Proteostasis in the aging and Alzheimers disease brain: are the ATases novel targets?

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Principal Investigators

PUGLIELLI, LUIGI

Institution

UNIVERSITY OF WISCONSIN-MADISON

Contact information of lead PI
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USA

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Proteostasis in the aging and Alzheimers disease brain: are the ATases novel targets?

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NIH (NIA)

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01/09/2016

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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... Genetics... Neurodegenerative... Neurosciences

Research Abstract

Project Summary Due to the increased lifespan of our population, problems linked to age-associated disabilities are becoming more important. In particular, the disability for cognitive loss and dementia combined is currently the second most expensive among medical conditions. Aging is also the most important risk factor for sporadic Alzheimer's disease (AD). Autophagy is an essential component of the cell degrading machinery. It helps dispose of large toxic protein aggregates that form within the cell. Malfunction of autophagy contributes to the progression of many chronic age-associated diseases. Studies in mouse models of aging and AD suggest that improving proteostatic functions by stimulating autophagy can be beneficial. As such, resolving age- and disease-associated proteostasis dysfunctions as well as improving normal proteostasis mechanisms is an active target for biomedical research and a key focal area for aging research. N?-lysine acetylation is an essential post-translational modification. For more than forty years it was assumed that lysine acetylation could only occur in the cytosol and nucleus. However, in 2007, we reported the transient lysine acetylation of endoplasmic reticulum (ER) cargo proteins. Subsequent studies revealed that the ER has two acetyltransferases (ATase1 and ATase2) as well as a membrane transporter (AT-1) that translocates acetyl- CoA into the ER lumen. Here, we report that N?-lysine acetylation in the ER lumen regulates normal proteostasis of the secretory pathway. Consistently, by targeting the ER acetylation machinery, we were able to rescue the phenotype of a mouse model of AD, but not Huntington disease or amyotrophic lateral sclerosis. These results were obtained by using a mouse model of reduced acetylation (generated in our laboratory) as well as biochemical inhibitors that target the ATases (identified in our laboratory). The general hypothesis of this research is that functional characterization of the biochemical and biological roles of ATase1 and ATase2 will help us dissect important molecular aspects of the cognitive decline that characterizes aging and AD; a corollary hypothesis is that ATase1 and ATase2 are valid targets to improve proteostatic functions of the secretory pathway during aging and AD. Specific Aim 1 will elucidate the mechanisms responsible for the transcriptional regulation of ATase1 and ATase2 during aging and AD. Specific Aim 2 will identify structural and enzymatic features (structural biochemistry) of the ATases that can be used for translational purposes. Specific Aim 3 will target the machinery down-stream of ATase1 and ATase2 to understand how they regulate the induction of autophagy and the disposal of toxic protein aggregates. Together, Aims 1-3 will dissect the biological and biochemical roles of the ATases as a function of age and AD neuropathology, and will identify new structure-specific inhibitors to improve proteostatic functions of the brain. These Aims include a combination of structural biochemistry as well as molecular and biophysical strategies. Finally, Specific Aim 4 will use newly developed mouse models and new ATase-specific inhibitors to determine therapeutic potential.

Lay Summary

Project Narrative This grant targets ATase1 and ATase2, two Endoplasmic Reticulum (ER)-based acetyltransferases. Both aging and Alzheimer's disease (AD) are characterized by dysfunctional proteostatic functions that lead to aberrant accumulation of toxic protein aggregates. Here, we show that inhibition of the ATases improves proteostatic functions of the brain and rescues the AD-like phenotype in the mouse. By studying their biochemistry and structural biology, we have obtained novel information that can be used for translational purposes. The long-term objective of this proposal is to dissect important molecular aspects of the cognitive decline that characterizes aging and AD and target the ATases to improve proteostatic functions of the secretory pathway during aging and AD.

Further information available at:

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Investments > €500k

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United States of America

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