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 and are abundant at the leading edge in chronic active lesions. Some studies have detected increased frequencies of myelin-specific CD8$^+$ T cells in patients with MS. 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$^*$1501, DQB$^*$0602) genes that encode MHC class II proteins used for antigen presentation to CD4$^+$ T cells. Furthermore, it has been demonstrated that myelin-specific CD8$^+$ T cells can induce an MS-like disease in HLA-A3 transgenic and wild-type mice. 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. 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) \( \alpha \) and \( \beta \) chain complementarity determining region (CDR) 3 regions, which are each formed by genetic recombination that links individual V\( \alpha \)-J\( \alpha \) segments and separately connects V\( \beta \)-D\( \beta \)-J\( \beta \) 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 V\( \beta \) sequencing. 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 \( \alpha \) and \( \beta \) chains within individual CD8$^+$ T cells. They observed that a particular CD8$^+$ T cell clonotype bearing the V\( \beta \)-J\( \beta \) sequence was expanded in active brain lesions and that this dominance persisted. Surprisingly, their analysis revealed that the subset of CD8$^+$ V\( \beta \)-J\( \beta \) T cell clones contained \( \alpha \) chains bearing the same CDR3\( \alpha \) sequence, V\( \alpha \)-J\( \alpha 

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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 B2, 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. The work of Held et al. provides a foundation to further study the potential role in CNS autoimmunity. The study of CD8+ T cells in multiple sclerosis revealed by novel flow cytometric assay. Blood 2004;103:4222–4231.

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DISCLOSURE

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