# microRNA (miRNA) signaling in Alzheimers disease(AD)

https://neurodegenerationresearch.eu/survey/microrna-mirna-signaling-in-alzheimers-diseasead/

**Principal Investigators**

LUKIW, WALTER J

**Institution**

LSU HEALTH SCIENCES CENTER

**Contact information of lead PI**
**Country**

USA

**Title of project or programme**

microRNA (miRNA) signaling in Alzheimers disease(AD)

**Source of funding information**

NIH (NIA)

**Total sum awarded (Euro)**

€ 1,674,311.93

**Start date of award**

01/08/2011

**Total duration of award in years**

6

**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**

microRNA (miRNA) signaling in Alzheimer’s disease (AD) Through extensive miRNA- and DNA-

based expression array-, LED-Northern-, ELISA, Western-, immunological and bioinformatics-based analysis we have discovered a highly interactive network of NF-kB sensitive, up-regulated pro-inflammatory microRNAs (miRNAs) and their down-regulated messenger RNA (mRNA) targets and the proteins these mRNAs encode in sporadic Alzheimer's disease (AD) brain. The up-regulation of these pathogenic miRNAs and their down-regulated mRNA targets has been further analyzed in stressed human brain cells in primary culture and in 5xFAD amyloid over-expressing transgenic mouse lines. Through miRNA and mRNA abundance analysis, miRNA-mRNA complementarity mapping, association energy (EA) indexing, ELISA and Western analysis we can explain much of the observed neuropathology characteristic of the AD process by analyzing significant disruptions in selective miRNA-mRNA signaling. Our hypothesis is that there exists a small family of at least 6 critical pro-inflammatory miRNAs in AD brains responsible for targeting and down-regulating a group of pathogenic messenger RNA (mRNA) targets responsible for amyloidogenesis, tau pathology and neuroinflammation with accompanying deficits in synaptogenesis, innate- immunity, phagocytosis and a progressive impairment in A?42 peptide clearance. This renewal of our previous 5 year NIA R01 will investigate the integrated actions of this group of 6 pro-inflammatory, pathogenic miRNAs up-regulated in sporadic AD brain, in stressed human brain cells in primary culture in the brains of 5xFAD mice. The 6 up-regulated pro- inflammatory microRNAs to be studied in detail are miRNA-7, miRNA-9, miRNA-34a, miRNA-125b, miRNA-146a and miRNA-155. Stressors will be those encountered as are found in aging AD brain – these include reactive oxygen species (ROS), the pro-inflammatory cytokines IL-1? and TNF? and A?42 peptides. Specific Aim 1 will analyze the contribution of these factors in moderate-to- advanced sporadic AD and Down's syndrome (DS) brain; Specific Aim 2 will analyze the contribution of these factors in stressed human brain cells, i.e. in neuronal-glial primary cell co- cultures; Specific Aim 3 will analyze the contribution of these factors in 5xFAD amyloid over- expressing transgenic mouse lines. We will specifically accentuate the study of the most up- regulated miRNAs: miRNA-7, miRNA-9, miRNA 34a and miRNA-146a and their targeted disruption of UBE2A (ubiquitin conjugase protein) and TREM2 (triggering receptor expressed in microglial cells) signaling in AD brain, and in in vitro and in vivo AD models. We will also analyze the applicability of selective NF-kB inhibitors and anti-miRNA (AM) strategies in restoring homeostasis in this system. Our long term goal is the therapeutic manipulation of these miRNA-regulated epigenetic pathways to provide an efficacious treatment for the clinical management of AD at an early stage.

**Lay Summary**

Project Narrative microRNA (miRNA) signaling in Alzheimer's disease (AD) To this date research from our lab and others indicates that because sporadic Alzheimer's disease (AD) is a uniquely human brain disease, the use of human (non-transformed) primary cell lines, humanized murine transgenic models for AD (Tg-AD) and short post-mortem interval (PMI) human AD and age-matched control brains of anatomical areas targeted by the AD process (such as the hippocampus and association neocortex) using as control an internal brain region (such as the thalamus and/or brainstem in the same brain) will yield the most relevant molecular-genetic and gene expression applicable to our understanding of the sporadic AD process. To this end our work has been carried out exclusively in cultured human brain cells (chiefly primary neuronal-astroglial co-cultures) that have been stressed with AD-relevant stressors [such as reactive oxygen species (ROS), IL-1?, TNF?, A?42 peptides and AD extracts], in short PMI AD and control tissues (anatomical regions targeted by AD) and in transgenic murine amyloid over-expressing AD models with particular focus on the murine 5xFAD Tg-AD model; through the

integrated analysis of over 160 early- and moderate-to-advanced sporadic AD brain samples, extensive human brain cell primary cultures and 5xFAD analysis we have identified a small up-regulated family of 6 inducible, NF-kB-regulated, miRNAs and have characterized the down-regulation of the expression of a 10-member messenger RNA (mRNA) group which is targeted by these up-regulated miRNAs. These miRNA-mRNA signaling data are the most extensive ever compiled for high quality short PMI sporadic AD brains; the data reveal a highly interactive, pathogenic gene regulatory signaling network which explains virtually all of the neuropathology of the AD brain that once begun, appears to be self- perpetuating due perhaps to chronic re-activation of NF-kB (p50/p65); inhibition of the NF-kB initiator(s) or individual blocking of the pathogenic induction of these 6 miRNAs using an anti-miRNA approach should re- establish brain cell homeostasis, provide novel therapeutic strategies and ultimately be of highly effective use in the clinical management of AD.

**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