An Overlooked Reservoir of Cancer-Fighting Cells

Cancerous tumors are hostile environments where T cells fight to kill cancer cells, which in turn try to kill or silence the T cells. "That's where we started," said Nikhil Joshi, PhD, Assistant Professor of Immunology. "We figured that if T cells inside the tumor constantly get killed or shut off, how are there still enough of them in there to get activated when a patient receives immunotherapy?"

The answer surprised him and Kelli Connolly, PhD, a postdoctoral associate in his lab. Using a mouse model, they found that dead or exhausted T cells in the tumor were constantly replenished by a slow trickle of fresh T cells that infiltrate the tumor from reservoirs in nearby tumor-draining lymph nodes. These T cell reinforcements fight the progression of the disease and likely boost the tumor's response to immunotherapy. Drs. Joshi and Connolly's findings were reported in September 2021 in *Science Immunology*.

Researchers previously knew that lymph nodes contain T cells that are activated to invade when tumor cells develop nearby. "What wasn't understood," said Dr. Connolly, "is that this migration continues as the tumor progresses, which could be for years."

"It never made sense to look for T cells in the lymph nodes," added Dr. Joshi, "because once they were activated, why would they stay in the lymph node and not go to the tumor? It's clever that the immune system hangs on to these cells offsite and sends them out later."

In fact, noted Dr. Connolly, clinicians often see these lymph nodes as places where the tumor might spread, so clinicians sometimes remove them, thus eliminating the reservoir of T cells. Dr. Connolly hopes the new paper shifts that perspective.

The discovery of this unknown migration was a breakthrough, but Drs. Joshi and Connolly are more energized by its implications for cancer treatment. Most tumors—typically about 80 percent—do not respond to immunotherapy. What would happen, wonder Drs. Joshi and Connolly, if that reservoir of T cells in the lymph nodes could be induced to migrate en masse into a tumor? Current immunotherapies do not seem to prompt the T cells to leave the lymph nodes.

"I would say the most exciting part of our findings is that they suggest we can target T cells in the draining lymph nodes to make some immunotherapies more effective," said Dr. Connolly.

Dr. Joshi agrees. In the future, cancer patients whose tumors don't contain enough T cells to fight the disease might be able to tap a reservoir close by. Figuring out how to make that happen is the next task for Drs. Joshi and Connolly.

They suspect that the T cells in the lymph nodes get a signal telling them to migrate. If the researchers can detect and mimic that signal, they could induce migration. "We envision finding the mechanism that gets T cells out of the lymph nodes and into the tumor," said Dr. Connolly. "I think that's what we see as most promising therapeutically. That could help the large group of patients who don't respond to immunotherapy." They envision this prospective immunotherapy augmenting current immunotherapy treatments, possibly along with chemotherapy and radiation.

Drs. Joshi and Connolly are already exploring prospects in mouse models, trying various drugs that might stimulate migration of T cells into the tumor. Dr. Connolly mentions another way to translate their research more quickly: CAR T cell therapy, an immunotherapy in which T cells from a patient's tumor are removed, genetically altered, then grown in high numbers and reinserted into the patient.

"Our research has lots of implications for therapies that currently use T cells from tumors," she noted, "because our findings show there is this other excellent source of T cells—the tumor draining lymph nodes—where you most likely will get more and better-functioning T cells than you can get from the tumor."

Drs. Joshi and Connolly have already been approached by clinical researchers at Yale who recognize the promise of this possibility. If the two immunologists can identify the mechanism that releases the T cells from the lymph nodes, there are also clinical collaborators at Yale interested in refining a drug design and running trials.

"Yale is great in that aspect," said Dr. Joshi, "There are a lot of people here eager to collaborate to solve these problems. So, the chances are high that this discovery gets translated into meaningful gains for patients."

Their paper also drew attention to Dr. Joshi's advanced mouse model, which took him eleven years to develop. It was a big reason Dr. Connolly wanted to work in his lab, and now researchers are requesting it from all over, which delights Dr. Joshi. "We're sending it out," he said, "and hoping that people will use it to achieve breakthroughs in their own work."