Tau-tubulin kinase 1 (TTBK1) expression induces region-specific axonal degeneration and phosphorylation of tau and CRMP2 in AD models

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Background: Rare genetic variations of the human TTBK1 gene are associated with late-onset AD in two cohorts of Chinese and Spanish populations. We have created a transgenic mice model of TTBK1 and reported that TTBK1 is highly expressed in the perforant path, and induces cognitive impairment as a major phenotype.
Hypothesis: We hypothesize that TTBK1 regulates axonal integrity of specific neurons via phosphorylation of microtubule-associated molecules, such as tau and CRMP2.
Results: Transient expression of TTBK1 in SH-SY5Y showed significant phosphorylation of CRMP2 at Ser-522 by CDK5 and Thr-514 by GSK3β. This phosphorylation was accelerated by Aβ42 peptide, and was blocked by over-expression of dominant negative Rho. Furthermore, transient expression of TTBK1 in primary cultured neurons reduced axonal length and branching in a Rho dependent manner. Next, we crossed TTBK1 transgenic mice with Tg2576 expressing mutant APP. APP/TTBK1 double transgenic mice showed severe spatial learning impairment, and somal accumulation of phosphorylated CRMP2 in layer II/III of entorhinal cortex (EC) and dentate gyrus of the hippocampus, suggesting axonal degeneration in the affected regions. CRMP2 binds to tau in a phosphorylation-dependent manner both in vitro and in vivo, suggesting its role in retrograde transport of phosphorylated tau for somal accumulation.
Conclusion: Enhanced TTBK1 expression as seen in AD brain accelerates axonal degeneration in EC and hippocampus, the brain regions physiologically involved in learning and memory and affected in AD brain.