PERK Inhibition in rTg4510 mouse model of tauopathy rescues impairment through eIF2α-independent pathway

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Background: The unfolded protein response (UPR) is vital for maintaining homeostasis during conditions of endoplasmic reticulum (ER) stress. However, prolonged UPR activity causes cellular dysfunction and death. Chronic activation of the Protein Kinase R-like ER Kinase (PERK) pathway of the UPR has been documented in many tauopathies; however, the mechanism by which the PERK pathway causes neuronal dysfunction in these diseases remains unknown.

Hypothesis: Tau mediates neuronal dysfunction through the PERK pathway, and inhibition of this pathway rescues impairment observed in the rTg4510 mice.

Methods: rTg4510 tau transgenic mice were treated with a PERK inhibitor (GSK2606414) at 50mg/kg twice daily. Neuronal function was measured using manganese-enhanced magnetic resonance imaging (MEMRI) with quantitative R1 mapping, the anxiety phenotype was measured using the open field behavioral test, tau and active PERK levels were measured using western blot analysis, and other targets of the PERK pathway were measured using immunohistochemistry and real-time PCR.

Results and Conclusions: Here we show that treatment led to improvement of neuronal function measured by MEMRI, reversed the anxiety phenotype observed in the rTg4510 model, and resulted in a significant reduction in hyperphosphorylated tau levels. We also found that PERK inhibition mediated these improvements via an eIF2α-independent mechanism. Our results show a novel mechanism of PERK-mediated tau phosphorylation that potentiates pathogenesis and progression of tau pathology. This study suggests that PERK is a viable therapeutic target to ameliorate neuronal function in tauopathies. Future efforts aim to delineate the mechanism governing the tau- PERK relationship.