Alzheimer's Disease and related mouse models: pE3-Abeta and Tau-associated pathology

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BACKGROUND

Alzheimer's disease (AD) is a neurodegenerative disease characterized by extracellular amyloid plaques and intracellular neurofibrillary tangles. Neuritic plaques often appear in N-terminally truncated forms with a cyclic glutamate residue. pE3 Aβ exhibits cellular toxicity, presents a high self-aggregation predisposition, and promotes co-aggregation of non-modified Aβ. The current study is designed to analyze features of AD-related pathological changes in human brain that are spatially associated with pE-Aβ immunoreactive structures, and to verify whether similar changes are present in different animal models of AD.

MATERIALS AND METHODS

Paraffin slides of AD patients as well as healthy controls and, cryosections of transgenic mouse models (5xFAD, APP_{SL}) and non-transgenic control mice were labelled by multichannel immunofluorescence to analyze the spatial relations of pE3 Aβ and ptau. Therefore, a rabbit polyclonal antibody against pE3 Aβ and a mouse monoclonal antibody (clone AT8) against pSer202/ Thr205 tau were used. All samples were digitized and immunofluorescent labelling was quantified by image analysis.

RESULTS

Brain slides of AD patients show an increasing pE3 Aβ expression with progressing Braak stages. Expression of ptau is only increased in patients of Braak stage V/VI. Additionally, a significant correlation between pE3 Aβ and pSer202/ Thr205 tau expression in human sections is observed (Fig.1).

Depending on genotype and age, mouse models manifest different expressions of pE3 Aβ and pSer202/ Thr205 tau. 5xFAD mice show a significantly increased pE3 Aβ and pSer202/Thr205 tau expression over age, while APP_{SL} mice show only a significant increase of pE3 Aβ at the age of 12 months. Furthermore, expression of pE3 Aβ and pSer202/Thr205 tau significantly correlated in both mouse models.

RESULTS

Human Samples

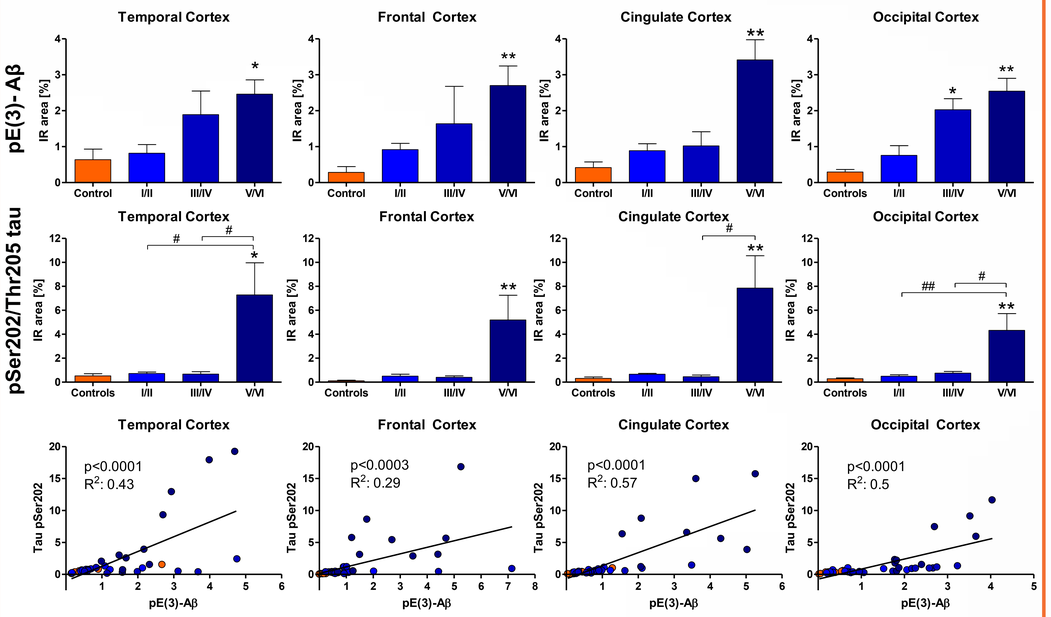


Figure 1. Pyroglutamate amyloid-β and pSer202/Thr205 tau expression in different cortical regions of AD patients' brain samples: A-D: Pyroglutamate amyloid-β (pE(3)-Aβ); E-H: pSer202/205 tau. I-M: Correlation analysis of pE(3)-Aβ and pSer202/Thr205 tau. n = 5 per group; mean + SEM; A-H: One-way-ANOVA followed by Bonferroni *posthoc* test; I-M: Pearson correlation. *compared to controls; # differences between Braak stages.

Murine Samples

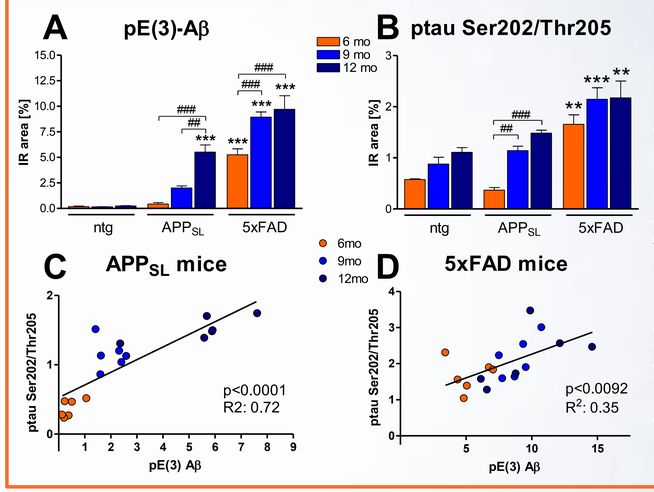
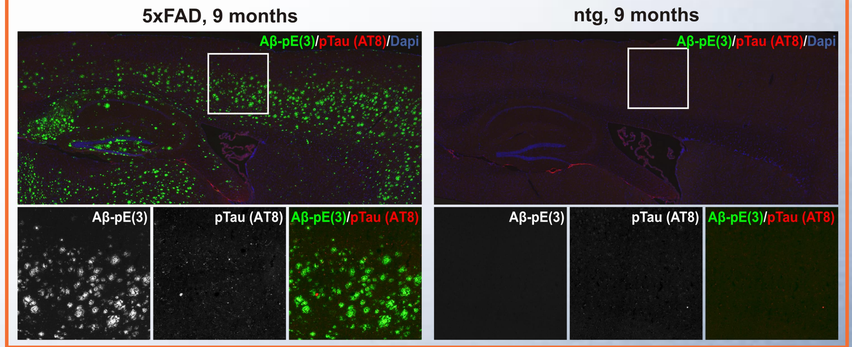


Figure 2. Pyroglutamate amyloid-β and pSer202/ Thr205 tau expression in the cortex of 6, 9 and 12 months old APP_{SL} and 5xFAD mice: A,B: Percentage of immunoreactive area of pyroglutamate amyloid-β (pE(3)-Aβ) and pSer202/ Thr205 tau. Two-way-ANOVA with Bonferroni *post hoc* test. Data are presented as means + SEM. *compared to ntgs; # differences between age groups of one genotype. C,D: Correlation analysis of Aβ-pE(3) and pSer202/ Thr205 tau in APP_{SL} and 5xFAD mice. n = 5 per group.

Murine Example Images



CONCLUSION

Correlation between pE(3)-Aβ and pSer202/Thr205 tau expression in human samples as well as in mouse model samples confirms an interdependent expression of pE(3)-Aβ and pSer202/Thr205 tau. Further studies will be required to investigate how these proteins affect each other.

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