Repertoire Remodeling through CD4$^+$ T-cell Depletion

Winnie Yao and Ansuman T. Satpathy

Understanding the cellular regulation of tumor-specific CD8$^+$ T-cell responses is critical to designing improved clinical strategies for cancer immunotherapy. In this issue, Aoki and colleagues deepen our knowledge of this topic by demonstrating that transient depletion of CD4$^+$ T cells in patients with gastrointestinal cancer induces remodeling of the T-cell repertoire, including clonal replacement and expansion of CD8$^+$ T-cell clones shared between the blood and tumor.

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The interplay of CD4$^+$ and CD8$^+$ T cells in the antitumor response is complex: CD4$^+$ Th cells can promote CD8$^+$ T-cell immunity, whereas CD4$^+$ regulatory T cells can do the opposite. In animal models, depletion of CD4$^+$ T cells enhances the expansion of intratumoral CD8$^+$ T cells and the resulting antitumor response (1, 2). Whether CD4$^+$ T-cell depletion would have the same effect in human cancers has remained an open question. In this issue, Aoki and colleagues characterize the clonal dynamics of the T-cell repertoire after transient CD4$^+$ T-cell depletion in the context of a first-in-human trial of the CD4-specific antibody IT1208 (3).

To analyze the T-cell response after CD4$^+$ T-cell depletion, Aoki and colleagues performed flow cytometry and T-cell receptor (TCR) repertoire sequencing of peripheral blood T cells in 11 patients with gastrointestinal cancer. They find that treatment with IT1208 leads to a transient decline in CD4$^+$ T-cell and CD8$^+$ T-cell numbers posttherapy, with peak depletion at day 15 posttherapy. Following T-cell repopulation, there are changes in the clonal composition of the circulating T-cell repertoire: namely, repopulation is driven by the expansion of CD4$^+$ and CD8$^+$ T-cell clones present at low frequencies in the blood pretherapy rather than by previously expanded clones. This clonal replacement of T cells posttherapy is accompanied by an increase in the total number of CD8$^+$ effector T cells.

To determine whether newly expanded T-cell clones traffic to the tumor microenvironment (TME), Aoki and colleagues analyzed the TCR repertoire of tumor biopsies obtained pre- and posttherapy and compared their clonal overlap with circulating T cells. They show that the frequency of blood–tumor overlapping clones increases posttherapy, and this effect is stronger in patients receiving a higher dose of IT1208, particularly in patients who had a clinical response to therapy. The blood–tumor clonal overlap includes the newly expanded CD8$^+$ T-cell clones present in the blood, suggesting that they could enter the TME and mediate an antitumor response. Most blood–tumor overlapping clones remain expanded at later posttherapy timepoints.

In summary, this study provides several new insights: (i) Transient depletion of CD4$^+$ T cells can lead to the clonal replacement of CD4$^+$ and CD8$^+$ T cells in the blood, (ii) new T-cell clones in the blood postdepletion are able to traffic to the tumor, and (iii) blood–tumor overlapping clones can persist long-term posttherapy. These insights lead to several open questions. First, is the effect of CD4$^+$ T-cell depletion mediated by the loss of specific CD4$^+$ T-cell populations, the nonspecific clearance of T-cell niches, or both? Second, what underlies the differences in TCR dynamics observed between responding and nonresponding patients? Perhaps such variability reflects differences in the cellular composition of the TME, for example, the balance of helper and regulatory CD4$^+$ T cells. Finally, how might CD4$^+$ T-cell depletion synergize with other immunotherapy agents? Prior studies in mice suggest synergy with PD-1 blockade, and indeed, clonal replacement following IT1208 treatment is reminiscent of a similar phenomenon observed following PD-1 blockade (4). It is possible that both treatment strategies may converge on synergistic cellular targets in the cancer–immunity cycle that ultimately lead to the priming or activation of new tumor-specific T-cell clones. Future work refining our understanding of these points of synergy may hold the keys for designing more effective immunotherapeutic strategies for cancer.

Authors' Disclosures

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Department of Pathology, Stanford University School of Medicine, Stanford, California.

Corresponding Author: Ansuman T. Satpathy, Stanford University, Stanford, CA 94305. E-mail: satpathy@stanford.edu

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