Killer T cells recognize cancer in pre-clinical tumors, but are silenced as tumor develops

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One of the challenges for developing truly successful immunotherapies is that cancer is a wily foe for the immune system. Tumors have multiple lines of defense against our immune cells' attempts to attack them. Although our immune cells are trained early in development to not recognize and harm our own cells, cancerous cells bear many tumor-specific molecules, or antigens—molecules which, in theory, could spur a potent immune response, if the tumors weren't able to block such a response. An outstanding puzzle in the immunotherapy field concerns the early stages of tumor development, in which cancerous cells acquire "driver" mutations in some of their genes. Such driver mutations are responsible for directing the cell to behave as a cancer, and can change the appearance of the cells to the point that they could be recognized as foreign by the immune system, but to date researchers have had difficulty finding evidence that our immune cells actually recognize these very early stages of tumor formation.

Now, a new study in mice demonstrates that certain immune cells, known as CD8+ T cells or killer T cells, can in fact recognize such driver mutations but are quickly and permanently silenced by the tumor—at stages before a human tumor would even be clinically recognizable. If researchers could figure out a way to reverse that silencing, such strategies could rescue the tumor-recognizing T cells and improve the performance of certain immunotherapies, including that of so-called checkpoint inhibitor drugs that release some of cancer's brakes on the immune system. Such inhibitors, which include the drug pembroluzimab, allow patients' bodies to mount an immune response to mutations that have cropped up later in cancer's progression.

"Our results highlight that driver mutations, which theoretically would be the most effective antigens to target because they represent the basis for a tumor behaving as a tumor, are not immunologically silent and can indeed be recognized," said Fred Hutchinson Cancer Research Center immunologist Dr. Phil Greenberg, who led the study along with Dr. Andrea Schietinger, a former Fred Hutch postdoctoral research fellow who now leads an immunotherapy lab at Memorial Sloan Kettering Cancer Center. The study was published Aug. 9 in the journal *Immunity*. Greenberg and his research team are now pursuing two strategies to build off their findings. These focus on:

- Defining the molecules that render the tumor-recognizing T cells dysfunctional, with the ultimate goal of disrupting those silencing molecules, and
- Engineering T cells in the laboratory for eventual therapeutic use that recognize the driver mutations but cannot be shut off by tumors.

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