Understanding the molecular functions of progranulin and granulin in FTLD

https://www.neurodegenerationresearch.eu/survey/understanding-the-molecular-functions-of-progranulin-and-granulin-in-ftld/

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Contact information of lead PI
Country

USA

Title of project or programme

Understanding the molecular functions of progranulin and granulin in FTLD

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,579,303.67

Start date of award

15/09/2015

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

granulin, PGRN gene, Frontotemporal Lobar Degenerations, protein TDP-43, Lysosomes

Research Abstract

? DESCRIPTION (provided by applicant): Despite recent progress, it remains unclear how progranulin deficiency leads to development of the neurodegenerative disease frontotemporal

lobar degeneration (FTLD). Progranulin is cleaved into multiple granulin peptides that are bioactive and may functionally oppose the progranulin holoprotein. Many believe that progranulin deficiency equally depletes progranulin and granulin levels yet this has never been directly measured. Fundamental knowledge gaps also exist regarding when, why and where progranulin is cleaved into granulins, what molecular functions progranulin and granulin play and how much progranulin and granulin are found in human CNS. The long-term goal of this research program is to understand how progranulin and granulins contribute to the pathophysiology of neurodegenerative disease. The overall objective of this application is to utilize C. elegans and human post-mortem tissue to understand progranulin cleavage into granulins, to determine the molecular function of the holoprotein and its cleavage products and to characterize the down- stream effects of progranulin mutations in human disease. The central hypothesis is that the cleavage of progranulin into granulins is tightly regulated in a temporal and spatial manner because the two species play reciprocal roles in stress response with progranulin being protective and granulins being toxic. The rationale for this work is that understanding the function and production of progranulin and granulins is critical to safely targeting these molecules in the treatment of FTLD and other disease. It will also provide fundamental new knowledge regarding the links between stress response, lysosome biology and neurodegeneration. The central hypothesis will be tested through three specific aims: 1) elucidate the timing, localization and proteases responsible for cleavage of progranulin into granulins in vivo, 2) identify the molecular mechanisms by which full- length progranulin promotes and cleaved granulins impair stress response, 3) determine the effects of disease and progranulin mutations on progranulin/granulin levels in human CNS tissue. Strong preliminary data sup- ports these proposed studies, including demonstration that progranulin protects against and granulins impair stress response and that progranulin production and cleavage increase with age and stressful stimuli. Two sets of novel anti-granulin antibodies (specific to either C. elegans or human granulins) have been generated for these studies. Additionally, a novel protocol for isolating intact lysosomes from C. elegans will be utilized. The proposed research is innovative because it seeks to directly implicate granulin toxicity, rather than or in addition to progranulin deficiency, as the driving force in neurodegeneration related to progranulin mutations. This contribution is significant because in order to understand progranulin haploinsufficiency and the consequences of progranulin replacement therapy, one must understand the normal biological functions and relative levels of both progranulin and granulins.

Lay Summary

PUBLIC HEALTH RELEVANCE: The proposed research is relevant to public health because, as our population ages, the financial and societal burden of neurodegenerative diseases will greatly expand over the coming decades. This proposal seeks to understand the functions, regulation and levels of progranulin and granulin, which will have several positive impacts, including understanding of potential negative consequence of progranulin replacement strategies and identification of novel targets for drug therapy in frontotemporal dementia, Alzheimer Disease and Parkinson Disease. The proposed research is relevant to the NIH’s mission of extending healthy life and reducing the burdens of illnesses like neurodegeneration, since its findings can be rapidly translated to mammalian systems.

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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