

Activation status of human microglia is dependent on lesion formation stage and remyelination in multiple sclerosis.

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Research question and background

We previously reported that preactive MS lesions are not associated with blood-brain barrier breakdown or leukocyte infiltration, suggesting that they are indeed composed of microglia rather than macrophages that have crossed the blood-brain barrier. In addition, microglia in preactive lesions express cytokines such as TNF, IL-10, and IL-23. Similar to macrophages, microglia adopt diverse activation states and contribute to repair and tissue damage in multiple sclerosis, however, a systematic analysis of classical M1 or M2 microglia phenotypes in these early preactive lesions and areas of remyelination in which activated microglia are observed has not been performed. Therefore, we examined whether changes in the balance of M1 and M2 microglia phenotypes in preactive lesions might explain why some preactive lesions may develop into active lesions whereas others resolve.

Methods and tissues used

Using reverse transcription-quantitative polymerase chain reaction and immunohistochemistry, we show that in vitro M1-polarized (proinflammatory) human adult microglia express the distinctive markers CD74, CD40, CD86, and CCR7, whereas M2 (anti-inflammatory) microglia express mannose receptor and the anti-inflammatory cytokine CCL22.

The expression of these markers was assessed in clusters of activated microglia in normal-appearing white matter (preactive lesions) and areas of remyelination, representing reparative multiple sclerosis lesions.

Results and conclusion

We show that activated microglia in preactive and remyelinating lesions express CD74, CD40, CD86, and the M2 markers CCL22 and CD209, but not mannose receptor. To examine whether this intermediate microglia profile is static or dynamic and thus susceptible to changes in the microenvironment, we polarized human microglia into M1 or M2 phenotype in vitro and then subsequently treated them with the opposing polarization regimen.

These studies revealed that expression of CD40, CXCL10, and mannose receptor is dynamic and that microglia, like macrophages, can switch between M1 and M2 phenotypic profiles. Taken together, our data define the differential activation states of microglia during lesion development in multiple sclerosis-affected CNS tissues and underscore the plasticity of human adult microglia in vitro.