Targeting the hematopoietic system: the role of hematopoietic growth factors in restricting A-beta accumulation in Alzheimers disease

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Country

USA

Title of project or programme

Targeting the hematopoietic system: the role of hematopoietic growth factors in restricting A-beta accumulation in Alzheimers disease

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NIH (NIA)

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30/09/2016

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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... Immune

System... Neurodegenerative... Neurosciences... Stem Cell Research

Research Abstract

Abstract Alzheimer’s disease (AD), a rapidly growing health problem in the United States, has created serious public and personal crises at both medical and financial levels. Developing therapeutic strategies for AD is of critical importance, as no cure is currently available. Accumulation of ?-amyloid (A?) in the CNS has been proposed to play a causative role in the pathogenesis of AD. Dysfunction of the innate immune system for A? clearance is crucially involved in cerebral A? deposition and in pathological progression. The resident microglia and bone marrow-derived monocytes/macrophages (BMDMs) are the key innate immune cells to clear A? in the CNS. During disease progression, microglia turn to a pathological phenotype and fail to clear A?. BMDMs show robust effects in A? elimination, revealing a target for developing A? clearance therapies for AD. In fact, the hematopoietic system for generating BMDMs is defective in AD patients. BMDMs as well as stem cell factor (SCF) and granulocyte-colony stimulating factor (G-CSF) are significantly reduced in AD patients. SCF and G- CSF are the essential hematopoietic growth factors that regulate blood cell generation. Critically, elucidating the role of SCF and G-CSF in generating BMDMs and in restricting A? accumulation may help in developing a cure for AD. We have recently discovered that SCF+G-CSF not only enhances BMDM generation but it also increases BMDM recruitment and enhances BMDM phagocytosis of A?, and ultimately induces long-term effects in A? reduction and cognitive improvement in APP/PS1 mice, a mouse model of cerebral amyloidosis. The objective of this project is to define how SCF+G-CSF regulates BMDMs to restrict A? accumulation and improve cognitive function in APP/PS1 mice. We hypothesize that the SCF+G-CSF-increased A? clearance in the brain with amyloidosis is coordinated through the enhancement of BMDM generation, of BMDM recruitment, and of BMDM function in A? removal. Using approaches ranging from molecular biology to live brain imaging, this hypothesis will be tested through the following 3 Aims: Aim 1 will determine how SCF+G- CSF enhances BMDM production in APP/PS1 mice, Aim 2 will examine how SCF+G-CSF regulates entry of BMDMs into the brains of APP/PS1 mice, and Aim 3 will define how SCF+G-CSF increases BMDM uptake of aggregated A?. Through these 3 Aims, the interaction between BMDM-related A? removal and neuroinflammatory changes will also be examined. We expect these studies to define the mechanisms underlying the SCF+G-CSF-increased A? clearance and cognitive improvement. This project is innovative in the unique approach, originally developed by our group, of targeting the hematopoietic system to enhance BMDM-mediated A? removal by SCF+G-CSF. This study is significant as it will shed light on how SCF+G-CSF ameliorates the defective innate immune system in the AD-like condition to reduce A? load. Importantly, this research could be readily translated into clinical trials because SCF+G-CSF therapy has been approved by the FDA for bone marrow stem cell recovery after chemotherapy in cancer patients.

Lay Summary

Public Health Relevance/Project Narrative This study highlights an important but less-investigated research field, the hematopoietic system—a system that generates scavenger cells for robust removal of amyloid-beta deposits in the brain is impaired in Alzheimer’s patients. We have recently discovered a unique approach to repair the hematopoietic system. The mechanistic understanding how this approach restricts amyloid-beta accumulation in the brain will facilitate the development of a new therapy for treatment of Alzheimer’s disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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N/A

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N/A