Donor T Cells May Enhance Immunotherapy

A new study suggests that T cells from healthy donors recognize many neoantigens—mutant peptides on the surface of tumor cells, formed as a result of DNA damage—that are often neglected by a patient’s own immune system (Science 2016;352:1337–41). As such, it may be possible to “outsource” neoantigen-induced immune reactivity to donor T cells, and thereby enhance patients’ response to immunotherapy.

In a healthy immune system, the T-cell receptor (TCR) of each T cell has the capacity to recognize a different peptide, explains co-senior author Tor Schumacher, PhD, of the Netherlands Cancer Institute in Amsterdam: The body’s own peptides are overlooked, while foreign or mutated peptides trigger T cells to proliferate and mount an attack. However, in the weakened immune system of a patient with cancer, endogenous T cells may lose their ability to recognize tumor-expressed neoantigens as foreign. In this setting, according to this proof-of-principle study, outfitting patient T cells with TCRs from healthy donor T cells that recognize specific neoantigens on their tumors could be a feasible strategy.

Schumacher and his colleagues used whole-exome and RNA sequencing to map all possible neoantigens on tumor cells from a patient with melanoma, endogenous T cells may lose their ability to recognize tumor-expressed neoantigens as foreign. In this setting, according to this proof-of-principle study, outfitting patient T cells with TCRs from healthy donor T cells that recognize specific neoantigens on their tumors could be a feasible strategy.

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The project’s investigators, led by Nikhil Wagle, MD, a medical oncologist at DFCI, aim to create a repository of mineable data to speed breast cancer genomics research, better understand drug resistance, and provide leads for the development of new therapies.

To that end, trial participants, all of whom have metastatic disease, agreed to share their medical records with investigators, provide saliva samples for the extraction of germline DNA, and make their tumor tissue available for next-generation sequencing.

Roughly 85% of patients with breast cancer are treated in community settings, where their tissue samples are collected only for initial diagnosis, then stored and not routinely made available for research, Wagle said. Until now, “no one has asked if they’d be willing to share [their samples] with researchers for discovery.”

Joanne Mortimer, MD, director of the women’s cancers program at City of Hope Comprehensive Cancer Center in Duarte, CA, who is not involved in the project, described it as “brilliant.” Patients want to contribute their data so they can better understand their own disease and help others, she said. “Nobody wants to feel like they’ve died in vain.”

To date, most of the project’s participants are white women, Wagle said. He has started additional outreach efforts with advocacy groups to diversify the patient cohort.

“We should be able to reach lots of different people who haven’t been studied using traditional approaches,” he said. Gathering data from patients of different racial and ethnic backgrounds will help fill gaps in knowledge, such as why black women with breast cancer have poorer outcomes than whites.

The power of such patient-driven research, Wagle said, is that it pools different people who haven’t been studied by cancer vaccines. The identification of these neoepitopes suggests that in NSCLC, a significant fraction of tumors may respond to immune checkpoint inhibitors, Meyerson observes.

Additionally, he says, this study shows that the two main NSCLC subtypes are more distinct than previously thought. Of 38 mutated genes detected in the lung ADC samples, and 20 detected in lung SCCs, only six were shared by both subtypes. In fact, the mutations and amplifications noted in lung SCC were found to be more similar to other cancers associated with smoking—including head and neck SCC and bladder cancer—than to lung ADC.

“It indicates that there are some very similar pathway abnormalities and mutations that accompany squamous cell tumors, regardless of where they originate,” says Stephen Baylin, MD, co-director of the cancer biology research program at the Sidney Kimmel Comprehensive Cancer Center in Baltimore, MD. “As such, there may be common management strategies that could be used to treat these types of cancer.”

Further research is needed into the role of neoepitopes in immunotherapy, Meyerson notes. “We need to understand the relationship between neoepitopes, especially recurrent ones, and patient responses to immune checkpoint inhibitors,” he says. “Future studies should seek to determine whether predicted cancer neoepitopes are in fact leading to immune responses in lung cancer.” -Janet Colwell ■

**New Driver Mutations Detected in NSCLC**

A comprehensive genomic analysis of non–small cell lung cancer (NSCLC) has identified additional driver mutations that may guide the development of new targeted drugs and immunotherapy. The findings also highlight key differences between subtypes of NSCLC that could inform future therapeutic management strategies (Nat Genet 2016;48:607–16).

The study researchers profiled two major subtypes of NSCLC via whole-exome sequencing: 660 lung adenocarcinoma (ADC) and 484 lung squamous cell carcinoma (SCC) samples. They found multiple mutated genes along the RAS–RAF signaling pathway that had not been associated with lung ADC, including SOS1, RAS1A1, and VAV1.

Current targeted therapy research in lung ADC is largely focused on inhibiting receptor tyrosine kinases, including EGFR, that activate RAS–RAF signaling and are often mutated in this disease. The discovery of previously unknown players along a main driver pathway in lung ADC extends the realm of possible therapeutic targets, says senior author Matthew Meyerson, MD, PhD, professor of pathology at Dana-Farber Cancer Institute in Boston, MA. It also underscores the importance of using large sample sizes in genomic studies, he adds. For example, SOS1 was already known to be mutated in patients with Noonan syndrome, a genetic disorder, but previous smaller studies failed to identify it in lung ADC.

The team also found that 47% of lung ADC and 53% of lung SCC samples had at least five neoepitopes—peptides arising from somatic tumor mutations—that could potentially be targeted by cancer vaccines. The identification of these neoepitopes suggests that in NSCLC, a significant fraction of tumors may respond to immune checkpoint inhibitors, Meyerson observes.

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**Single-Agent Abemaciclib Active in Breast Cancer**

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