E. Reilly Helm, L3[1]

Chunlai Wu[2], Nathan Le[2], Elizabeth Reilly Helm[1], Lauren E. Meyer[1] and Xiaolin Tian[2]

[1]LSU Health Sciences Center, New Orleans, LA, 2LSUHSC Neuroscience Center of Excellence
Department of Cell Biology and Anatomy

"Mouse Expression of ANKHD1 and Its Protective Role in Human Tauopathies"

Background: Tauopathies are neurodegenerative diseases characterized by abnormal filamentous tau protein accumulation. The hallmark Alzheimer's disease, a tauopathy, is neurofibrillary tangles (NFT) composed of tau filaments and Aβ deposits. The mutated tau proteins are hyperphosphorylated, making them less soluble and leading to the aggregation and deposition of aberrant tau in the hippocampus. When the human P301S mutant tau protein was expressed and studied in transgenic mice, it provided evidence of synaptic gliosis at 3 months of age and neuronal dysfunction and NFT formation at 6 months of age. These findings suggest that a neuroinflammatory response leading to synaptic dysfunction occurs earlier in the disease process of tauopathies, well before the observed aggregation of mutated tau. In previous studies done in Drosophila, the expression of Mask, an Ankyrin repeat and KH domain containing protein, suppresses the neuronal degeneration induced by the accumulation of mutated tau. This study focuses on the ability of ANKHD1, the human homolog of Mask, to modulate neuropathology and cognitive functions in the mouse models for AD.

Methods: We generated a Cre-inducible ANKHD1-expressing transgenic mouse line that allows neuronal specific expression of ANKHD1 in a Cre-dependent manner. This transgenic line was then combined with the PS19 transgenic mouse model that expresses the TauP301S mutant Tau protein in neurons. Imaging and molecular and histopathological analysis was performed in cultured cells and mouse brain slices. Whole animal behavior tests were performed to determine the ability of ANKHD1 to modify neurodegeneration in the mouse brain.

Results: Quantifications and comparisons of markers for neuropathological gliosis between the control (PS19) mice and the PS19-ANKHD1 mice showed a statistically significant ($p<0.05$) reduction of hyperphosphorylated Tau at 6 months of age in the PS19-ANKHD1 mice. At 9 months, there is also a statistically significant increase in the novel object recognition index in the female PS19-ANKHD1 mice compared to the control mice.

Conclusion: ANKDH1, a human homolog of the Drosophila Mask gene, is indicated to suppress pathogenic tau protein accumulation seen in the mouse model for the Tau related Alzheimer's dementia. The expression of ANKHD1 in transgenic mouse lines suppresses the hyperphosphorylation of tau and the gliosis associated with tauopathies in the mouse brain. Additionally, there is evidence that expression of ANKDH1 can partially restore cognitive functions. These findings set a foundation for the development of therapeutic strategies for AD and for research that would unravel the molecular mechanisms through which ANKHD1 confer neural protective effects.