Administrative Supplement: Neurobiological role of MicroRNA in Alzheimers

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Country

USA

Title of project or programme

Administrative Supplement: Neurobiological role of MicroRNA in Alzheimers

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01/09/2015

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2

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... Translational Research

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer's disease (AD) is the most common cause of dementia in the elderly. Because current treatments provide modest symptomatic relief and do not slow AD progression, a better understanding of molecular bases of AD pathology is needed. This proposal will identify and validate microRNAs (miRNAs) as a new class of drug targets. miRNAs are endogenous, short, non-coding RNAs that typically inhibit protein expression by interacting with specific recognition elements of target transcripts. AD is believed to result from overproduction of amyloid-ß peptide (Aß), derived from Aß precursor protein (APP), and dysregulation of proteins involved in Aß production (e.g. APP, ß-secretase/BACE1) contributes to excess Aß deposition. We have also recently found that miRNA can stimulate APP expression in interaction with iron homeostasis. We propose to study APP and BACE1 regulation by miRNA. We hypothesize specific miRNAs regulate endogenous levels of APP and BACE1, are dysfunctional in AD, and manipulation will reduce Aß. Specific Aim 1(SA1) will identify functional miRNA target sites in APP and BACE1 and validate miRNA post-transcriptional regulation of native APP and BACE1 expression. Rationale: Discover functional miRNA targets in UTRs of APP and BACE1 transcripts using. Endpoints are APP and BACE1 mRNA & proteins, and Aß peptides, which we predict to change with miRNA. Impact: Manipulation of miRNA regulation is a novel therapeutic approach and may be feasible for correcting gene dysregulation in AD. SA2 will test physiological interactions between miRNA validated in SA1 and their regulatory networks over APP and BACE1 expression. Rationale: Test other mechanisms of regulation likely linked to maintain homeostasis of APP, BACE1 and Aß. Identifying roles of miRNA in this network is vital to pharmacologically target miRNA-transcript interactions. Impact: Reveal novel mechanisms for miRNA function in AD. SA3 will assess effects of in vivo manipulation of validated miRNA in AD animal models. Rationale: Test our validated miRNAs as therapeutic targets in AD transgenic animals, including interaction with iron homeostasis, by inducing miRNA-dependent changes in translation. Impact: Validate specific miRNAs as drug targets in vivo and identify novel AD-related regulatory networks. SA4 will examine whether miRNAs implicated in regulatory control of gene products involved in Aß homeostasis are dysregulated in AD patients. Rationale: In SA1-3, we will identify pertinent miRNAs that modulate expression of gene products implicated in Aß production. If these miRNAs are also involved in AD pathology, we expect their regulation to vary in anatomical- and pathology-dependent patterns. Impact: Further demonstrate validity of miRNAs as therapeutic targets to treat AD-related dysregulation. Research dictated by our central hypothesis could cause a significant paradigm shift on the field by elucidating novel regulatory mechanisms and identifying specific miRNAs that regulate important gene products implicated in AD. Final impact will be in eventual use of these new drug targets to produce therapeutic agents to slow or halt progression in AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is the most common cause of dementia in the elderly, but current treatments provide only modest symptomatic relief and do not slow disease progression. We propose to employ microRNA (miRNA) to study novel mechanisms that regulate amyloid-ß (Aß) precursor protein (APP) and ß-secretase (or BACE1) as well as their associated pathways. MiRNAs are short, non-coding RNAs that typically regulate protein levels by inhibiting translation of messenger RNA. The significance of this proposal is that miRNA regulation of APP represents a novel strategy to reduce toxic Aß peptide levels and restore AD-associated dysregulation in the brain; the proposed work will identify and validate members of a new class of drug targets, and the impact of this work will be eventual

use of these new drug targets to generate better therapeutic agents to slow or reverse disease progression in AD.

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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2016

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