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Certain cancer therapies' success depends on presence of immune cell: study

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The immune system may play a critical role in ensuring the success of certain types of cancer therapies, according to a new study by researchers at the Stanford University School of Medicine. The research showed treatments that disable cancer-promoting genes called oncogenes are much more successful in eradicating tumors in the presence of a signaling molecule secreted by kind of immune cell called a T helper cell.

The finding is important because many drugs now in use in humans are often tested in lab animals with weakened immune systems and many human cancer therapies actually compromise a patient's immune system.

"We may be biasing ourselves by expecting these drugs to work on their own, without factoring in the effect of the immune system," said Dean Felsher, MD, PhD, associate professor of medicine and of pathology and the leader of the Stanford Molecular Therapeutics Program. "We're looking for efficacy while ignoring a whole part of biology. What we're choosing as the best candidates may not in fact be the best drugs for patients."

Felsher, who is also a member of the Stanford Cancer Center, is the senior author of the research, which will be published online Oct. 28 in *Cancer Cell*.

Oncogenes are genes that, when mutated, contribute to the development of many cancers including leukemias and lymphomas. Although cancers

are by nature quite complex, some types of tumors rely so completely on the activity of the mutated genes that researchers have coined the term "oncogene addiction." Blocking the effect of these oncogenes — the focus of several current cancer therapies — can cause the tumors to shrink. For instance, the drug imatinib, marketed as Gleevec, targets a key oncogene in chronic myelogenous leukemia and gastrointestinal stromal tumors.

"Researchers and clinicians know that blocking the activity of oncogenes can confer dramatic clinical benefit," said Felsher. "But until recently all of us had assumed that most of the effects we saw on the tumor were relatively independent of the microenvironment of the host."

In contrast, Felsher and his colleagues found that disabling an oncogene called Myc in mice with Myc-dependent leukemias caused complete regression of tumors only in mice with intact immune systems. Tumors in mice with completely or partially compromised immune systems shrank more slowly and were left with a thousand-fold more residual disease. These tumors were also significantly more likely to recur during the 80 days after treatment was stopped.

When the researchers investigated more closely, they found that it was the absence of a type of T cell called CD4 helper cells that was responsible for the differences in recurrence rates (28.5 percent of animals lacking CD4-positive cells had tumor recurrence vs. none in animals missing another type of T cell called a CD8-positive cell). After the researchers added CD4-positive cells to immunocompromised animals, the mice regained the ability to eliminate the tumor and none experienced tumor recurrence during the follow-up period.

Examining the tumor cells after Myc inactivation indicated that the differences in tumor regression and recurrence were not due to an inability of the immune-compromised animals to trigger tumor cell death

(known as apoptosis) or to stop the cells from dividing. Rather, the cancer cells in the immunocompromised animals were less likely to slide into a state of inactivity called senescence and, unlike in the wild-type mice, continued to recruit new blood vessels to the tumor site (a process called angiogenesis).

"This was already provocative," said Felsher. "When the immune system was impaired, the treatment didn't work as well. But we then went a step further. We wanted to know specifically what it was about the CD4-positive cells that influenced tumor regression and recurrence."

They began by looking at signaling molecules secreted by immune cells. These molecules, called cytokines, relay instructions to other cells in the area to coordinate the body's response to infection or disease. Felsher and his colleagues found that the expression levels of many cytokines varied between the wild-type mice and those with compromised immune systems. One in particular, a molecule called thrombospondin-1, was especially interesting. It is produced by CD4-positive T cells, and it regulates angiogenesis.

"We knew that if we replaced CD4-positive cells in immune-compromised mice, we repaired their ability to reject the tumors when Myc was inactivated," said Felsher. "When we tried the same experiment with CD4 cells that couldn't express thrombospondin, the mice couldn't reject the tumor."

Therefore, the presence of thrombospondin is important to the process of tumor rejection caused by oncogene inactivation. Felsher and his colleagues saw a similar effect in a mouse model of another type of leukemia that is dependent on the expression of different oncogenes, suggesting that their findings may translate to other instances of oncogene addiction. They also showed that wild-type mice treated with an immune suppressor called cyclosporine A (commonly used in human

organ transplant recipients to prevent rejection) had a similar effect on angiogenesis and the ability of the tumor cells to enter senescence.

"The problem is, many treatments for patients with lymphoma and leukemia attack both the cancer cells and the immune system," said Felsher. "So we really have to think about this. We can't assume that therapies that target oncogenes act independently of the rest of the body. They may depend on an intact immune system."

Although many patients believe that their immune systems are inherent cancer fighters, it's not always the case, said Felsher. Rather, most cancers occur and progress in the presence of the immune system, each shaping the other. Under some conditions the immune system can actually facilitate cancer progression, while in others it helps to dismantle established tumors.

"Think of the immune system as a contractor," said Felsher. "They come in and do what they're paid to do. In the presence of thrombospondin, and when oncogenes are inactivated, the immune system can help destroy the cancer. In other situations it facilitates the cancer's growth. So we have to think about this very carefully."

Provided by Stanford University Medical Center