The Role of Drosha in the Pathogenesis of Alzheimers Disease

https://www.neurodegenerationresearch.eu/survey/the-role-of-drosha-in-the-pathogenesis-of-alzheimers-disease/

Principal Investigators

MAO, ZIXU

Institution

EMORY UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

The Role of Drosha in the Pathogenesis of Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,958,082.57

Start date of award

01/08/2016

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

MicroRNAs, Biogenesis, Alzheimer's Disease, Ribonuclease III, MAPK14 gene

Research Abstract

Neurons are highly sensitive to changes in their environment, and have developed dynamic adaptive processes to sense and copy with stress caused by such changes. The long-term goal of our research is to understand the mechanisms by which neurons respond to stress. MiRNAs

(microRNAs) are a recently discovered class of non-coding small RNAs that are involved in regulating many cellular processes including stress. Dysfunction of miRNAs has been implicated in many pathological processes. MiRNA biogenesis is controlled by several tightly coupled sequential steps governed by multiple protein complexes and subjected to intricate regulation. The entire process is initiated in the nucleus by the conversion of the long primary miRNA transcripts to the hairpin structured precursor miRNA (pre-miRNAs) by the RNase III enzyme Drosha. Whether Drosha itself is a direct regulatory target is unknown. A growing body of data suggests that stress conditions and miRNAs are highly intertwined at several levels. However, signals and pathways directly modulating Drosha under either physiological or pathological stress condition remain to be identified. There are multiple lines of evidence indicating that miRNAs are especially important to the brain function and modulate pathways and key genes relevant to genetic and sporadic AD pathogenesis. Many of these miRNAS are themselves altered in AD. Furthermore, inhibiting miRNA biogenesis by conditionally knocking out Dicer in neurons, which blocks miRNA biogenesis at a step downstream of Drosha, causes mice to develop progressive neurodegeneration and AD-like tau hyperphosphorylation. This offers perhaps the strongest evidence for a potential link between miRNA biogenesis and AD. However, how these findings translate into animal AD models and human disease remains to be tested. Recently, we have revealed that a variety of stress conditions exert a direct and tight control of Drosha. This involves a stress-induced, p38 MAPK dependent phosphorylation and inhibition of Drosha, and loss of Drosha triggers cell death under stress (Molecular Cell in press). In a series of preliminary studies, we have extended this set of key findings to primary cortical neurons and shown that a) stress signals cause p38 MAPK-mediated direct phosphorylation and inhibition of Drosha in neurons; b) A? appears to engage this pathway and reduces the level of Drosha in primary cortical neurons; c) increasing Drosha protects neurons from A?-induced toxicity; and d) the levels of the nuclear Drosha are significantly reduced in the cortex of a transgenic AD rat and the postmortem AD brains. Together, these highly significant findings support an intriguing hypothesis that A? signals via p38 MAPK-Drosha pathway to inhibit miRNA biogenesis and interfere neuronal homeostasis and survival. Loss of Drosha may underlie in part the neurodegenerative process in AD. We propose to use a combination of molecular and cellular methods to assess whether loss of Drosha underlies A?-induced toxicity and pathogenesis using cultured primary neurons, a new established rat model of Alzheimer's disease, and human postmortem AD brains.

Lay Summary

Project Health Relevance Statement: Chronic neurodegenerative disorders including Alzheimer's and Parkinson' diseases are characterized by the loss of specific populations of brain cells but how toxic stress leads to this loss is complex and not well understood. MiRNAs play important roles in maintaining cellular homeostasis and are known to respond to cellular stress. Our study will delineate a critical link between miRNA biogenesis and Alzheimer's disease relevant stress-induced toxicity in neurons, and establish its role in the pathogenic process of the disease.

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