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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.[1] PD-1 was initially described as an apoptosis-associated gene[2] 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.[3] In chronic infections and malignancies, exhausted CD8$^+$ T cells prominently express PD-1.[4] 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.[5] In recent years, antibodies against PD-1 and its ligands, PD-L1/L2, have become an important therapy for people having malignancies.[4] 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.[6] 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.[7]

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.[8] 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.[8] 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.[9] Because IFN-β suppresses VLA-4 expression on lymphocytes,[10] 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[11] as well as in clusters of CSF CD8$^+$ T cells associated with (premorbid) MS.[12] Accordingly, Koto et al.[6] 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$^+$.[13] Koto et al.[6] 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

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B cells, IL-10 expression has been mostly associated with anti-inflammation, which could be beneficial for the course of MS.[14] Anti-inflammatory IL-10$^+$ CD8$^+$ T cells have been identified in the experimental autoimmune encephalomyelitis mouse model of neuroinflammation.[15] 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.[6] 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 regulator of CD8$^+$ T-cell exhaustion in the context of melanoma-derived T cells.[16] Accordingly, c-Maf has previously been identified to induce coinhibitory receptor expression in CD4$^+$ and CD8$^+$ T cells[17] and to promote IL-10 and suppress IL-2 production in CD4$^+$ T cells.[18]

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 diverse differentiation, activation, and exhaustion states. Techniques 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, gene sets identified by Koto et al. to be enriched in circulating PD-1$^+$ CD8$^+$ T cells, such as chemokine receptors (high CXCR6 and CCR5 and low CCR7) and lytic mediators (high granzyme K) show a phenotypic similarity with cells isolated from MS and non-MS brain tissue.[11,19] This observation suggests this CD8$^+$ T-cell fraction to be enriched for precursors of cells, which home into the brain parenchyma in MS.

On the whole, Koto et al. draw the spotlight on the role of CD8$^+$ T cells in MS and show that a distinct profile of inhibitory receptors and transcriptional regulators characterizes 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.[6] 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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