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Microglia Get a Little Help from "Th"-eir Friends

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The pre ence of CD4+ T cell in he heal h brain parench ma remain con ro er ial d e o he barrier f nc- ion of he glia limi an . Pa ci o, B r on, Roca e al. in *Cell* de cribe he d namic recr i men of CD4$^+$ T cell i hin he brain parench ma, heir ne pec ed con rib ion o microglial ma ra ion, and, l ima el , heir in- ence on beha ior.

While central nervous system (CNS) invasion and disease-shaping functions of T cells in neurological disorders have been a major research subject for decades, the presence and role of adaptive immune cells in the mammalian immune privileged CNS parenchyma at steady state remain a matter of debate. Making use of interdisciplinary methodology from neuroimmunology, bioinformatics, and applied mathematics, a recent study by Pasciuto et al. (2020) published in *Cell* provides convincing evidence for the presence of rare and distinct subsets of brain resident CD4$^+$ T cells in the healthy mouse and human brain parenchyma, offering novel insights on density and localization of these lymphocytes and altogether proposing a model for their immigration dynamics. Furthermore, the study unveils an unexpected function of rare brain resident CD4$^+$ T cells in supporting the final steps of microglial development, thus influencing synaptic pruning and ultimately behavior.

In a detailed analysis that combines confocal microscopy of brain tissue sections, multidimensional flow cytometry and single-cell RNA sequencing, Pasciuto, Burton, Roca et al. report the presence of about 2,000 CD4$^+$ T cells in the mouse brain at steady state. Harboring 25% of these brain resident CD4$^+$ T cells, the meninges are confirmed as a key brain compartment ensuring T cell mediated CNS immune surveillance. Nevertheless, the remaining 75% CD4$^+$ T cells were found located within the brain parenchyma beyond the glia limitans. Notably, the number of brain CD4$^+$ T cells was maximal around birth, declined in the post-natal period and slowly increased with age,

protect neurons from degeneration as proposed in the concept of ''protective autoimmunity'' coined by Michal Schwartz that assigns CNS-specific effector and regulatory T cells a role in CNS maintenance and repair.

Lastly, the actual action radius of a $CD4^+$ T cell within the brain parenchyma remains to be unraveled. The $CD4^+$ T cell density reported by Pasciuto, Burton, Roca et al. in the mouse cortex is $\sim$4 cells/mm^3, an extremely rare population considering the local density of microglia ($\sim$26,231 cells/mm^3) and neurons ($\sim$102,320 cells/mm^3) (Erö et al. 2018). While the authors propose that $CD4^+$ T cells can reach the proximity of this vast number of microglia by fast Lévy walk behavior, such kinetic pattern may rather apply for T cells scanning the leptomeninges, a location likely governed by different physical restrictions when compared to the brain parenchyma harboring extremely narrow extracellular spaces.

Taken together, this significant study from Pasciuto, Burton, Roca et al. lays the groundwork for a novel understanding of adaptive immune cell actions within the brain, underscoring unexpected roles of brain $CD4^+$ T cells that go beyond maintaining CNS immunity. More in-depth understanding these functions will be of fundamental importance for considering potential adverse effects of T cell targeting therapies as used for the treatment of multiple sclerosis.

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