Function of TMEM106B in neurodegeneration

https://neurodegenerationresearch.eu/survey/function-of-tmem106b-in-neurodegeneration/

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Country

USA

Title of project or programme

Function of TMEM106B in neurodegeneration

Source of funding information

NIH (NIA)

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01/08/2014

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

PGRN gene, Frontotemporal Lobar Degenerations, Lysosomes, Nerve Degeneration, Neuronal Ceroid-Lipofuscinosis

Research Abstract
DESCRIPTION (provided by applicant): Lysosomal dysfunction has been implicated in many neurodegenerative diseases, including adult onset Alzheimer’s and Parkinson’s diseases. Several lines of evidence point to lysosomal dysfunction as a critical disease mechanism in frontotemporal lobar degeneration with ubiquitin positive inclusions (FTLD-U)-the most prevalent

early onset dementia after Alzheimer’s disease. The haplo- insufficiency of the Progranulin (PGRN) gene has been identified as a major cause of FTLD-U, and patients with homozygous PGRN mutations develop neuronal ceroid lipofuscinosis (NCL), a lysosomal storage disorder. This suggests that PGRN plays a central role in regulating lysosomal function. Other genes mutated in FTLD-U-VCP/p97 and CHMP2B-also regulate endolysosomal trafficking. Further, TMEM106B, a newly identified genetic risk factor for FTLD-U with PGRN mutations, is a lysosomal membrane protein, and increased TMEM106B levels result in lysosomal dysfunction and increased risk for FTLD-U. Our research will examine the physiological functions of TMEM106B in lysosomes and their role in neurodegeneration. In Aim1, we will use molecular and cell biological approaches to determine how TMEM106B regulates lysosomal activities and lysosomal dynamics. Potential TMEM106B binding partners will also be tested for their function in lysosomes. In Aim2, we will probe cellular mechanisms that regulate TMEM106B levels and function. In particular, our research will examine the role of regulated intramembrane proteolysis (RIP) and ubiquitination. In Aim3, we will compare the in vitro and in vivo phenotypes of elevated TMEM106B levels in wild type and PGRN deficient conditions using virus mediated gene delivery to mimic FTLD-U cases. We will also explore the effect of TMEM106B on PGRN metabolism. These proposed studies will shed light on TMEM106B function in lysosomes and cellular pathways that regulate TMEM106B. We hope this research will illustrate the interaction between TMEM106B and PGRN in FTLD-U and provide the foundation for FTLD-U therapeutics. Importantly, this work will also generate broader insights into the regulation of lysosomal function that may be applied in a variety of other neurodegenerative diseases.

Lay Summary

PUBLIC HEALTH RELEVANCE: We aim to determine the physiological functions of TMEM106B, a newly identified risk factor for Frontotemporal Lobar Degeneration with protein aggregates containing TDP-43 (FTLD-U). Function of TMEM106B in the lysosomes, regulation of TMEM106B by cellular pathways and the interaction between TMEM106B and Progranulin, the main gene mutated in FTLD-U, will be studied.

Further information available at:

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Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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