ACCELERATED HUMAN MUTANT TAU AGGREGATION BY KNOCKING OUT MURINE TAU IN A TRANSGENIC MOUSE MODEL


Laboratory of Histology, Neuroanatomy and Neuropathology, Université Libre de Bruxelles, Brussels, Belgium

Numerous neurodegenerative disorders, including Alzheimer’s disease, are neuropathologically characterized by the presence of neurofibrillary tangles (NFT) composed of abnormally hyperphosphorylated and aggregated protein tau. Tau pathology is supposed to play a central pathogenic role in these diseases. Many models of human tauopathies have been produced in mice by expression of a human mutant tau in presence of endogenous murine tau. Since murine tau might interfere with the toxic effects of human mutant tau, we generated a model in which a pathogenic human tau protein is expressed in absence of wild-type murine tau protein. The Tg30 line is a tau transgenic mouse model overexpressing a human 1N4R double mutant tau (P301S and G272V) that develops AD-like neurofibrillary tangles (NFTs) in an age-dependent manner. By crossing Tg30 mice with mice invalidated for their endogenous tau gene, we have obtained Tg30xTau−/− mice that express only exogenous human double mutant 1N4R tau. Whilst Tg30xTau−/− mice express less tau proteins compared to Tg30, they show signs of decreased survival, increased proportion of Sarkosyl insoluble tau in the brain and in the spinal cord, increased number of Gallyas positive NFTs in the hippocampus, increased number of inclusions in the spinal cord and a more severe motor phenotype. In conclusion, deletion of murine tau accelerated tau aggregation during aging of this mutant tau transgenic model, suggesting that murine tau could interfere with the development of tau pathology in transgenic models of human tauopathies.