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Mouse model exposes a new type of T cell to target melanoma

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Cancers arise in the body all the time. Most are nipped in the bud by the immune response, not least by its T cells, which detect telltale molecular markers—or antigens—on cancer cells and destroy them before they grow into tumors. Cancer cells, for their part, evolve constantly to evade such assassination. Those that succeed become full-blown malignancies. Yet, given the right sort of help, the immune system can destroy even these entrenched tumors.

In the October 22nd issue of the Journal of Experimental Medicine, researchers led by Jedd Wolchok, MD, PhD, of the Ludwig Center for Cancer Immunotherapy at Memorial Sloan-Kettering Cancer Center (MSKCC) in New York describe one way in which that might be achieved. The paper relates how the cancer drug cyclophosphamide (CTX) and OX86—an antibody that activates a molecule named OX40 on T cells—were combined with a cutting-edge therapy known as adoptive T cell transfer to eradicate advanced melanoma tumors in mice.

Wolchok and his colleagues had previously shown that CTX and OX86 treatment caused the regression of such tumors. Now they wanted to see if adding T cell transfer to the mix would further improve outcomes. T cell transfer is an investigative immunotherapy in which T cells that target tumors are isolated from patients, manipulated, expanded and then transfused back into those patients.

A variety of T cells are of relevance to this approach. One is the CD8+ T cell, which can directly kill diseased and cancerous cells. Another is the

CD4+ T cell, whose general role is to orchestrate the immune assault. It comes in several varieties—examples are the T helper 1 (Th1) and T helper 2 (Th2)—each of which elicits a distinct sort of immune response . And then there is the regulatory T cell, which keeps a lid on the last two responses.

The activation of OX40 on T cells has varying effects. "When OX40 is activated on regulatory T cells in the tumor, they get so stimulated that they actually die," explains Wolchok. Other CD4+ T cells, on the other hand, step up the immune attack following OX40 activation.

To harness that phenomenon, Wolchok's team transplanted melanoma tumors into mice and allowed them to grow until they got to be about as advanced as permitted. They then gave the mice CTX and OX86, waited a day and transfused them with T helper cells engineered to target a tumor antigen known as Trp1.

The results were as surprising as they were swift: tumors expressing the Trp1 antigen didn't just get smaller. They were eradicated. What's more, the combination therapy also destroyed tumors composed of a mix of cells that display the Trp1 antigen and those that do not. This is significant because most human tumors are built from such mixed populations of cells.

"These T cells are so exquisitely tuned," says Wolchok, "that they induce collateral damage to cells in the tumor that don't even express the targeted antigen."

Wolchok and his colleagues discovered that OX40 activation dramatically altered the transfused T helper cells. They remained CD4+ T cells, yet became capable of destroying cancer cells themselves. Further, they took on traits common to long-lived memory cells, which ensure that any future tumors expressing the targeted antigen are quickly

destroyed. Finally, these entirely novel T cells also had qualities of both Th1 and Th2 subtypes of T helper cells. This might explain how they induced an anti-tumor response vigorous enough to kill tumor cells that did not even bear the antigen they were targeting.

"This is not just of academic interest," says Wolchok, pointing out that most T cell transfer studies have so far focused on CD8+ T cells. "If these killer-memory CD4+ T cells are the ones that are really important to tumor killing then they are the ones we should be trying to transfer."

Further, combining other immunotherapies with OX40-stimulation could by itself boost T cell activity against tumors to significant effect. "Ideally," says Wolchok, "if one could make the endogenous immune response sufficiently robust, you might not need to do the adoptive transfer." That idea could soon be put to the test. Ludwig and the Cancer Research Institute signed an agreement with MedImmune, the global biologics arm of AstraZeneca, that will enable the examination of the clinical effects of an OX40-activating antibody as well as two other antibodies that disrupt the suppression of immune responses by tumors.

The new findings on how OX40 activation affects T helper cells will doubtless inform those studies.

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