AGGRAVATED TAU-PATHOLOGY IN A NOVEL MOUSE MODEL WITH COMBINED AMYLOID AND TAU-PATHOLOGY IS PRECEDED BY DYSREGULATED GSK3B SIGNALING AND AUTOPHAGY

I.-C. Stancu, C. Marinangeli, B. Vasconcelos, B. Tasiaux, C. Dehalleux, V. Laporte, L. El Haylani, N. Pierrot, P. Kienlen-Campard, J.-N. Octave, I. Dewachter

Alzheimer's Dementia, Institute of Neuroscience, Université Catholique de Louvain, Brussels, Belgium

Objectives: Amyloid plaques and neurofibrillary tangles represent the diagnostic hallmarks of AD. Several data have indicated beta-amyloid induced aggravation of tau-pathology in vitro and in vivo. However, the molecular mechanisms of the communication between ABeta and Tau remain a major black box in the pathogenesis of AD. We here aimed at the generation of a novel model with combined amyloid and tau-pathology to study the link between both. The analysis of different models, varying in degree, region and type of amyloid (intra- and extra-cellular) pathology is important to uncage different aspects of this link.

Methods: We have crossbred 5xFAD transgenic mice with TauP301S transgenic mice, to generate mice with combined amyloid and tau-pathology, further denoted F+/T+. Comparative immunohistochemical analysis of F+/T+ transgenic mice and F+/T- and F-/T+ parental strains was performed at 3, 6 and 9 months of age for intraneuronal and plaque-associated ABeta, P-Tau, NFTs, GSK3b, LC3 and CathepsinD.

Results: Immunohistochemical analysis demonstrated a dramatic aggravation of Tau-pathology in F+/T+ mice compared to F-/T+ mice. Aggravated Tau-pathology was associated with increased GSK3b-Y216P staining and changes in LC3 and CathepsinD autophagic markers. Longitudinal and spatial immunohistochemical analysis demonstrated that these abnormalities preceded Tau-pathology.

Conclusions: We have generated a novel model with robust combined amyloid and tau-pathology, providing a preclinical model to evaluate therapeutic targets for their combined and specific modulatory effects on amyloid and tau-pathology. Furthermore, our data demonstrate a dramatic amyloid-induced Tau-pathology and support a role for dysregulated GSK3b-signaling and autophagy as contributing mechanisms.