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LETTER TO THE EDITOR

Tissue-resident CD8$^+$ memory T cells in multiple sclerosis

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We read with interest the article by Fransen *et al.* (2020) in *Brain*. The authors studied the role of CD8$^+$ T cells in a large cohort of chronic multiple sclerosis autopsy cases from the Netherlands Brain Bank. In all white matter samples, CD8$^+$ T cells were conspicuous in the perivascular space (PVS; Virchow-Robin space). At the level of postcapillary venules where lymphocyte extravasation takes place, this specialized compartment is bordered by the endothelial basement membrane on the vascular side, and the glia limitans on the brain parenchymal side (Engelhardt *et al.*, 2017). A large proportion of the CD8$^+$ cells displayed the phenotype of tissue-resident memory cells (T_{RM}) (CD69$^+$, CD103$^{+/-}$, S1P1$^-$, CCR7$^-$, CXCR6$^+$), similar to observations previously reported by Machado-Santos *et al.* (2018).

T_{RM} cells have emerged as an important subset of memory T cells. Unlike central memory and effector memory T cells, T_{RM} cells do not recirculate but are sessile residents in various tissues, including the brain, where they provide a first line of protection, especially against local viral spread (Mueller and Mackay, 2016; Smolders *et al.*, 2018).

Fransen *et al.* suggest that (re)activation of CD8$^+$ T_{RM} cells in the PVS 'is a key mechanism in the maintenance of white matter lesion activity in advanced progressive multiple sclerosis' (Fransen *et al.* 2020). Recruitment of CD8$^+$ T_{RM} cells might reflect an antiviral response that drives or facilitates the autoimmune process in a similar way as recently described in an animal model of multiple sclerosis (Steinbach *et al.*, 2019).

It is interesting to compare the findings by Fransen *et al.* in late chronic multiple sclerosis with our observations in subjects with early prodromal (sublinical) multiple sclerosis (Beltran *et al.*, 2019). In our cohort of monozygotic twins who are clinically discordant for multiple sclerosis, we identified a subgroup of clinically healthy co-twins who show evidence of 'subclininal neuroinflammation' on MRI or CSF analysis. Using single-cell transcriptomics (RNA-seq) we found that activated, clonally expanded CD8$^+$ T_{RM} cells are conspicuous components of the CSF from subjects with subclinical neuroinflammation (prodromal multiple sclerosis) (Beltran *et al.*, 2019).

The anatomy of the PVS and especially its connection with the CSF is complicated and controversial (Wardlaw *et al.*, 2020). Nevertheless, there are obvious links and parallels between the CD8$^+$ T_{RM} cells observed in the PVS of autopsy cases with late-stage chronic multiple sclerosis (Fransen *et al.*, 2020), and the CD8$^+$ T_{RM} cells detected in the CSF of subjects with early prodromal multiple sclerosis (Beltran *et al.*, 2019). We conclude that CD8$^+$ T_{RM} cells are not just involved in the chronic late phase of multiple sclerosis, but are key players even in the earliest detectable (prodromal) stage of the disease process.

Data availability

Data availability is not applicable to this article as no new data were created or analysed in this study.

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Competing interests

The authors report no competing interests.

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