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PARTIAL INHIBITION OF CSF1R SIGNALING REVERSES LONG-TERM MICROGLIAL PRIMING

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Abstract Body

Microglial cells are main actors in acute neuroinflammation, during which they activate to later return to a basal resting state. Sometimes they retain immune memory of previous neuroinflammatory events, turning into primed microglia, which develop exacerbated responses to new stimuli. Brain can be depleted of microglia by treatment with the CSF1R inhibitor PLX5622. Treatment termination allows for microglia regeneration, new cells presenting a resting state. However, unwanted side effects of high PLX5622 doses have been reported. Here we aimed to explore if treatment with lower doses of PLX5622 can reverse microglial priming. We induced microglial priming in mice by provoking acute neuroinflammation with intracerebroventricular administration of neuraminidase. After 3 weeks, when neuroinflammation is largely solved, mice were treated with a daily dose of PLX5622 for 12 days. Then, microglial repopulation was allowed for 7 weeks. Finally, a second stimulus was applied (intraperitoneal LPS) to induce inflammatory activation of primed microglia, and animals were sacrificed 12 hours later. Brains were collected to analyze microglial cell number and activation by morphological analysis, and expression level of key genes by qPCR; these parameters were evaluated in two regions: the periventricular area of the hypothalamus and the hippocampus. In hypothalamic paraventricular nucleus the number of microglial cells was the same regardless the treatment; however, it was slightly reduced in the dentate gyrus of the hippocampus of PLX5622 treated mice. Morphological analysis of microglial cells was carried out by fractal, sholl and skeleton analysis. All of them pointed that microglia sampled from NA injected mice had a more activated profile (less ramified cells), which was reversed by PLX5622 treatment. Besides, expression of pro-inflammatory related genes (IL1β, IL6, TNFα, NLRP3, TLR4) pointed to the same direction. Thus, our results suggest that PLX5622 used at low doses reverses microglial priming, while does not fully deplete microglial population.

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