microRNA-758-3p in cognition and Alzheimers disease

https://www.neurodegenerationresearch.eu/survey/microrna-758-3p-in-cognition-and-alzheimers-disease/

Principal Investigators

KIM, JUNGSU

Institution

MAYO CLINIC JACKSONVILLE

Contact information of lead PI
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1

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Research Abstract

? DESCRIPTION (provided by applicant): 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. Here, we seek to define the role of miR-758 in cognition and Amyloid ? (A?) metabolism. A? peptide is known to impair synaptic functions, contributing to cognitive dysfunction in a manner that depends on the cAMP responsive element binding protein (CREB) signaling pathway. CREB is a transcriptional master regulator of synaptic plasticity and neuronal survival. In support of the notion that dysregulation of CREB is a key event underlying A?-mediated synaptic deficits and memory loss, we found that CREB levels in the frontal cortex of AD patients are dramatically decreased. Activation of the CREB pathway has been shown to confer resistance to A?-mediated synapse loss and restores learning and memory functions in APP transgenic mouse models. Apolipoprotein E (APOE) genotype is the strongest genetic risk factor for AD. Lipidation of ApoE by ATP- binding cassette transporter A1 (ABCA1) is known to facilitate A? clearance. Previously, we demonstrated that only a two-fold overexpression of ABCA1 is sufficient to increase ApoE lipidation and decrease A? accumulation by more than 60% in an APP mouse model. Therefore, identifying regulatory mechanisms of CREB and ABCA1 expression may provide new therapeutic targets for AD. Using unbiased miRNA screening, we identified miR-758 as one of the most significantly upregulated miRNAs by A?42. Most interestingly, miR- 758 expression levels are ~100-fold higher in the brain than in most other organs and our innovative systems biology approach indicates that neuronal function and survival pathways are the most significantly enriched functional groups among miR-758 targets. More specifically, we identified CREB and ABCA1 as direct targets of miR-758. In this application, we propose to investigate the role of miR-758 in cognition and Alzheimer’s disease by using primary neuronal cells (Aim 1) and an APP knock-in mouse model (Aim 2). Because APP knock-in mouse model expresses human APP at physiological level under the control of endogenous regulatory sequences, it is an ideal model to study synaptic plasticity affected by A? and CREB. We will determine whether overexpression of miR-758 impairs learning and memory and trigger neuronal cell death by downregulating CREB. If so, this mouse line will be a valuable model system to test neuroprotective therapeutics in vivo, overcoming the lack of overt cell death in most APP transgenic mouse models. We also aim to determine whether inhibition of miR-758 activity can be a novel therapeutic strategy by increasing CREB and ABCA1 levels. Collectively, this work will facilitate our understanding of microRNAs in cognitive function and A? metabolism and may spur further interest in non-coding RNAs and other epigenetic factors.

Further information available at:

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