Severity of COVID-19 disease is greater in patients with cancer and further increased if the cancer has metastasized (1). The ability of patients with cancer to control SARS-CoV-2 infection depends on the cancer type. Patients with hematologic malignancies are at highest risk of severe COVID-19. Lung cancer is also associated with increased severity of COVID-19 disease compared with breast and gastrointestinal cancers.

CD4 T-cell activity is progressively amplified during SARS-CoV-2 infection, with frequency of SARS-CoV-2–specific CD4 T cells increasing within days after onset of symptoms during acute infection (2). Frequencies of SARS-CoV-2–specific CD4 T cells are significantly reduced in COVID-19 patients with most severe disease. Thus, an effective CD4 T-cell response appears to be critical for proper control of COVID-19 disease. SARS-CoV-2–specific CD4 T cells increase in numbers with age in COVID-19 patients, although their function becomes skewed toward IL2 over IFNγ production with increasing age. Preexisting CD4 memory T cells specific to common cold coronavirus infections may cross-react to SARS-CoV-2 epitopes. These cross-reactive CD4 T cells are reactivated upon primary COVID-19 vaccination and can expand during primary SARS-CoV-2 infection. The frequency of cross-reactive CD4 T cells correlates with the amount of serum antibodies directed toward the spike protein. This suggests a favorable effect of preexisting CD4 T-cell cross-reactivity on humoral response to SARS-CoV-2, although further studies are needed to better assess the functional role of CD4 T-cell cross-reactivity in COVID-19 patients (3).

In this issue of *Cancer Discovery*, Bilich and colleagues characterize the effects of cancer on T-cell responses to SARS-CoV-2 infection in patients with cancer (4). T-cell cross-reactivity to SARS-CoV-2 was first assessed in non–SARS-CoV-2–infected patients with cancer (n = 199) and healthy donors (n = 94) using IFNγ ELISpot assays. HLA class I–restricted SARS-CoV-2 cross-reactive T cells are reduced in cancer, with the greatest effect in patients with hematologic malignancies, while frequencies of HLA-DR–restricted cross-reactive T cells remain unchanged. This reveals an impairment of the preexisting SARS-CoV-2–reactive CD4 memory T-cell compartment in patients with cancer. SARS-CoV-2–specific T-cell responses were then characterized in COVID-19 patients with (n = 17) and without (n = 193) cancer. Recognition of HLA-DR–restricted SARS-CoV-2–specific epitopes is significantly decreased in patients with hematologic malignancies or solid tumors. In addition, SARS-CoV-2–specific CD4 T cells recognize a more limited epitope repertoire in COVID-19 patients with cancer. This loss of CD4 T-cell diversity in patients with cancer associates with higher severity of the disease. The authors further highlight elevated expression of the exhaustion marker PD-1 on CD4 T cells in uninfected patients with cancer, with the highest levels observed in patients with hematologic malignancies.

This is the first study to demonstrate impaired CD4 T-cell response to SARS-CoV-2 infection in patients with cancer, both for preexisting cross-reactive and for newly generated SARS-CoV-2–specific CD4 T cells. Patients with hematologic malignancies display the most pronounced impairment of SARS-CoV-2 cross-reactive CD4 T cells, in parallel with highest expression of PD-1 on CD4 T cells. Upregulation of PD-1 on T cells is part of a dysregulation process that limits T-cell function in cancer and in response to chronic viral infections (5). Thus, immune checkpoint blockade strategies targeting PD-1 and PD-1 ligands have been developed and have transformed cancer therapy. In fact, PD-1 expression has recently been shown to increase on SARS-CoV-2–specific CD4 T cells during acute infection and followed by a decrease in expression upon convalescence (2). However, expression levels of PD-1 on SARS-CoV-2–specific CD4 T cells do not associate with severity of the disease. In addition, emerging evidence suggests that PD-1+ CD8 T cells are more potent in producing IFNγ than PD-1− CD8 T cells in convalescent COVID-19 patients (6). PD-1 expression on both CD4 and CD8 T cells further associates with stronger response to SARS-CoV-2 antigen presentation by autologous dendritic cells (7). Thus, PD-1 may be marking activated SARS-CoV-2–specific CD4 T cells that are recruited upon acute infection and might not further induce functional exhaustion of these cells.

The results obtained by Bilich and colleagues suggest that CD4 T cells need to be reinvigorated in patients with cancer to respond to SARS-CoV-2 infection. Does cancer
have a similarly negative impact on CD4 T-cell response to COVID-19 vaccine? A recent study evaluated CD4 T-cell response to primary COVID-19 vaccination (BNT162b2) in patients with chronic myeloid leukemia receiving tyrosine kinase inhibitors (8). Nine of the 15 (60%) patients displayed a polyfunctional CD4 T-cell response, as defined by a 3-fold increase in production upon vaccination of at least two cytokines among IL2, TNFα, and IFNγ. Of note, patients under nilotinib treatment had the highest numbers of polyfunctional TNFα+ IFNγ+ CD4 T cells following vaccination. Future studies should further assess the effects of cancer and anticancer therapy on CD4 T-cell response to COVID-19 vaccine. In addition, impaired CD4 T-cell response to SARS-CoV-2 infection provides new rationale for considering PD-1 blockade therapy in patients with cancer with COVID-19 disease. Administration of anti–PD-1 therapy prior to SARS-CoV-2 infection has been evaluated in patients with lung cancer who received anti–PD-1 within 6 weeks (n = 20), 3 months (n = 13), or 6 months (n = 30) of COVID-19 diagnosis (9). Anti–PD-1 treatment globally does not affect the course of COVID-19 disease in these patients. However, patients receiving anti–PD-1 within 6 weeks prior to COVID-19 diagnosis tend to develop less severe disease compared with patients receiving anti–PD-1 within 3 to 6 months prior to diagnosis. In addition, severe disease was found in only 2 of 13 patients with melanoma treated with anti–PD-1 antibody alone or in combination with CTLA4 blockade therapy within 0 to 51 days prior to SARS-CoV-2–positive test (10). The evidence to date suggests that SARS-CoV-2 infection does not enhance immune-related toxicities associated with PD-1 and CTLA4 blockade immunotherapies when administered prior to infection. However, abrogating PD-1–mediated inhibition during SARS-CoV-2 infection also raises concerns, as adverse events for this therapy may include cytokine storms, which are also found in severe COVID-19 disease. Clinical trials are evaluating the safety and efficacy of PD-1 blockade strategies in COVID-19 (e.g., NCT04356508, NCT04335305, NCT04413838, NCT04343144). If proven safe, this therapy might be of choice to unleash SARS-CoV-2–reactive CD4 T-cell inhibition in patients with cancer, especially with hematologic malignancies.

Should patients with cancer and COVID-19 be treated with anti–PD-1 blockade? Bilich and colleagues provide new rationale for considering immune checkpoint blockade in patients with cancer and COVID-19, although safety and efficacy of this therapeutic strategy remain to be further investigated in future studies.

Authors’ Disclosures

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REFERENCES
