Strong grasp of immune response dynamics will enhance checkpoint blockade

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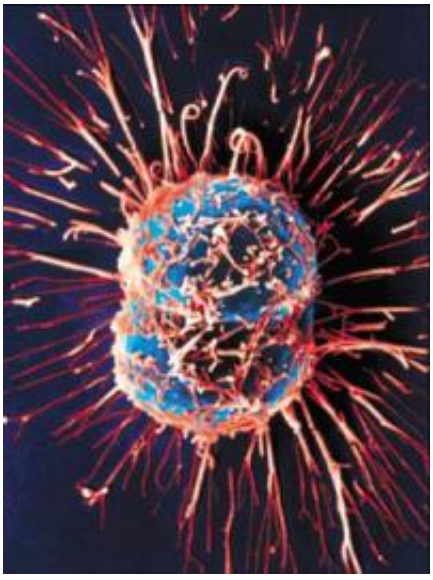

Dividing Cancer Cells. Credit: University of Birmingham

Spreading the success of cancer immunotherapy beyond those patients currently enjoying powerful, long-term responses to treatment requires greater understanding of the immune response to tumors, two leaders in the field note in a review in the April 3 *Science*.

"Identifying in advance who will benefit from treatment and developing combination therapies to improve and expand on current results will require us to decipher the dynamics of human immune response to tumors and their surrounding microenvironment," said co-author

Padmanee Sharma, M.D., Ph.D., professor of Genitourinary Medical Oncology and Immunology at The University of Texas MD Anderson Cancer Center.

Immune checkpoint blockade, the unleashing of immune response against cancer by blocking molecules on T cells that shut down those attacking cells, produces durable results and long-term survival in a substantial fraction of patients with some cancers. For example, 22 percent of advanced melanoma patients treated with ipilimumab (Yervoy), the first checkpoint inhibitor, live for four years or longer. Right now there's no way to identify those most likely to benefit.

Ipilimumab and a second group of drugs that thwart a different brake on the immune system both set off a complicated cascade of events, said co-author Jim Allison, Ph.D., chair of Immunology at MD Anderson, who pioneered checkpoint blockade as a cancer therapy.

"We know the constantly evolving nature of immune responses makes it highly unlikely that a single biomarker could predict a patient's response to one of these drugs," Allison said. The goal should be to develop biomarker panels to help cultivate combination therapies and then examine tumor tissues for changes in those biomarkers to increase treatment impact.

Allison is executive director and Sharma scientific director of the immunotherapy platform for MD Anderson's Moon Shots Program. The program is designed to accelerate the conversion of scientific discoveries into clinical advances that significantly reduce cancer deaths. The platform has conducted immune monitoring analysis of tumor tissues in more than 50 MD Anderson clinical trials in the past two-plus years.

Barriers to T cell activation and attack

Targeted cancer therapies, designed to hit specific mutations on a cancer cell, come with ready-made predictive biomarkers. Patients whose tumors have the mutation receive the targeted therapy. In contrast, immune checkpoint blockade doesn't directly target tumors. It treats the immune system, freeing it to find and kill cells bearing recognized tumor antigens.

Immune response, the authors note, particularly regulation of T cells, consists of opposing pathways both to stimulate immune response and to inhibit it. Ipilimumab blocks a molecule on T cells called CTLA-4, which is turned on by the same binding molecules, or ligands, that stimulate a T cell response. CTLA-4's job is to block runaway immune response.

Once a T cell attack is launched, the review notes, it then faces a variety of barriers and defenses mounted by the tumor cells, supportive tissue, regulatory T cells and other inhibitory cells, as well as chemical signaling agents in the tumor microenvironment.

PD-1 checkpoint blockade

One such barrier is a target for the second type of checkpoint blockade. T cells have another checkpoint, called PD-1. PD-1 is turned on by two ligands, one of which, PD-L1, is found on tumors and other cells in the tumor microenvironment, including blood vessels and supportive tissue. PD-L1 provides these cells with a direct off switch for activated T cells.

Two antibodies to thwart PD-1, nivolumab (Opdivo) and pembrolizumab (Keytruda) have been approved for advanced melanoma and nivolumab recently was approved for advanced non-small cell lung cancer. Both drugs are also in clinical trials against a variety of cancers.

Early work indicated that expression of PD-L1 in a patient's tumors

could be a precise predictive biomarker for treating patients with drugs that block either PD-1 or PD-L1. The review notes that an initial clinical trial for melanoma reported a 37 percent overall response rate for patients treated with nivolumab whose tumors expressed PD-L1 and zero responses for those lacking it.

Other phase I and II clinical trials demonstrated higher response rates for those with PD-L1 expression, ranging from 43-46 percent of patients, yet also showed significant response rates among those without PD-L1 expression, ranging from 11 to 17 percent. This complex twist would exclude patients who might otherwise benefit if PD-L1 expression dictates treatment.

"On the basis of data reported so far, it seems fair to conclude that PD-L1 expression in tumor tissues shouldn't be used as a predictive biomarker for selection or exclusion of patients for treatment with anti-PD-1 or anti-PD-L1 antibodies," Sharma and Allison note.

Monitoring multiple components in the microenvironment

More immune checkpoints and stimulatory molecules have been identified on T cells, presenting new potential targets for therapy. And the potential combinations of checkpoint blockade with surgery, radiation, chemotherapy, hormonal therapy and targeted agents are legion.

Efficiently sorting this out, Sharma and Allison note, will require monitoring of multiple immunologic biomarkers in tumors and related tissues before, during and after treatment.

The authors note a useful distinction might be made between tumor

microenvironments that are "hot" or inflamed by immune response with abundant presence of immunologic markers, including PD-L1; and those that are "cold" with fewer or virtually no signs of immune response.

"Hot" environments will lend themselves more to PD-1 or PD-L1 blockade, while CTLA-4 and combinations therapies can work better in the "cold" environment, in part by turning it hot.

Another important research avenue is genetic analysis of mutations in tumors that might, cumulatively, make them more vulnerable to checkpoint blockade. Researchers analyzing melanoma tumors treated with ipilimumab have found that tumors with higher numbers of mutations - mutational load - correlate with better clinical response to the drug, possibly by creating new antigens on tumors for T cells to recognize and attack.

Specificity, adaptability and memory increase curative possibilities

The immune system's ability to launch specific T cell attacks against tumor cells, then adapt that attack as cancer cells change, and to remember all of the target antigens provide an opportunity to monitor multiple components with therapeutic potential over time, the review notes.

"(These attributes) make it essential to expand our efforts to find rational combinations to unleash antitumor immune responses that will benefit cancer patients. Properly done, it seems likely that cures for many types of cancer will soon become a reality," the review concludes.

More information: The future of immune checkpoint therapy, www.sciencemag.org/lookup/doi/ … 1126/science.aaa8172

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