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Siponimod favours expression of less pro-inflammatory, alternatively activated microglia in a microglia repopulation model of progressive multiple sclerosis - implication for neuroprotection

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Background: In progressive forms of multiple sclerosis (MS), central nerveous system (CNS)-resident immune cells such as microglia are contributors of chronic inflammation. The second generation sphingosin-1-phosphate receptor modulator siponimod, licensed for secondary progressive MS, exerts presumably modulatory properties on microglia.
Aim of the study: We hypothesized that depleting microglia during experimental autoimmune encephalomyelitis (EAE) might lead to a renewal of neuroprotective microglia in the presence of siponimod in a mouse model of progressive MS.
Methods: We induced EAE in CX3CR1CreER/iDTR mice to perform a conditional microglia knock out (MG^{ko}). Siponimod was administered from one day after immunization (dpi) orally dissolved in rapeseed oil. Microglia depletion was induced during the chronic phase of EAE, mice were sacrificed during subsequent repopulation of microglia. CNS, blood and lymphatic organs were analyzed by flow cytometry.
Results: Siponimod reduced EAE scores significantly, while MG^{ko} showed a trend towards worsening of EAE. Repopulating microglia were characterized by lower expression of steady state markers and upregulation of inflammatory markers (CD86, MHC-II). Siponimod reduced expression of pro-inflammatory markers (CD86, MHC-II) and, additionally, elicited upregulation of alternative activation markers (CD206) during repopulation. Immune cell composition was unaffected apart from restrained $CD19^{+}$B cells and $CD4^{+}CD25^{+}FoxP3^{+}$ regulatory T cells in lymph nodes by siponimod. Macrophages in the brain directly correlated with lower microglia numbers. Histologically, immune cell infiltration in the spinal cord was reduced both following MG^{ko} and stronger under siponimod treatment,.
Conclusions: Siponimod treatment reduced pro-inflammatory repopulating microglia after a conditional MG^{ko} and favoured the renewal of less pro-inflammatory, alternatively activated, potentially phagocytic microglia. This effect adds more mechanistic insight regarding microglia modulatory properties of siponimod with implications for putative neuroprotection during progression.
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