Characterization of Glial Fibrillary Acidic Protein (GFAP) isoform expression in plaque related astrogliosis in human Alzheimer Disease

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In Alzheimer's disease (AD) amyloid plaques are surrounded by a network of reactive astrocytes with an increased expression of their intermediate filament network. The upregulation of the astrocyte-specific intermediate filament Glial Fibrillary Acidic Protein (GFAP) plays an essential role in this. Several isoforms of GFAP have been identified that confer different properties to the intermediate filament network of astrocytes and may be associated with specific subpopulations of astrocytes; the GFAPδ isoform is expressed by neurogenic astrocytes in the human brain and the reading-frame shifted isoform ($GFAP^{+1}$) is expressed in a specific subpopulation of astrocytes in the aging brain (Middeldorp *et al*., 2009b). To gain insight in the role of the different isoforms in AD-related gliosis, we characterized gene expression levels and protein expression patterns of all known GFAP isoforms in human hippocampal AD tissue at different stages of the disease.

Transcripts for GFAPα, GFAPβ, GFAPγ, GFAPδ, GFAPκ, GFAPζ, GFAPΔ135, and the frame-shifted $GFAP^{+1}$ isoforms GFAPΔEx6, GFAPΔ164, and GFAPΔEx7 were detected at different abundances. All isoform transcript levels increased with progression of AD. Most GFAPα-immunopositive hippocampal astrocytes were also GFAPδ-positive, while no GFAPκ immunostaining was observed. In AD, astrocytes nearby plaques displayed increased staining of both GFAPα and GFAPδ. $GFAP^{+1}$ staining was confined to a subset of astrocytes with long processes and the number of $GFAP^{+1}$ cells increased in the course of AD. Application of Aβ to cells in culture resulted in the induction of $GFAP^{+1}$ staining in few cells.

In conclusion, the various GFAP isoforms show differential transcript levels and are all upregulated in a concerted manner in AD. The $GFAP^{+1}$ isoform defines a unique subset of astrocytes with numbers increasing with AD progression. These data denotes the need for future exploration of underlying mechanisms concerning the function of $GFAP^{+1}$ proteins and the role of these specific astrocytes in AD.