Targeting a Novel Regulator of Brain Aging and Alzheimers Disease

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Country

USA

Title of project or programme

Targeting a Novel Regulator of Brain Aging and Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 4,455,363.30

Start date of award

15/09/2014

Total duration of award in years

3

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)... Behavioral and Social Science... Biotechnology... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences... Translational Research

Research Abstract

DESCRIPTION (provided by applicant): This R01 grant proposal is in response to RFA-AG-13-013 “”Interdisciplinary Approach to Identification and Validation of Novel Therapeutic Targets for Alzheimer’s Disease””. The aging of the brain is a cause of cognitive decline in the elderly and the major risk factor for Alzheimer’s disease (AD). Despite this central role in disease, the molecular underpinnings of brain aging and the transition from normal to pathological aging are poorly understood. The overall goal of this proposal is to gain new insights into healthy brain aging and the transition to AD by exploring the role of a newly identified neuroprotective regulatory network. We have recently discovered that the master developmental regulator REST/NRSF is induced in the aging human brain and together with HDAC1 coordinates the expression of a gene network that may protect aging neurons from neurotoxic stress, synapse loss and overexcitation. This pathway regulates the expression of a large number of genes in the aging brain that are involved in cell death, inflammation, oxidative stress and AD pathology. Induction of REST correlates with preservation of cognitive function during aging, whereas loss of function is associated with onset of cognitive decline in patients with mild cognitive impairment. REST function is almost completely abrogated in affected brain regions in AD. Our preliminary results implicate this pathway in the regulation of two major cell types in the aging brain, neurons and microglia. The studies in this proposal seek to elucidate the regulatory role of the REST network in protecting aging neurons from age-related stressors, reducing neuroinflammation and preserving cognitive function using REST and HDAC1 conditional knockout mice. New high-sensitivity transcriptome sequencing technology together with informatics analysis using tools from the Personal Genome Project will be used to define the REST-regulated gene network. By applying this systems genetics approach to well-characterized human brain samples from the Religious Orders study, we will attempt to define REST-regulated gene networks predictive of successful aging, early cognitive decline and AD. A central question is how this gene network systematically fails in individuals who develop AD, and whether this decline can be reversed. The discovery that REST can be activated through stimulation of Wnt signaling using known drugs, as well as newly identified small molecule agents, raises the exciting possibility that the aging brain could be protected by a novel therapeutic approach based on activation of the REST network. These studies will bring together three principal investigators and many collaborators with diverse but complementary areas of expertise in a multidisciplinary approach to understand the transition from normal brain aging to AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: We have identified a novel regulator of brain aging and Alzheimer’s disease that may protect the brain from neurodegeneration, inflammation and cognitive decline. This proposal will explore the role of the REST- regulated gene network in brain aging and Alzheimer’s disease. Using a directed drug screening approach, we will attempt to identify novel therapeutic agents that can activate this neuroprotective pathway at early stages of cognitive decline.

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