New insights could unlock immunotherapy for rare, deadly eye cancer

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New research from the University of Pittsburgh explains why metastatic

uveal melanoma is resistant to conventional immunotherapies and how adoptive therapy, which involves growing a patient's T cells outside the body before reinfusing them, can successfully treat this rare and aggressive cancer.

In a paper published in *Nature Communications*, the Pitt researchers also explain how they developed a new clinical tool that predicts which patients will respond to adoptive therapy. The work is helping improve personalized therapies and avoid futile treatments for metastatic uveal melanoma.

"The dogma was that uveal melanoma is a 'cold' cancer, meaning that T cells can't get into these tumors," said senior author Udai Kammula, M.D., associate professor of surgery at Pitt and director of the Solid Tumor Cell Therapy Program at UPMC Hillman Cancer Center.

"We show that T cells are in fact infiltrating metastases and they're getting activated, but they're just sitting there in a dormant state because something in the tumor is suppressing them. Adoptive therapy allows us to rescue these cells from the suppressive tumor microenvironment and successfully treat some patients."

Uveal melanoma originates in the uveal tract of the eye but has a tendency to aggressively spread throughout the body, often to the liver. When metastasis occurs, this cancer is very difficult to treat and the prognosis for patients is almost always grim.

"Cutaneous melanoma, which affects the skin, is the poster child of immunotherapy. It responds incredibly well to immune checkpoint inhibitor drugs," said Kammula. "None of these conventional immunotherapies work for uveal melanoma, but we hadn't known why—until now."

In a previous *Lancet Oncology* study, Kammula and his team used adoptive therapy to surgically extract metastatic tumors from 19 uveal melanoma patients and grow T cells from these tumors in the laboratory. When they infused the cells back, 35% of patients had either partial or complete regression of their cancer, evidence against the assumption that cancer-fighting cells called tumor-infiltrating lymphocytes (TILs) aren't found in uveal melanoma. But it was still a mystery why immune checkpoint inhibitors, which rev up the activity of these T cells, are ineffective in treating this disease.

Kammula saw an opportunity to answer this question using a unique resource that he and his team have been building for the last decade: the largest known repository of uveal melanoma samples, corresponding tissues and clinical information.

When the researchers analyzed 100 metastases from 84 patients, they found that over half of these tumors were chock-full of T cells. Next, they performed single cell RNA sequencing to measure gene expression in almost 100,000 cells from six metastases. They found that the TILs in some of these tumors were activated and capable of attacking tumor cells in a dish, but they weren't proliferating to high numbers in the tumor.

"We found that TILs from metastatic uveal melanoma have the potential to attack the tumor, but something in the tumor microenvironment is shutting them down, so they're in a dormant, or quiescent, state," explained Kammula. "By liberating these cells from the suppressive environment and growing them in the lab, we can rescue their tumor-fighting capacity when infused back into the patient."

But TIL therapy doesn't work for everyone, as the researchers found in their earlier study. To predict which patients will respond and which will not, Kammula and lead author Shravan Leonard-Murali, M.D., a post-

doctoral fellow in the lab, developed a clinical tool called Uveal Melanoma Immunogenic Score (UMIS), a holistic measure of the tumor that reflects the activity of more than 2,000 genes expressed by tumor cells, immune cells and other cells that form the tumor microenvironment. UMIS ranged from 0.114 to 0.347 across 100 metastases, with higher values indicating tumors with more potent TILs.

When the researchers looked at patients who received adoptive therapy in the earlier study, they found that patients with higher UMIS scores had better tumor regression, suggesting that this biomarker could predict which patients are likely to respond.

They also found that patients with metastases scoring above 0.246 had significantly improved progression-free survival and overall survival than those with UMIS below this cutoff.

"If a patient's UMIS level is below this threshold, we think that adoptive therapy is not appropriate. Using a biopsy to calculate a patient's UMIS could help avoid futile therapies and unnecessarily subjecting patients to invasive operations," said Kammula.

"But the immune system is not static. UMIS offers a window into the tumor that could also help us find the optimal time to treat a patient with adoptive therapy, like picking a fruit when it's at its ripest."

Kammula is now evaluating the score prospectively in an ongoing TIL therapy clinical trial at Pitt for patients with metastatic uveal melanoma.

He and his team are also taking what they've learned from uveal melanoma to tackle other difficult-to-treat tumors such as pancreatic cancer, and they are developing a pan-cancer version of UMIS that will predict how well a patient with any type of cancer is likely to respond to adoptive therapy.

More information: Uveal melanoma immunogenomics predict immunotherapy resistance and susceptibility, *Nature Communications* (2024). DOI: 10.1038/s41467-024-46906-4