Actions of Nuclear Receptors on TREM2+ myeloid cells and microglia in AD brain

https://neurodegenerationresearch.eu/survey/actions-of-nuclear-receptors-on-trem2-myeloid-cells-and-microglia-in-ad-brain/

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Contact information of lead PI
Country

USA

Title of project or programme

Actions of Nuclear Receptors on TREM2+ myeloid cells and microglia in AD brain

Source of funding information

NIH (NIA)

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€ 1,817,660.55

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01/04/2016

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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... Genetics... Immune System... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): This application is focused on the delineation of the functional differences in the biology of two distinct lineages of myeloid cells which coinhabit the Alzheimer's disease (AD) brain and together constitute the innate immune system in this organ. We provide preliminary data demonstrating that plaque-associated myeloid cells, which were historically presumed to be brain resident microglia, are in fact derived from peripheral blood borne monocytes which infiltrate the AD brain and subsequently acquire certain features shared with the resident microglia. Remarkably, the ability of monocytes to invade the brain is reliant upon Trem2 expression. Variant forms of Trem2 confer greatly increased risk for AD. It is the infiltrating monocytes which are the predominant plaque-associated cell type and exhibit a robust proinflammatory phenotype but are unable to mount an effective phagocytic response directed to amyloid deposits in the AD brain. In contrast, the endogenous microglia do not appear to accumulate on plaques and in the absence of TREM2 expression have an `alternative activation' phenotype. This application arises from a fundamental rethinking of how the different myeloid lineage cells participate in the disease process, which new data suggest involves two quite distinct types of responses. The phenotypic status of myeloid cells is subject to regulation by a related family of type II nuclear receptors which serve as master regulators of their phenotype, suppressing inflammatory gene expression and promoting tissue repair and phagocytosis. This application has as a primary goal to ascertain if the salutary effects of nuclear receptor agonists in AD pathogenesis arise from the selective action of these drugs on either the infiltrating monocytes, promoting their entry and actions within the brain, and /or promoting an anti-inflammatory, tissue repair phenotype in resident microglia. The principal goal of Aim 1 is to use contemporary genetic mouse models that selectively express fluorescent markers in blood borne inflammatory monocytes to definitively establish the peripheral origins of the plaque-associated cells and to determine the effect of nuclear receptor activation on their entry and persistence in the AD brain. The primary objective of Aim 2 is to ascertain if the different lineages of monocytes and microglia confer different gene expression profiles and if nuclear receptor activation elicits the same or different transcriptional responses. Moreover, activation of each of the nuclear receptors elicits the conversion of myeloid cells in the brain ino an `alternative activation' phenotype. Our objective is to identify a panel of genes that are activated in common by the nuclear receptors that are responsible for the phenotypic conversion. In Aim 3, we will test the normal roles of nuclear receptor-regulated genes in the two lineages by abrogating nuclear receptor action by inactivating RXR?, the common type II nuclear receptor subunit, in either monocytes or in microglia in the 5XFAD mice and determine their contributions to ameliorating AD pathogenesis.

Lay Summary

PUBLIC HEALTH RELEVANCE: This application is focused on understanding the biological basis of Alzheimer's disease. Specifically, the study explores the biology of myeloid cells in the AD brain based on new understanding that both microglia and cell derived from blood borne monocytes are present in the AD brain. This application investigates how a newly recognized class of drugs can act on the myeloid cells in the brain to ameliorate AD pathogenesis and provide potential new therapeutic approaches for the treatment of AD

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:
Alzheimer's disease & other dementias

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2016

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