Role of microRNA-33 in Alzheimers disease

https://neurodegenerationresearch.eu/survey/role-of-microrna-33-in-alzheimers-disease/

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Country

USA

Title of project or programme

Role of microRNA-33 in Alzheimers disease

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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)... Biotechnology... Brain Disorders... Dementia... Genetics... Neurodegenerative... Neurosciences

Research Abstract

PROJECT SUMMARY/ABSTRACT Mounting evidence suggests that microRNA (miRNA) dysregulation may contribute to psychiatric disorders and neurodegenerative disorders. Although modulations of miRNA function have generated promising clinical data for several

diseases, miRNA’s role in Alzheimer’s disease (AD) has not been investigated thoroughly. Apolipoprotein E (ApoE) genotype is the strongest genetic risk factor for AD. In addition to ApoE isoform, alterations in ApoE levels and lipidation status have been shown to influence A? aggregation. We and others reported the critical roles of ATP-binding cassette transporter A1 (ABCA1) in regulating ApoE lipidation and A? levels in the brain and its therapeutic potential. Increasing evidence suggests that neuroinflammation plays a critical role in AD pathogenesis. Therefore, targeting inflammatory pathways is an emerging therapeutic strategy, along with the direct targeting of ApoE/A? pathway, for AD therapy. Recently, we found that miR-33 gene deletion significantly increases ABCA1 levels and soluble A? clearance, leading to reduction of soluble A? levels in the brain of APP/PS1 mouse model. We also identified that miR-33 regulates neuroinflammation by directly targeting transforming growth factor ? (TGF?) receptor 1 (TGF?R1) gene. Here, we now seek to define the role of miR-33 in ApoE and Amyloid ? (A?) metabolism in mice (Aim 1) and neuroinflammation (Aim 2). In Aim 1, we will use ABCA1 knockout and ApoE knockout mice along with miR-33 knockout mouse models. In Aim 2, we will use TGF?R1 knockout mouse model. Importantly, we demonstrated that antisense oligonucleotide (ASO)-based pharmacological inhibition of miR-33 efficiently increases ABCA1 levels and reduces soluble A? levels in the brain. In Aim 3, we will assess the effect of long-term treatment of anti-miR-33 ASO on A? deposition, neuroinflammation, and behavior in mice. We will assess the preventive and therapeutic effect by treating anti-miR-33 ASO before and after the development of A? plaques and memory deficits in APP/PS1 mice.

Lay Summary
PROJECT NARRATIVE Alzheimer’s disease is clinically characterized by progressive memory loss and pathologically characterized by the accumulation of toxic protein. In this project, we propose to study role of a newly discovered biomolecule, microRNA, in cognition and toxic protein aggregation. Our study may offer novel mechanistic insights into Alzheimer’s disease pathogenesis.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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