

## **P001** p70 S6 kinase and tau in Alzheimer's disease

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The 70-kDa S6 kinase (p70S6K) is a S/T kinase. *In vitro* experiments showed that p70S6K can phosphorylate tau at S262, S214 and T212 sites seen in Alzheimer's disease (AD) brains. Evidence from AD brains indicated an aberrant accumulation of active p70S6K as well as its up-stream regulator mammalian target of rapamycin (mTOR) in tangle-bearing neurons. Manipulation of p70S6K activity increased level and phosphorylation of tau in different cellular models of AD. Homolog analysis of the first 20 nucleotides of mRNAs encoding proteins such as p70S6K, S6 and tau revealed that the 5' untranslated region of tau mRNA has a 5'-terminal oligopyrimidine tracts (5'TOP)-like structure similar to that of S6 mRNA. A dramatic increase of levels of total tau and S6, but not total p70S6K was seen in both zinc-treated SH-SY5Y cells and AD brains. Global protein translation was not altered in SH-SY5Y cells that were treated with zinc and p70S6 kinase is activated. Taken together, our previous studies suggested that p70S6K is a tau kinase and that mTOR/ p70S6K signaling regulates the translation of a set of 5'TOP-containing mRNAs including tau mRNA rather than an overall protein synthesis. The continual synthesis of tau is probably the primary event prior to the hyperphosphorylation and aggregation of tau in neurons as tangles in AD brains.