MicroRNA modulation of tau expression and phosphorylation in tauopathy

https://neurodegenerationresearch.eu/survey/microrna-modulation-of-tau-expression-and-phosphorylation-in-tauopathy/

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MicroRNA modulation of tau expression and phosphorylation in tauopathy

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Alzheimer's disease & other dementias

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Research Abstract

Intracellular accumulation of hyperphosphorylated misfolded tau proteins is one of the main hallmarks in many neurodegenerative diseases. Hence, knowledge and understanding of

disease mechanisms that impact tau production and accumulation, altering overall tau proteostasis is critical. Recently, abnormalities in microRNAs (miRNAs) have been linked to neurodegeneration. However, the extent to which dysregulation of miRNAs directly alters tau proteostasis by modifying tau expression, phosphorylation or both is currently unknown. Each miRNA is capable of binding to and silencing many target transcripts, providing an additional level of regulation that complements canonical transcriptional pathways. We have recently found in autopsy brain tissue that miR-219 is downregulated in Alzheimer disease (AD) compared to controls. Using mammalian cell cultures and a novel transgenic Drosophila model, we have also found that miR-219 directly binds to the tau mRNA 3? untranslated region (UTR) and silences its expression at the post-transcriptional level. Strikingly, our bioinformatics analysis indicates miR-219 is also predicted to target Calcium/calmodulin-dependent protein kinase 2 gamma subunit (CAMK2?), Tau tubulin kinase 1 (TTBK1) and Glycogen synthase kinase 3 beta (GSK3?), which are all implicated in the generation of abnormal hyperphosphorylated tau. The interaction between microRNAs and tau/tau kinases 3? UTR and its implication in the regulation of tau expression, phosphorylation and overall tau proteostasis in vivo and the influence of this interaction on the disease will be assessed in three specific aims in this application. In Aim 1, we will determine in primary hippocampal cultures the extent to which miR-219 modulates (i) the synthesis of potential miR-219 targeted kinases (i.e. CAMK2?, TTBK1, GSK3?) and (ii) tau phosphorylation and cell toxicity. In Aim 2 we will investigate the role miR-219 plays in the post-transcriptional regulation of tau and tau kinases in both wild type and in the htau transgenic mice. In Aim 3 we will determine the extent to which tau/ tau kinases 3? UTR-microRNA interactions influence tau toxicity and neurodegeneration in the transgenic hTau model of AD tau pathology. This proposal is innovative because looking at miRNA regulation has forced a re-assessment of gene expression that will provide a new perspective on the pathogenesis of AD and related tauopathies as well as will provide a new framework and new models to investigate mechanisms of tau proteostasis regulation and toxicity. Together, these studies will help us address the critical need of understanding the earliest events in AD and help pave the way towards future strategies to address AD with miRNA-based biomarkers and therapeutics.

Lay Summary
This proposal focuses on characterizing microRNA-mediated regulatory post-transcriptional mechanisms that modulate tau proteostasis and toxicity by controlling tau expression and phosphorylation. The insights gained will provide novel entry points into the etiology, diagnosis and treatment of Alzheimer disease and the related dementias.

Further information available at:

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