Molecular mechanisms in progranulin deficient frontotemporal dementia

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Country

USA

Title of project or programme

Molecular mechanisms in progranulin deficient frontotemporal dementia

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NIH (NIA)

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Basic Behavioral and Social Science... Behavioral and Social Science... Brain Disorders... Dementia... Frontotemporal Dementia (FTD)... Immune System... Neurodegenerative... Neurosciences... Rare Diseases

Research Abstract
? DESCRIPTION (provided by applicant): Frontotemporal dementia (FTD) is the second most common dementia syndrome in the elderly, and the most common for people under 65 years. There are currently no treatments. Loss-of-function mutations in the progranulin (PGRN, GRN) gene are an important cause of familial frontotemporal lobar degeneration with TAR DNA-binding protein 43 (TDP-43)-positive inclusions (FTLD-TDP). The underlying mechanisms are largely unknown. PGRN in the brain is expressed in neurons and microglia. PGRN-deficient mouse models exhibit FTD-related behavioral deficits. One of the major pathologies is altered innate immune responses, in the forms of exacerbated microglial activation and elevated inflammatory responses associated with NF-kappaB hyperactivation. Our recent published study showed that selective reduction of microglial PGRN markedly enhances amyloid beta (Abeta) deposition, mostly likely via impairing phagocytosis, and exacerbates Abeta toxicity in Alzheimer’s disease (AD) mouse models. In preliminary studies, we showed that selective deletion of PGRN in adult microglia recapitulates the FTD-like behavior alterations observed in Grn-/- mice. These studies strongly support the importance of microglial PGRN in balancing innate immune response and maintaining cognition in aging brain. Besides altered innate immune response, mice lacking PGRN also exhibit an early onset of lipofuscinosis reminiscent of that in lysosomal storage diseases. Based on these findings, we hypothesize that PGRN deficiency-induced endolysosmal dysfunction underlies aberrant microglial activation, leading to FTD- related dysfunction in circuits and cognition. Three Aims are proposed to test this hypothesis. Aim 1 is designed to determine decisively if GRN haploinsufficiency leads to endolysosomal dysfunction in human iPSC-derived neurons with GRN mutations and isogenic controls. Unbiased proteomic and pathway analyses will also be performed to probe the underlying mechanisms. In Aim 2, we will test the hypothesis that PGRN deficiency-induced endolysosmal dysfunction underlies hyperactive NF-kappaB signaling, leading to microglial dysfunction. Specifically, we will determine if PGRN deficiency impairs endocytic turnover of innate response receptors and intracellular NF-kappaB signaling molecules. We will also determine if inactivating IkappaB kinase beta in PGRN deficient microglia restores microglial function. In Aim 3, we will address how PGRN-deficient microglia lead to FTD-like cognitive deficits. Based on our preliminary studies, we will focus on medium spinal neurons (MSNs) in striatum, which exhibited elevated excitability in Grn-/- mice. Hyperactivity of MSNs has been associated with compulsive behaviors often observed in FTD patients. We will determine if PGRN-deficient microglia are sufficient to induce alterations in striatal circuits, and if selectiv inactivation of NF-kappaB rescues cognitive and circuit deficits induced by PGRN-deficient microglia. Completion of the aims will yield fundamental insights into the role of innate immunity in FTD-related behavioral disturbance and circuit dysfunction, which could lay the foundation for development of disease-modifying therapies for FTD patients.

Lay Summary
PUBLIC HEALTH RELEVANCE: This project aims at investigating mechanisms underlying frontotemporal dementia associated with progranulin deficiency. This study may provide new

therapeutic avenue for treating this devastating disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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2016

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