doi:10.1093/brain/awaa352 BRAIN 2021: 144; 1–2 | e7

BRAIN
A JOURNAL OF NEUROLOGY

LETTER TO THE EDITOR

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

Reinhard Hohlfeld,[1,2] Eduardo Beltran,[1,2] Lisa Ann Gerdes[1,2] and Klaus Dornmair[1,2]

1 Institute of Clinical Neuroimmunology, Biomedical Center and Hospital of the Ludwig-Maximilians-University Munich, Munich, Germany
2 Munich Cluster of Systems Neurology (SyNergy), Munich, Germany

Correspondence to: Dr Reinhard Hohlfeld
Institut für Klinische Neuroimmunologie
Biomedical Center-LMU
Großhaderner Str. 9
D-82152 Planegg-Martinsried
Germany
E-mail: reinhard.hohlfeld@med.uni-muenchen.de

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.

December 13, 2020
© The Author(s) (2020). Published by Oxford University Press on behalf of the Guarantors of Brain. All rights reserved.
For permissions, please email: journals.permissions@oup.com

Downloaded from https://academic.oup.com/brain/article/144/1/e7/6032479 by guest on 11 June 2024

Funding

The authors' studies were supported by the German Research Council through CRC128-A5, DO 420/3-1 DACH, the Munich Cluster for Systems Neurology (SyNergy EXC 2145, project 390857198), the Dr. Leopold und Carmen Ellinger foundation, the Gemeinnützige Hertie Stiftung, the national division of the German MS Society (DMSG), the Bavarian association of the German MS society (DMSG-Bayern), the BMBF organization "Krankheitsbezogenes Kompetenznetz Multiple Sklerose", and the association "Verein zur Therapieforschung für MS Kranke e. V.".

Competing interests

The authors report no competing interests.

References

Beltran E, Gerdes LA, Hansen J, Flierl-Hecht A, Krebs S, Blum H, et al. Early adaptive immune activation detected in monozygotic twins with prodromal multiple sclerosis. J Clin Invest 2019; 129: 4758–68.

Engelhardt B, Vajkoczy P, Weller RO. The movers and shapers in immune privilege of the CNS. Nat Immunol 2017; 18: 123–31.

Fransen NL, Hsiao CC, van der Poel M, Engelenburg HJ, Verdaasdonk K, Vincenten MCJ, et al. Tissue-resident memory T cells invade the brain parenchyma in multiple sclerosis white matter lesions. Brain 2020; 143: 1714–30.

Machado-Santos J, Saji E, Troscher AR, Paunovic M, Liblau R, Gabriely G, et al. The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8 + T lymphocytes and B cells. Brain 2018; 141: 2066–82.

Mueller SN, Mackay LK. Tissue-resident memory T cells: local specialists in immune defence. Nat Rev Immunol 2016; 16: 79–89.

Smolders J, Heutinck KM, Fransen NL, Remmerswaal EBM, Hombrink P, ten Berge IJM, et al. Tissue-resident memory T cells populate the human brain. Nat Commun 2018; 9: 4593.

Steinbach K, Vincenti I, Egervari K, Kreutzfeldt M, van der Meer F, Page N, et al. Brain-resident memory T cells generated early in life predispose to autoimmune disease in mice. Sci Transl Med 2019; 11: eaav5519.

Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, et al. Perivascular spaces in the brain: anatomy, physiology and pathology. Nat Rev Neurol 2020; 16: 137–53.

Downloaded from https://academic.oup.com/brain/article/144/1/e7/6032479 by guest on 11 June 2024