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### Microglial responses in the human Alzheimer's disease frontal cortex

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The continuing failure to develop an effective treatment for Alzheimer's disease (AD) reveals the complexity for this pathology. Increasing evidence indicates that neuroinflammation involving particularly microglial cells contributes to AD pathogenesis. The actual view, based on the findings in APP based models, gives a cytotoxic/proinflammatory role to activated microglia. However, we have previously reported a limited activation and microglial degeneration in the hippocampus of AD patients in contrast with that observed in amyloidogenic models. Here, we evaluated the microglial response in a different region of AD brains, the frontal cortex. *Post mortem* tissue from controls (Braak 0-II) and AD patients (Braak V-VI) including familial cases, were obtained from Spain Neurological Tissue Banks. Cellular (immunohistochemistry and image analysis) and molecular (qPCR and western blots) approaches were performed. Frontal cortex of AD patients (Braak V-VI) showed strong microglial activation similar to that observed in amyloidogenic mice. These strongly activated microglial cells, predominantly located surrounding amyloid plaques, could drive the AD pathology and, in consequence, could be implicated in the pathology progression. Furthermore, different microglial responses were observed between sporadic and familial AD cases. These findings in the frontal cortex were highly in contrast to the attenuated activation and degenerative morphology displayed by microglial cells in the hippocampus of AD patients. Regional differences in the microglial response suggest different functional states of microglial cells in a region-specific manner. All together, these data provide a better understanding of the immunological mechanisms underlying AD progression and uncover new potential therapeutic targets to fight this devastating neurodegenerative disease.

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