INFLAMMATORY PROCESSES IN THE THY-TAU22 MODEL OF AD-LIKE TAU PATHOLOGY: A GENE EXPRESSION PROFILING STUDY

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Introduction: Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by amyloid deposits and neurofibrillary degeneration made of aggregated hyper- and abnormally phosphorylated Tau protein, the latter being correlated with the progression of cognitive deficits. We have generated a Tau transgenic mouse model (THY-Tau22) exhibiting progressive neuron-specific AD-like Tau pathology in parallel to progressive memory impairments. These changes are observed before overt neuronal death until 12 months of age.

Aims: To uncover transcriptome changes associated with established Tau pathology and memory alterations, we used a microarray strategy applied to 12 month-old control and THY-Tau22 mice.

Methods: Gene expression profiling was realized using Agilent Whole Mouse Genome Microarrays, 4x44K Microarray and analyzed by GeneSpring 10.0 (Agilent Technologies). We applied a fold change threshold of 2. Term Enrichment analysis of differentially expressed genes was realized using AmiGO. Differential expression was validated using quantitative PCR.

Results: 32 genes were identified as differentially expressed. 28 of these genes showed increased expression while only 4 were downregulated. Using GO Term Enrichment analysis and quantitative PCR, we found that most of the upregulated genes were related to immune response suggesting that the development of Tau pathology and memory dysfunctions in THY-Tau22 mice were associated with inflammatory processes and involved chemokines, complement and component of the histocompatibility complex. Additional inflammation-related markers have also been validated in the THY-Tau22 model using QPCR (MAC-1, CD68, TNFα) and immunohistochemistry (GFAP).

Conclusions: Progressive development of Tau pathology is sufficient to produce AD-related neuroinflammation and must be considered as a therapeutic target.