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?”

“Tumor immunologists have known for years 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,” said Dr. Joshi. “We’re excited to make that connection to the cancer patients’ longitudinal persistence of the disease and likely boost the tumor’s response to immunotherapy. Dr. 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.”

“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 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 we suspect we 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 do not contain enough T cells to fight the disease might be able to tap a reservoir close by. Experimenting out how to make that happen is the next task for Drs. Joshi and Connolly.

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“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 might likely get more and better-functioning T cells than you can get from the tumor.”

An Overlooked Reservoir of Cancer-Fighting Cells

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

“T cells are great at that,” said Dr. Joshi. “There are a lot of people keen 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.”