CD4+ T cells isolated from brain tissue had a unique gene-expression profile, including increased expression of markers of tissue residency such as CD69. Overall, the relative frequency of CD4+ T cells in the mouse brain was highest at birth and then declined with age. Notably, similar observations were made in studies using resected human brain tissue, indicating a conserved ‘brain-resident’ CD4+ T cell phenotype. Parabiosis studies in mice indicated that CD4+ T cells acquired this resident phenotype in the brain following entry from the blood. Most CD4+ T cells entered the brain transiently, but activated CD4+ T cells entered at higher rates than naive CD4+ T cells, and a small fraction of these activated T cells acquired the brain-resident phenotype. Further experiments with T cell receptor transgenic CD4+ T cells suggested that Treg cells in the brain are specific for brain-expressed antigens, whereas the activated CD4+ T cells in brain do not necessarily recognize brain-expressed antigens, but instead depend on peripheral activation for brain entry. Microbiota depletion studies supported this idea.

The authors proceeded to show that microglia in MHC class II-deficient mice (which lack CD4+ T cells) maintain an immature fetal-type transcriptional profile and fail to turn on key microglial transcription factors. Experiments in other systems also indicated that CD4+ T cells are necessary for microglial maturation, with imaging studies suggesting that CD4+ T cells support the acquisition of microglial synaptic pruning functions. Strikingly, in the absence of CD4+ T cells, cortical pyramidal neurons showed increased spine density at synapses, similar to what is seen in human neurological conditions such as Down syndrome and Rett syndrome. Accordingly, MHC class II-deficient mice showed many behavioural abnormalities, including reduced mobility, increased anxiety, depressive-like behaviour and impaired contextual and spatial learning.

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