Presenilin1/g-secretase regulate miRNAs and neuronal survival

https://www.neurodegenerationresearch.eu/survey/presenilin1-g-secretase-regulate-mirnas-and-neuronal-survival/

Principal Investigators

ROBAKIS, NIKOLAOS K

Institution

ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI

Contact information of lead PI
Country

USA

Title of project or programme

Presenilin1/g-secretase regulate miRNAs and neuronal survival

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,579,584.40

Start date of award

01/08/1988

Total duration of award in years

27

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

Research Abstract
DESCRIPTION (provided by applicant): Research in the last decade indicates that reduced

cerebral glucose utilization is an early sign of AD that correlates with clinical progression of th disease. In vivo imaging studies indicate severe reduction of glucose metabolism in regions of the AD brain affected at early stages of the disease such as hippocampus, entorhinal formation and temporal cortex. Reduction in brain glucose metabolism is also observed in familial AD (FAD) patients and may occur years before disease onset in carriers of presenilin-1 (PS1) FAD mutations implicating PS1 in the regulation of brain metabolic activity. Glucose deprivation leads to neuronal death, a process associated with expression changes of genes involved in neuronal survival. In recent years a new mechanism of transcriptome regulation via the action of microRNAs (miRs) has emerged. MiRs are short, non-coding RNAs that suppress gene expression by post-transcriptional mechanisms including destabilization and inhibition of translation of mRNAs. By regulating gene expression, miRs regulate physiological processes including neuronal survival, synaptic plasticity and memory and emerging evidence supports a role for miRs in neurodegenerative disorders. We obtained evidence that the PS1/?-secretase system regulates the expression of miR-212 that targets the mRNA of PED/PEA-15 (PEA15), a protein known to promote cell survival under reduced glucose. We also observed that absence of PS1 sensitizes neurons to glucose deprivation and correlates with increased expression of neuronal miR-212 and decreased levels of both PEA15 mRNA and protein. Furthermore, we obtained evidence that PS/?-secretase regulate neuronal survival by controlling the expression of miR-212. Based on our data, we hypothesize that the increased expression of miR-212 and the resultant decrease in PEA15 contribute to the increased vulnerability displayed by PS1 null neurons under reduced glucose. Importantly, in this submission, we present new data that downregulation of neuronal PS1 with siRNA technology increases miR-212 and decreases PEA15 indicating PS1 controls a cascade that regulates production of cell survival factor PEA15. Here we examine the relationship between PS1, miR-212 and its target protein PEA15 and test their effects on neuronal survival under stress conditions. In addition, we ask how the ?-secretase function affects miR-212 and PEA15 and whether PS1/?-secretase modulate the glucose deprivation-induced survival signaling of PEA15. We also ask whether expression of miR-212 and its target PEA15 protein changes in brains of AD patients and in FAD mutant knockin animal models. Our data may indicate whether PS1 promotes neuronal survival by controlling the PS1/miR- 212/PEA15 cascade and whether antagonists of miR-212 rescue neurons from stress-induced death.

Lay Summary

PUBLIC HEALTH RELEVANCE: Glucose metabolism plays crucial roles in neuronal function and survival and evidence suggests that abnormalities in glucose metabolism play important roles in Alzheimer’s disease (AD). We found that PS1, a protein involved in AD, suppresses miR-212 thus increasing the levels of pro-survival factor PED/PEA-15 and promoting neuronal survival under glucose deprivation. Here we will examine mechanisms by which the PS1/?-secretase system regulates miR-212 and PED/PEA-15 and how this factor promotes neuronal survival under stress conditions. We will also ask whether expression of miR- 212 and PED/PEA-15 change in brains of sporadic and familial AD patients. Our data may indicate whether antagonists of miR-212 will promote neuronal survival under stress conditions. If successful, this work could benefit millions of people.

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