Programmed Cell Death Protein 1–Positive CD8⁺ T Cells in Multiple Sclerosis

Exhausted Fighters or Peacekeepers

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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
B cells, IL-10 expression has been mostly associated with anti-
inflammation, which could be beneficial for the course of MS. Anti-inflammatory IL-10+ CD8+ T cells have been identified in the experimental autoimmune encephalomyelitis mouse model of neuroinflammation. Alternatively, high IL-10 expression is a hallmark of exhausted CD8+ T cells. However, exhausted CD8+ T cells also show low expression of proinflammatory cytokines and lytic mediators, which was not found by Koto et al. The increased expression of inhibitory receptors (also CTLA-4 and TIGIT) is consistent with an exhausted phenotype, as is the high expression of the transcription factor c-Maf. c-Maf has been identified as key reg-
ulator of CD8+ T-cell exhaustion in the context of melanoma-
derived T cells. Accordingly, c-Maf has previously been identified to induce coinhibitory receptor expression in CD4+ and CD8+ T cells and to promote IL-10 and suppress IL-2 production in CD4+ T cells.

One explanation for the variation in phenotypic and functional characteristics could be the fact that the PD-1+ CD8+ T cells likely make up a heterogeneous polyclonal population with di-
verse differentiation, activation, and exhaustion states. Tech-
niques allowing clustering of subsets within such populations, like single-cell RNA sequencing, could provide more insights in the functional interpretation of PD-1 expression. Intriguingly, this compartment in MS. The fact that patients with the largest accumulation of these cells in the CSF benefit most from steroid treatment supports the idea that PD-1+ CD8+ T cells play an important role in the inflammatory response in early MS. The work by Koto et al. provides a framework to further study these cells in association with CNS surveillance, disease activity, and treatment responses in MS.

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