that chronic neuroinflammation associated with AD is important for control of A¿ accumulation. In studies supported by this grant we found that sustained interleukin-1 (IL-1) expression led to significant reduction of plaque pathology in APP/PS-1 mice and was associated with accumulation of microglia around plaques rather than changes in A¿ processing. We have further data that the process does not depend on recruitment of peripheral CCR2 expressing myeloid cells. Instead, we find that sustained IL-1 expression leads to an accumulation of arginase-1 positive microglia that arise from local microglia, and which appear to have the capacity to phagocytize aggregated A¿; Preliminary data also suggests that IL-4 is elevated in our chronic model of neuroinflammation. Together, these findings support the new hypothesis that chronic neuroinflammation arising from sustained IL-1 expression in AD reduces plaque accumulation through IL-4 dependent alternative activation of endogenous microglial cells. Additional studies in the 3xTgAD and JNPL3 mouse models reveal a negative impact of IL-1 expression on tau pathology and suggest the hypothesis that the chronic neuroinflammatory response to amyloid, which helps to control plaque accumulation, leads to enhanced tau pathology. This differential effect of chronic neuroinflammation on pathological processes in AD may help to explain the disappointing results of clinical studies aimed at modulating inflammation for AD therapy. However, they suggest the possibility that components of chronic neuroinflammation can be selectively modulated to reduce plaque accumulation without affecting tau phosphorylation. To explore these ideas we will: 1) Verify the involvement of alternatively activated, arginase-1 positive microglia in amyloid clearance, in APP/PS-1 mice with chronic neuroinflammation. We will also determine the origin of arginase-1 positive cells in our model system. 2) Characterize the molecular and cellular environment following sustained IL-1 expression to better understand the balance between pro- and anti-inflammatory cytokines, chemokines, and cellular changes associated with chronic neuroinflammation and carry out similar studies with human AD tissues. In addition, we will identify the cellular source of IL-4 by overexpressing IL-1 in an IL-4 reporter mouse. 3) Assess the requirement of IL- 4 for alternative activation and amyloid phagocytosis following sustained IL-1 expression in APP/PS-1 mice with a targeted deletion of IL-4, and by expressing IL-4 in APP/PS-1 mice. 4) Utilize an IL-4 expression vector in the 3xTgAD mouse to determine whether amyloid clearance occurs without increased tau phosphorylation. Together these aims will help us to better understand the role of chronic neuroinflammation in modulating the two hallmark pathologies of AD. Moreover, they also test a possible strategy for therapeutic intervention that selectively targets amyloid plaque clearance. This may ultimately represent a more selective approach than current immune-based therapies for AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's Disease is a devastating neurodegenerative disorder that affects millions of older Americans and currently costs the country upwards of $200 billion dollars. Brain inflammation, which is always seen as part of the disease, has been therapeutically targeted in the past with little evidence of direct benefit. More recently we have come to realize that brain inflammation can play a protective role in Alzheimer's disease. This grant proposal explores a cell type that appears to confer protection and the signals that

regulate it. Information gained in these studies will impact our current understanding of brain inflammation in Alzheimer’s disease and may allow us modulate beneficial immune pathways to help patients with the 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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