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# Alterations in cell cycle profile and cell cycle protein expression in neuroblastoma cells stably transfected with tau protein

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Alzheimer's disease is characterized by extracellular deposition of beta amyloid peptide and intracellular deposition of hyperphosphorylated tau protein in isocortical brain areas. Recently, we and others have shown that vulnerable neurons or tau aggregate-bearing neurons aberrantly express cell cycle proteins namely cdk inhibitors. In order to analyse which factors trigger the aberrant expression of cell cycle proteins we tested whether the intracellular accumulation and hyperphosphorylation of tau protein may contribute to this response. In addition, we wanted to know which alterations in cell cycle dynamics are induced by tau protein overexpression in dividing cells. Therefore, we generated SH-SY5Y neuroblastoma cell lines stably overexpressing wildtype tau or pseudophosphorylated tau mutants and analyzed their cell cycle profile. We found that overexpression of wildtype tau lead to an increase of cells residing in G1-phase and a reduction of cells in G2-phase compared to a vector-only expressing cell line. However, the doubling time of the cell lines was largely unaffected. The same profile was observed for most of the pseudophosphorylated tau proteins and was similar for three-repeat and four-repeat tau protein. Next, using a cDNA array we looked whether these cell cycle changes can be attributed to alterations in gene expression in SH-SY5Y cells. We observed that tau overexpression upregulates neuronal markers (such as L1 NCAM, muscarinic acetylcholine receptor M4), downregulates tumor markers such as several matrix metalloproteinases and changes expression of several cell cycle-related genes such as CKS1, CKS2 and p21waf.

Analysis of protein levels by Western Blotting revealed an upregulation of survivin and p27kip1 which was most pronounced in the wildtype tau expressing cell line. Increased MAPK activity was detected in all tau expressing cell lines.

We showed that tau expression in neuroblastoma cells alters gene expression, leads to an activation of MAPK signal transduction and changes the cell cycle profile. These results suggest a link between tau accumulation and aberrant expression of cell cycle proteins in neurons.