Molecular interplay between A?, tau and mTOR: Mechanisms of neurodegeneration

https://neurodegenerationresearch.eu/survey/molecular-interplay-between-a-tau-and-mtor-mechanisms-of-neurodegeneration/

Principal Investigators

ODDO, SALVATORE

Institution

ARIZONA STATE UNIVERSITY-TEMPE CAMPUS

Contact information of lead PI
Country

USA

Title of project or programme

Molecular interplay between A?, tau and mTOR: Mechanisms of neurodegeneration

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,791,915.60

Start date of award

01/08/2011

Total duration of award in years

7

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... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): Converging data suggest that in Alzheimer's disease (AD), the accumulation of amyloid-? (A?) and tau leads to a progressive deterioration of memory and other cognitive functions. However, the molecular pathways linking the buildup of A? and tau to cognitive deficits remain elusive. During the current grant cycle, we have shown that the mammalian target of rapamycin (mTOR) is hyperactive in neurons and astrocytes of human AD cases and in animal models of AD. We found that reducing mTOR signaling improved AD-like pathology in mice by restoring deficits in protein synthesis and by increasing A? and tau turnover. Furthermore, our preliminary data suggest that hyperactive mTOR signaling contributes to neurodegeneration in AD by facilitating necroptosis, a programmed form of necrosis. This novel and exciting finding may answer a key, and yet unresolved question: which mechanisms govern cell loss in AD. The overall hypothesis of this application is that hyperactive mTOR contributes to AD pathogenesis by disrupting protein homeostasis in neurons and glia leading to cell loss. To this end, we propose three Specific Aims. Specific Aim 1 will test the hypothesis that hyperactive S6K1, a downstream effector of mTOR, contributes to AD pathogenesis by altering protein translation. Our preliminary data implicate S6K1 hyperactivity as a previously unidentified mechanism underlying synaptic and cognitive deficits in AD. Indeed, reducing S6K1 hyperactivity improves AD-like pathology in 3xTg-AD mice. Here we will use complementary approaches to dissect the mechanisms downstream of mTOR/S6K1 that link this pathway to AD pathogenesis. Specific Aim 2 will test the hypothesis that hyperactive mTOR contributes to neurodegeneration in AD by facilitating necroptosis. Our preliminary data indicate that necroptosis, a programmed form of necrosis, contributes to neurodegeneration in AD. Consistent with our hypothesis, data from the literature show that mTOR plays a key role in regulating necroptosis. To test our hypothesis, we will systematically modulate necroptotic signals in animals and cells with different levels of mTOR activity. Specific Aim 3 will test the hypothesis that hyperactive mTOR in astrocytes contributes to A? accumulation, cognitive dysfunction, and neurodegeneration. Our preliminary data show that mTOR is hyperactive in astrocytes of AD mice as well as of human AD cases. This is extremely exciting not only because mTOR regulates the scavenger functions of astrocytes but also because activated astrocytes are known to secrete toxic factors that may induce necroptosis. We will use newly developed genetic tools to modified mTOR in animal models of AD and in human primary astrocytes isolated from human AD cases. Taken together, the experiments proposed in this application will identify the mechanistic links among mTOR, A? and tau accumulation, as well as neurodegeneration and cognitive deficits. Furthermore, given the role of mTOR signaling in aging, our results may unveil new mechanisms by which aging contributes to the development of AD. Elucidating these mechanisms will likely identify several novel putative therapeutic targets.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is the most common form of dementia among the elderly and the sixth leading cause of death in the United States. This application aims at identifying the molecular bases underlying cognitive deficits in AD. Elucidating these mechanisms will likely highlight several novel and clinically translatable targets; thus, that data obtained here will aid in the development of new treatment for AD.

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