Programmed cell death protein 1 (PD-1, CD279) is a pleiotropic inhibitory receptor expressed, among others, by several subsets of CD8+ T cells. It not only inhibits T-cell receptor signaling but also suppresses expression of the costimulatory molecule CD28. PD-1 was initially described as an apoptosis-associated gene but has since been attributed multiple functions. It is readily upregulated after T-cell receptor triggering on naive CD8+ T cells, resulting in a controlled expression of granzyme B during acute T-cell responses. In chronic infections and malignancies, exhausted CD8+ T cells prominently express PD-1. Not surprisingly, the presence of PD-1 is associated with memory-type CD8+ T cells and figures prominently in the signature of tissue-resident memory T cells. In recent years, antibodies against PD-1 and its ligands, PD-L1/L2, have become an important therapy for people having malignancies. The role and therapeutic potential of PD-1 in chronically activated inflammatory responses, such as multiple sclerosis (MS), is so far less clear.

In this issue of Neurology® Neuroimmunology & Neuroinflammation, Koto et al. investigated the association of CD8+ T cells positive for PD-1 with the disease course of MS and provide a further transcriptional characterization of these cells. They show a reduced presence of PD-1+ CD8+ T cells in the circulation of people with MS, which was recovered by interferon beta (IFN-β) therapy. An induction of PD-1 on CD8+ T cells by IFN-β was shown in an anti-CD3/CD28-stimulated peripheral blood mononuclear cell (PBMC) culture. The latter observation is in accordance with the potentiating role of type 1 interferons in CD8+ T-cell memory formation.

A relevant question is what the reduced frequency of circulating PD-1+ CD8+ T cells in people with MS means. A relative lack of effector memory (EM) and effector memory re-expressing CD45RA CD8+ T cells in people with MS has been reported. The lower abundance of PD-1+ cells could reflect a distinct distribution and/or defective formation of memory T cells, as has been hypothesized to underlie the defective control of Epstein-Barr virus (EBV) by CD8+ T cells in MS. Vice versa, a higher expression of PD-1 by CD8+CD57+ T cells has been described as phenotypic characteristic of CD8+ T cells defective in the control of EBV in stable MS. Because IFN-β suppresses VLA-4 expression on lymphocytes, PD-1+ CD8+ T cells could migrate toward the CNS and therefore be reduced in the circulation. Indeed, CD8+ PD-1+ T cells make up a major part of T cells observed in MS lesions as well as in clusters of CSF CD8+ T cells associated with (premorbid) MS. Accordingly, Koto et al. show a higher expression of PD-1 on CSF CD8+ T cells in MS compared with PBMC.

Regardless of their frequency, the functional interpretation of PD-1+ CD8+ T cells in MS remains intriguing. The high expression of PD-1 on CSF CD8+ T cells could reflect cellular activation because these cells are also CD69+. Koto et al. show that circulating PD-1+ T cells in IFN-β-treated individuals highly expressed IL-10, whereas expression of proinflammatory cytokines or lytic mediators was not distinct from circulating PD-1- cells. In CD4+ T cells and...
PD-1+ CD8+ T cells, such as chemokine receptors (high gene sets identified from steroid treatment supports the idea that PD-1+ CD8+ T cells may play an important role in the inflammatory response in early MS. The work by Koto et al. provides a framework to study these cells in association with CNS surveillance, disease activity, and treatment responses in MS.

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References
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