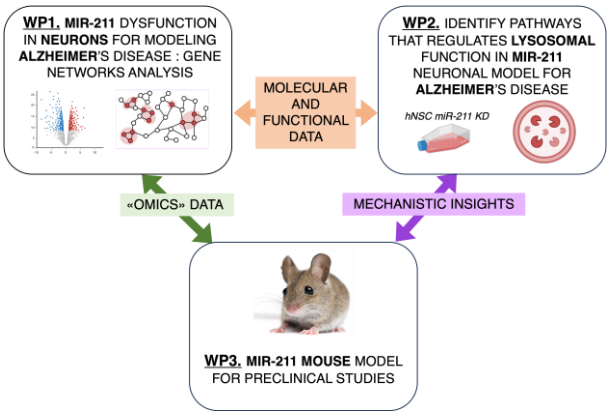
Project title: The role of miR-211 in neuronal aging: From Disease Mechanisms to Therapy



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Description:

Growing evidence suggests that altered ubiquitin-proteasome function may cause an age-related buildup of toxic debris, leading to neuronal dysfunction and loss, which contribute to neurodegenerative disorders like Alzheimer's disease (AD). AD is marked by amyloid-β plaques, leading to neuron death and cognitive decline. These aggregates are primarily removed by autophagy, which is impaired in AD. Recent studies identified miR-211 as a key factor in AD and that autophagy in neurons is post-transcriptionally regulated by a gene network employing miR-211/Ezrin axis. In miR-211-deficient mice, impaired lysosomal degradation leads to amyloid plaque accumulation.

Aims:

We aim to demonstrate that targeting the miR-211/Ezrin axis can restore autophagy and offer therapeutic potential for AD. The project will focus on the following aims: 1) miR-211 dysfunction in human Neural Stem Cells (hNSC)-derived neurons for modeling AD: building a pathological signature of AD gene network by omics analysis. 2) identifying the signaling pathways that regulate lysosomal function in a miR-211 in hNSC-derived model for AD. 3) generation of a miR-211-/- mouse model for AD preclinical studies.

Expected results:

The expected outcomes will help develop a new combinatorial diet/drug therapy for AD. This project will address key questions: How do miR-211-regulated molecular networks relate to neuronal aging and AD? Can nutrition slow AD progression? Do autophagy-inducing drugs enhance amyloid-β degradation and treat AD? Using molecular biology, "Omics", biochemical, computational, and imaging techniques, the project will make a concerted interdisciplinary effort to provide answers to these questions.

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