Behavioral and cell-based complementary screens to identify druggable targets modulating tau protein levels

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Research Abstract

? DESCRIPTION (provided by applicant): Evidence from a number of neurodegenerative proteinopathies, including Alzheimer’s disease (AD), indicates that the levels of disease-specific proteins are important in pathogenesis. This is sustained by observations in animal models as

well as genomic analysis of human patients. Interestingly, decreasing the levels of the disease driving proteins can delay and even reverse neurodegeneration in animal models. Especially relevant to AD is the fact that reducing the levels of tau in mouse models ameliorates not only tau- induced deficits, but also the neuronal dysfunction triggered by amyloid-? (A?). Therefore decreasing tau levels can mitigate the deleterious effects induced by the two key pathogenic players in AD. Despite this therapeutic potential, little is known about the specific genes that modulate endogenous tau protein levels in neurons. We believe that harnessing these genes as therapeutic targets to decrease endogenous tau levels in patients could delay the onset and progression of AD, even in patients with the more common sporadic forms. Here we propose complementary screens of the “”druggable”” genome to identify targets that can attenuate tau-induced neuronal dysfunction by lowering endogenous tau levels. For this, we will first use a behavioral readout to screen for modifiers in vivo using a Drosophila model expressing human tau. Behavioral assays can reveal genes that attenuate not only tau-induced cell loss, but also the neuronal dysfunction that precedes it, therefore identifying ideal targets for early therapeuti intervention. Hits from this behavioral screen will then be tested in a high-throughput, FACS-based cell assay, to identify the targets that can decrease the levels of human tau. This two-step screen not only takes advantage of the strengths inherent to each of the systems used, but also decreases significantly the amount of false positives. Finally, we will validate the best hits from the above complementary screens using shRNAs and pharmacologic inhibitors. We will assess their potential to decrease endogenous tau levels in human cells of neuronal lineage and in mouse primary neuronal cultures. The confidence in this strategy is backed by our recent work. First, we have successfully applied a similar approach to the neurodegenerative disorder SCA1 and discovered that genetic and pharmacologic inhibition of the MAPK/MSK1 pathway reduces ATXN1 levels and toxicity in Drosophila, cells and mice. Second, we have carried out a pilot “”kinome”” screen with the same tau Drosophila model and cell lines that we will use for the work proposed here. This screen has identified eight kinases not previously known to regulate tau levels. The proposed work will pave the road for future mouse work. It will produce a number of druggable targets with high translational value and potential for early intervention. For these targets we will have shRNAs ready for AAV mediated viral delivery into the mouse brain (for validation), and a number of pharmacologic inhibitors for preclinical assessment.

Further information available at:

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