ANALYZING HIPPOCAMPAL SYNAPTIC DAMAGE AND GLIAL RESPONSE IN A MOUSE MODEL OF TAUOPATHY

JJ. Fernandez-Valenzuela[1], R. Sanchez-Varo[1], V. Navarro[2], S. Jimenez[2], E. Sanchez-Mejias, C. Nuñez-Díaz, A. Gomez-Arboledas, M. Vizuete, J.C.Davila[1], J. Vitorica[2] and A. Gutierrez[1]
[1]Faculty of Sciences, University of Malaga/IBIMA, CIBERNED, Malaga, Spain.
[2]Faculty of Pharmacy, University of Seville/IBIS, CIBERNED, Seville, Spain.

INTRODUCTION

Tau pathology is highly related to synaptic and neuronal loss, leading to cognitive decline and dementia in Alzheimer's disease (AD) and other tauopathies. Tau transgenic mice are widely used to investigate the specific contribution of this protein to AD since they reproduce the synaptic and cognitive dysfunction in parallel to an age-dependent accumulation of hyperphosphorylated forms of tau (phospho-tau). The aim of this study was to investigate the progression of tau aggregation and analyze its relationship with microglial activation and synaptic damage within the hippocampus of a transgenic tau model. 2, 6, 9, 12 and 18 month-old THY-Tau22 transgenic and WT mice were analyzed. Tau pathology was assessed by western blotting and immunohistochemistry (AT8, AT100). Confocal microscopy was used to study microglial/phospho-tau relationship, and Thioflavin-S staining to evidence fibrillar aggregates. Levels of general (Synaptophysin) and subtype-specific (ChAT, VGAT, VGLUT-1) synaptic proteins were determined by WB and immunohistochemistry. Inflammatory markers were assessed by quantitative PCR (CD45, CD68, TREM2), immunohistochemistry (Iba-1) and image analysis. Tau pathology was detectable in the hippocampus from 2 months of age and increased progressively during aging. Presynaptic protein levels were significantly decreased from 9-12 months compared to age-matched WT mice. Even though some inflammatory markers were slightly increased in the hippocampus, microglial reactivity was found to be generally attenuated and some cells even exhibited reduction in their prolongations and a clear degenerative phenotype at advanced ages similar to that seen in the hippocampus of AD patients. Finally, this model could be a relevant tool to further understand the specific role of tau in both microglial response and synaptic pathology in AD.

TOPIC 6. Disorders and nervous system repair