MICROGLIAL RESPONSE DIFFERENCES BETWEEN AMYLOIDOGENIC TRANSGENIC MODELS AND ALZHEIMER'S DISEASE PATIENTS

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Aims: The continuing failure to develop an effective treatment for Alzheimer's disease (AD) reveals the complexity for AD pathology. Increasing evidence indicates that neuroinflammation involving particularly microglial cells contributes to disease pathogenesis. Here we analyze the differences in the microglial response between APP/PS1 model and human brains.

Methods: RT-PCR, western blots, and immunostaining were performed in the hippocampus of human *post mortem* samples (from Braak II to Braak V-VI) and APP751SL/PS1M146L mice. *In vitro* studies to check the effect of S1 fractions on microglial cells were assayed.

Results: In APP based models the high Abeta accumulation triggers a prominent microglial response. On the contrary, the microglial response detected in human samples is, at least, partial or really mild. This patent difference could simple reflect the lower and probably slower Abeta production observed in human hippocampal samples, in comparison with models or could reflect the consequence of a chronic long-standing microglial activation. However, beside this differential response, we also observed a prominent microglial degenerative process in Braak V-VI samples that, indeed, could compromise their normal role of surveying the brain environment and respond to the damage. This microglial degeneration, particularly relevant at the dentate gyrus of the hippocampal formation, might be mediated by the accumulation of toxic soluble phospho-tau species.

Conclusions: These differences need to be considered when delineating animal models that better integrate the complexity of AD pathology and, therefore, guarantee clinical translation. Correcting dysregulated brain inflammatory responses might be a promising avenue to restore cognitive function.

Supported by grants FIS PI15/00796 and FIS PI15/00957 co-financed by FEDER funds from European Union, and by Junta de Andalucia Proyecto de Excelencia CTS385 2035.

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