Role of LIPL-4 in lysosomal lipolysis and aging

https://neurodegenerationresearch.eu/survey/role-of-lipl-4-in-lysosomal-lipolysis-and-aging/

Principal Investigators

LAPIERRE, LOUIS RENE

Institution

BROWN UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Role of LIPL-4 in lysosomal lipolysis and aging

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 908,030.28

Start date of award

01/02/2015

Total duration of award in years

4

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)... Biotechnology... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Translational Research

Research Abstract

PROJECT SUMMARY Dysfunctions in the autophagy/lysosomal pathway are pathologically significant in the development of age-related diseases, such as neurodegeneration. In C. elegans, several longevity models rely on increased autophagy for lifespan extension,

suggesting a critical role for autophagy in aging. Animals can also enjoy longer lifespan when the nutrient-sensor TOR, a negative regulator of autophagy, is inhibited. Nonetheless, how autophagy mediates its beneficial effects is poorly understood. We recently reported that autophagy could be induced by over-expressing the putative lysosomal lipase LIPL-4, which resulted in a significant lifespan extension, enhanced lipolysis and altered TOR signaling, suggesting a link between lipid metabolism, autophagy and aging. LIPL-4 displays strong homology with human lysosomal acid lipase (LAL), a key enzyme in the hydrolysis of cholesterol via autophagy. Notably, impaired LAL-mediated cholesterol processing has been linked to the development of Alzheimer's disease. My new results show that over-expressing LIPL-4 ameliorates A? toxicity in a C. elegans model of Alzheimer's disease. Therefore, this proposal will test the hypothesis that LIPL-4, similar to LAL, mediates lysosomal lipid hydrolysis and will aim to elucidate how LIPL-4 modulates autophagy and mitigates A? toxicity. In Aim 1, I will confirm the intracellular site of action of LIPL-4 and determine its relationship to TOR signaling. In Aim 2, I will test whether LIPL-4 and LAL are functionally interchangeable in C. elegans. The mechanism of action by which LIPL-4 induces autophagy and modulates aging will also be elucidated. In Aim 3, I will investigate how LIPL-4 mediates a delay in the onset of Alzheimer's disease in C. elegans. I will also perform a high-throughput screen (HTS) to discover novel and specific candidate that activates LAL-mediated lipolysis, as a strategy against neurodegeneration. By determining the role of lysosomal lipolysis in aging, my proposal will provide a basis on which novel drugs can be discovered to prevent Alzheimer's disease. The 2-year postdoctoral K99 phase will consist in the characterization of the role of LIPL-4 in lysosomal function, lipid metabolism and aging. Cell-based assay reporter systems compatible with HTS will be used to find novel drugs to enhance LAL expression. The 3-year independent R00 phase will serve to further understand the role of LIPL-4 in lysosomal lipolysis, lipid signaling and aging and expand into studies on lipid dynamics, metabolism and proteostasis. Lead candidate activators of LAL will be validated using Alzheimer's disease model in C. elegans and cell culture models. This proposal includes cutting-edge approaches, such as proteomic analyses, CARS microscopy and HTS combined with the innovative use of disease models in C. elegans. In summary, the K99/R00 grant represents a unique opportunity for me to learn new technologies and develop my professional skills to successfully transition into an independent scientist in aging research.

Lay Summary

PROJECT NARRATIVE The benefit of the autophagy/lysosome pathway on longevity is well documented, yet how this process prevents aging is poorly understood. This proposal investigates the role of LIPL-4 in lysosomal lipolysis and aging in C. elegans and evaluates the potential of activating lysosomal lipolysis to protect against neurodegeneration. These studies have the potential to lead to new treatments for Alzheimer's disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A