Conditional deletion of Mapt in the adult mouse brain

https://www.neurodegenerationresearch.eu/survey/conditional-deletion-of-mapt-in-the-adult-mouse-brain/

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Research Abstract

? DESCRIPTION (provided by applicant): Specific protein inclusions define most neurodegenerative diseases at the pathological level. The conversion of soluble to insoluble filamentous tau protein is central to many human neurodegenerative diseases such as Alzheimer disease (AD), frontotemporal dementia and parkinsonism-17 (FTDP-17T), Pick disease, Argyrophilic grain disease, Corticobasal degeneration, among many others. Multiple studies have looked at the biochemical basis of tau aggregation and its role in

neurodegenerative diseases by analyzing Mapt mutations associated with FTDP-17T. More recently, an interest in tau-targeted treatments has been growing because of the central role of tau in neurodegeneration and the discovery of abnormal tau propagation through the brain. Therefore, tau may be an excellent potential therapeutic target for many neurodegenerative diseases. Since tau aggregation is energetically unfavorable and concentration dependent, a reduction of tau concentration is an attractive treatment approach that might be achieved through decreased tau expression. As no conditional Mapt knockout mice have yet been reported, it is unclear if tau is critical for normal neuronal function in vivo, and whether reducton of tau in adult individuals may be well tolerated. The animal models generated in this application will allow investigators to solve this problem, with the long term goal of developing some form of prevention of tau aggregation and propagation in tauopathies by a mechanism-based therapy. In order to test our hypothesis, our specific aims are: Specific Aim 1: To generate conditionally knock-out (cKO) Mapt mice, and determine the consequences of Mapt gene knock-out in discrete cell populations of the CNS of adult mice. We hypothesize that lower overall tau protein levels in a potentially therapeutically productive way may be beneficial for patients with tauopathies. Knock-out (KO) models of Mapt have been developed, but they show adaptive responses, and cannot be used as models for Mapt KO in adult individuals. We will generate cKO tau mice and investigate for the first time the biological consequences of the loss of function of tau in vivo in adult mice using our “”floxed”” Mapt mice in combination with transgenic mice expressing the CreERT2 protein under the control of specific promoters. This approach is particularly appealing since the mice will have allele deletion only at the desired time/brain area which may avoid confounding issues such as developmental compensation. These animals will allow the testing of abnormal tau propagation through the brain and whether therapeutic approaches aimed at reducing (or eliminating) tau expression are viable approaches for patients with tauopathies.

Further information available at:

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