UNRAVELLING MICROGLIAL CELL PARTICIPATION IN ALZHEIMERS' DISEASE: AGING, TGFB AND MICROGLIAL DYSREGULATION

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Introduction: Microglia are the brain main immune effectors. Responsible of many protective functions, microglia also undergo cytotoxic activation, which appear to mediate damage in Alzheimer's disease (AD). Microglial cytotoxic activation can be modulated by transforming growth factor β (TGFβ). On the other hand, TGFβ is increased in aged individuals and AD patients, but the expression of Smad3, its main signaling pathway, is decreased.

Aims: To assess if changes on TGFβ-dependent signal pathways lead to changes on the activation pattern of microglia.

Methods: TGFβ-Smad3 signaling pathway in WT and APP/PS1 mice was assessed in vivo during aging and after acute and chronic inflammatory stimulation. The participation of TGFβ-Smad3 activity on microglial cell activation, phagocytosis, scavenger receptor (SR) expression and uptake of Aβ was evaluated by in vitro assays.

Results: Whereas Smad3 is induced by acute inflammatory activation, it shows no change or is reduced in mice exposed to chronic inflammation. Chronic inflammation also increased hippocampal TGFβ and decreased phospho-Smad3 levels, differences that are more robust in APP/PS1 mice. In turn TGFβ-Smad3 activation induces changes in the expression pattern of SR, with a conspicuous increase of SR-A. In culture, TGFβ increased Aβ uptake by microglia and reduced inflammatory activation, both effects depending on Smad3 activation. SRs, besides participating in phagocytosis, play a key role in regulating the inflammatory activation of glia.

Conclusions: TGFβ-Smad3 pathway is relevant for microglial inflammatory activation and cytotoxic response. Aging and inflammation dependent inhibition of Smad can participate in the pathogenesis of AD by changing microglial regulation.