Immune responses against a virus-related skin cancer suggest ways to improve immunotherapy

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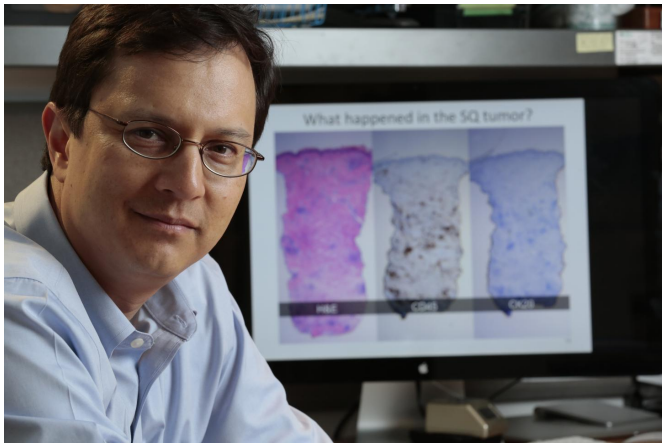

"We found that a surprisingly low number of patients -- only about 20 percent -- had T cells specific for the 'KLL' region of the virus. This suggests that about 80 percent of patients aren't making T cells that recognize this very prominent target," said Dr. Paul Nghiem, affiliate investigator of the Clinical Research Division at Fred Hutch, and professor of medicine, Division of Dermatology at the University of Washington School of Medicine. Credit: Fred Hutch News Service

Researchers at Seattle's Fred Hutchinson Cancer Research Center and the University of Washington say a new study suggests ways to improve immune therapy for certain cancers including a virus-associated form of Merkel cell carcinoma, a rare, aggressive skin cancer.

Merkel cell carcinoma, or MCC, is 35 times less common than melanoma, but on average, it is about three times more likely to be deadly. There are currently no therapies approved by the Food and Drug Administration for this cancer. About 80 percent of the 2,000 new cases diagnosed in the U.S. each year are caused in part by a virus - Merkel cell polyomavirus - that is often present on normal skin without consequence.

Previous studies have linked a weaker immune system with poorer survival in patients with the disease. In this study, researchers at UW and Fred Hutch, a leading center developing experimental, genetically engineered T-cell therapies, conducted an unprecedented in-depth analysis of the immune system's "killer" (CD8) T cells that respond to a specific part of the Merkel cell polyomavirus.

The immune system's effectiveness is determined by many factors, including how well T cells can infiltrate a tumor and bind to the "foreign" proteins, or antigens. More specifically, T cells seek out and attach to antigens using their highly diverse T-cell receptors. In this multicenter study, the researchers focused on T cells that target a piece of the virus referred to as "KLL".

"We found that a surprisingly low number of patients - only about 20 percent - had T cells specific for the 'KLL' region of the virus. This suggests that about 80 percent of patients aren't making T cells that recognize this very prominent target," said Dr. Paul Nghiem, affiliate investigator of the Clinical Research Division at Fred Hutch, and professor of medicine, Division of Dermatology at the University of Washington School of Medicine.

Nghiem, senior author of an article published online Jan. 16 in *Cancer Immunology Research*, said the study is important because an increase in the KLL-specific T cells infiltrating the tumor is associated with a striking improvement in patient survival.

First author Natalie Miller, an MD/PhD student in Nghiem's research lab, performed in-depth analysis on blood and tumors from 12 patients who had T cells that could recognize KLL.

"T cells that recognize this part of the virus are incredibly diverse. In fact, among these 12 patients, there were 397 unique ways for the T cells to recognize this single short piece of the virus; only one T-cell receptor was shared between two patients," Miller said. "In addition, T cells from patients with better outcomes tended to stick to the viral target more tightly. This suggests that while nature has created many ways for the immune system to fight this cancer, some ways are better than others. Our hope is that these 'better' T-cell receptors can be turned into a therapy for patients who do not have them."

At diagnosis, virus-associated MCC is typically treated with surgery and radiation, and although 95 percent of patients appear to be cancer-free, the disease returns in about half of cases, Nghiem said. The cancer often responds to chemotherapy, but the response is short-lived, with most tumors progressing about three months after treatment begins.

In April, Nghiem's group published findings of a phase 2 clinical trial of the immunotherapy drug pembrolizumab, reporting that the "checkpoint inhibitor" helped to revive "exhausted" T cells, providing significant and lasting responses in more than half of patients.

With their new findings, the research team expects to propose the launch of a clinical trial in which T cells engineered with the most effective tumor tracking and attacking receptors would be transferred to patients who are unable to mount an effective immune response of their own.

"Like Merkel cell carcinoma, cancers that have a viral component provide a variety of potential targets for immunotherapy. We're eager to find out if transgenic T cell therapy can 'reprogram' lymphocytes to eliminate tumors in combination with checkpoint inhibition," Nghiem said.

More information: Natalie J. Miller et al. Tumor-Infiltrating Merkel Cell Polyomavirus-Specific T Cells Are Diverse and Associated with Improved Patient Survival, *Cancer Immunology Research* (2017). DOI: 10.1158/2326-6066.CIR-16-0210

Provided by Fred Hutchinson Cancer Research Center

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