Unique invariant CD8$^+$ T cell population persists in MS

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Although historically overshadowed by CD4$^+$ T cells, and more recently by B cells, a number of lines of evidence point toward a potentially vital role of CD8$^+$ T cells in multiple sclerosis (MS) pathogenesis. CD8$^+$ T cells outnumber CD4$^+$ in the parenchyma of MS lesions[1] and are abundant at the leading edge in chronic active lesions.[2] Some studies have detected increased frequencies of myelin-specific CD8$^+$ T cells in patients with MS.[3,4] Human leukocyte antigen (HLA)-A3 (A*0301), which encodes one of the major histocompatibility complex (MHC) class I proteins used for antigen recognition by CD8$^+$ T cells, doubles the risk of MS even in the absence of HLA-DR2 (DRB*1501, DQB*0602) genes that encode MHC II proteins used for antigen presentation to CD4$^+$ T cells.[5] Furthermore, it has been demonstrated that myelin-specific CD8$^+$ T cells can induce an MS-like disease in HLA-A3 transgenic[6] and wild-type mice.[7] If antigen-specific CD8$^+$ T cells participate in MS pathogenesis, one might ask whether certain ones expand selectively and whether they persist.

In this issue of *Neurology® Neuroimmunology & Neuroinflammation*, Held et al. examined CD8$^+$ T cells in 1 patient with MS over 18 years.[8] A brain biopsy shortly after presentation demonstrated inflammatory demyelination. Using high-throughput Next Generation Sequencing, these investigators examined the CD8$^+$ T cell repertoire in this MS lesion and compared it to that found in the peripheral blood at subsequent time points. Each T cell recognizes a unique antigen and its specificity is primarily shaped by the combination of T cell receptor (TCR) α and β chain complementarity determining region (CDR) 3 regions, which are each formed by genetic recombination that links individual Vα-Jα segments and separately connects Vβ-Dβ-Jβ sequences. Because the naive T cell repertoire is highly diverse, identification of a narrow array of T cell receptors in a particular location suggests clonal expansion of a small subset of antigen-specific T cells. Oligoclonal CD8$^+$ T cell populations in the blood, CSF, and brain of patients with MS were previously observed by TCR Vβ sequencing.[1,9] Held et al. took their clonal analysis a step further by combining the use of laser microdissection and single-cell PCR sequencing to analyze both the TCR α and β chains within individual CD8$^+$ T cells. They observed that a particular CD8$^+$ T cell clonotype bearing the Vβ1-Jβ2.3 TCRβ chain was expanded in active brain lesions and that this dominance persisted. Surprisingly, their analysis revealed that the subset of CD8$^+$ Vβ1$^+$ T cell clones contained α chains bearing the same CDR3α sequence, Vα7.2-Jα33, that is unique to mucosal-associated invariant T (MAIT) cells, an innate-like CD8$^+$ T cell subset that accounts for up to 4% of peripheral T cells in humans.[10] MAIT cells are identified by coexpression of CD161, which has been associated with secretion of proinflammatory cytokines, including interleukin-17. They are restricted by a unique nonpolymorphic MHC I–like molecule, MR1.[10] Unlike classic MHC I–restricted CD8$^+$TCRα/β$^+$ T cells, which recognize peptide antigens, MAIT cells recognize bacterial-derived metabolites, in particular derivatives of riboflavin, and are dependent on gut microbiota for their development. Even though MAIT cells made up only 1% of all CD8$^+$ T cells in MS brain lesions examined, persistent MAIT cell–related clonal populations were found in the blood 18 years after clinical onset. This is in contrast to other CD8$^+$ T cells, which lost their preferential clonal expansion and became polyclonal, similar to CD4$^+$ T cells. MAIT cells also exhibited a memory phenotype, indicating that they had been previously exposed to antigen. These results highlight the complexity of the CD8$^+$ T cell repertoire in MS.

This report by Held et al. represents an important step forward in the analysis of the T cell repertoire found in MS. The degree of subclonal expansion of Vα7.2$^+$/Vβ1$^+$ CD8$^+$ T cells strongly suggests a local antigen-driven process, possibly within inflammatory

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MS lesions. A limitation of the analysis is that the antigen specificity of the clonally expanded $CD8^+$ T cells is not known. In the absence of CNS infection, bacterial products should not necessarily be present within the CNS. Although MAIT cells are known to recognize derivatives of vitamin B_2, it is currently unclear whether the nonpolymorphic MHC-like MR1 can present other antigens. Furthermore, because the studies were limited to a single patient, it is unclear whether similar clonal $CD8^+$ T cell populations are found in other patients with MS. Most importantly, the clinical significance of invariant $CD8^+$ T cells remains largely unknown. The presence of clonal $CD8^+$ T cell populations in MS brain lesions shortly after clinical onset raises the possibility that these cells have an important pathogenic role in early MS. Therefore, it would be worthwhile to evaluate $CD8^+$ T cell clonotypes during relapses and remissions in multiple patients with MS. The functions of invariant $CD8^+$ T cells, such as cytokine secretion, cytolytic capabilities, and interactions with $CD4^+$ T cells, have not been elucidated in MS. More detailed characterization of various $CD8^+$ T cell populations is therefore needed in order to determine whether they participate in MS pathogenesis and, if so, whether they are proinflammatory or protective in MS. Natural killer (NK) T cells, another invariant T cell subset, recognize glycolipids, including myelin-derived sulfatide, via a nonpolymorphic MHC 1-like molecule, CD1d. Of interest, data suggest that NK T cells may have a protective role in MS.[11] Currently, mice that selectively express MAIT cell–associated TCR α and β chains exist. Thus, studying the role of $CD8^+$ T cells and invariant T cell populations like MAIT cells in the gastrointestinal tract and the CNS in acute or spontaneous MS models may provide useful insight regarding their potential role in CNS autoimmunity. The work of Held et al. provides a foundation to further study invariant $CD8^+$ T cells in MS.

DISCLOSURE

J.J. Sabatino reports no disclosures. S.S. Zamvil received honoraria for serving on data safety monitoring boards for MS trials conducted by BioMS, Teva Pharmaceuticals, Inc., and Eli Lilly and Co.; is a member of the clinical advisory board for the Myelin Repair Foundation; is deputy editor for *Neurology: Neuroimmunology & Neuroinflammation*; holds a patent for aquaporin-4 peptides and methods for using same; received speaker honoraria from Biogen-Idec, Teva Neuroscience, and Genzyme; has consulted for Biogen-Idec, Teva Neuroscience, EMD-Serono, Genzyme, and Novartis; is on the speakers' bureau for Advanced Health Medica and Biogen-Idec; and received research support from NIH, NMSS, Guthy-Jackson Charitable Foundation, and June L. Maisin Foundation. Go to Neurology.org/nn for full disclosure forms.

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