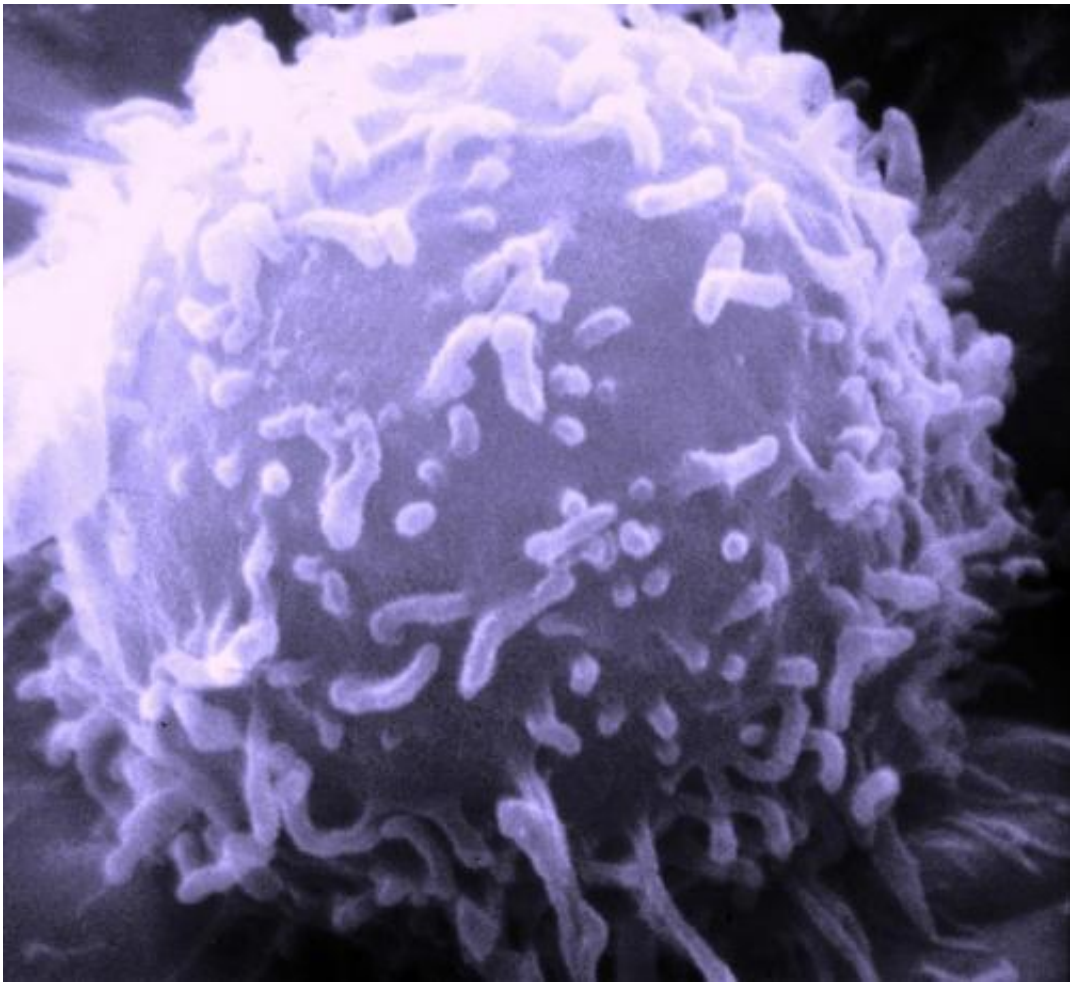
Protein increases signals that protect cancer cells, study finds

March 10 2016



Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Researchers have identified a link between the expression of a cancer-related gene and cell-surface molecules that protect tumors from the immune system.

A cancer-associated protein called Myc directly controls the expression of two molecules known to protect tumor cells from the host's immune system, according to a study by researchers at the Stanford University School of Medicine.

The finding is the first to link two critical steps in the development of a successful tumor: uncontrolled cell growth—when mutated or misregulated, Myc causes an increase in the levels of proteins that promote cell division—and an ability to outwit the immune molecules meant to stop it.

The study will be published online March 10 in *Science*. Dean Felsher, MD, PhD, a professor of oncology and of pathology, is the senior author. The lead author is postdoctoral scholar Stephanie Casey, PhD. The work was conducted in collaboration with researchers at the University of Wurzburg.

"Our findings describe an intimate, causal connection between how oncogenes like Myc cause cancer and how those cancer cells manage to evade the immune system," Felsher said.

'Don't eat me' and 'don't find me'

One of the molecules is the CD47 protein, which researchers in the Stanford laboratory of Irving Weissman, MD, have discovered serves as a "don't eat me" signal to ward off cancer-gobbling immune cells called macrophages. Weissman is the Virginia and D.K. Ludwig Professor for Clinical Investigation in Cancer Research and the director of Stanford's Institute for Stem Cell Biology and Regenerative Medicine.

Nearly all human cancers express high levels of CD47 on their surfaces, and an antibody targeting the CD47 protein is currently in phase-1 clinical trials for a variety of human cancers.

The other molecule is a "don't find me" protein called PD-L1, known to suppress the immune system during cancer and autoimmune diseases but also in normal pregnancy. It's often overexpressed on human tumor cells. An antibody that binds to PD-L1 has been approved by the U.S. Food and Drug Administration to treat bladder and non-small-cell lung cancer, but it has been shown to be effective in the treatment of many cancers.

In cancer, Myc a usual suspect

Researchers in Felsher's laboratory have been studying the Myc protein for more than a decade. It is encoded by a type of gene known as an oncogene. Oncogenes normally perform vital cellular functions, but when mutated or expressed incorrectly they become powerful cancer promoters. The Myc oncogene is mutated or misregulated in over half of all human cancers.

In particular, Felsher's lab studies a phenomenon known as oncogene addiction, in which tumor cells are completely dependent on the expression of the oncogene. Blocking the expression of the Myc gene in these cases causes the complete regression of tumors in animals.

In 2010, Felsher and his colleagues showed that this regression could only occur in animals with an intact immune system, but it wasn't clear why.

"Since then, I've had it in the back of my mind that there must be a relationship between Myc and the immune system," said Felsher.

Turning off Myc expression

Casey and Felsher decided to see if there was a link between Myc expression and the levels of CD47 and PD-L1 proteins on the surface of cancer cells. To do so, they investigated what would happen if they actively turned off Myc expression in tumor cells from mice or humans. They found that a reduction in Myc caused a similar reduction in the levels of CD47 and PD-L1 proteins on the surface of mouse and human acute lymphoblastic leukemia cells, mouse and human liver cancer cells, human skin cancer cells, and human non-small-cell lung cancer cells. In contrast, levels of other immune regulatory molecules found on the surface of the cells were unaffected.

In publicly available gene expression data on tumor samples from hundreds of patients, they found that the levels of Myc expression correlated strongly with expression levels of CD47 and PD-L1 genes in liver, kidney and colorectal tumors.

The researchers then looked directly at the regulatory regions in the CD47 and PD-L1 genes. They found high levels of the Myc protein bound directly to the promoter regions of both CD47 and PD-L1 in mouse leukemia cells, as well as in a human bone cancer cell line. They were also able to verify that this binding increased the expression of the CD47 gene in a human blood cell line.

Possible treatment synergy

Finally, Casey and Felsher engineered mouse leukemia cells to constantly express CD47 or PD-L1 genes regardless of Myc expression status. These cells were better able than control cells to evade the detection of immune cells like macrophages and T cells, and, unlike in previous experiments from Felsher's laboratory, tumors arising from

these cells did not regress when Myc expression was deactivated.

"What we're learning is that if CD47 and PD-L1 are present on the surfaces of cancer cells, even if you shut down a cancer gene, the animal doesn't mount an adequate immune response, and the tumors don't regress," said Felsher.

The work suggests that a combination of therapies targeting the expression of both Myc and CD47 or PD-L1 could possibly have a synergistic effect by slowing or stopping tumor growth, and also waving a red flag at the immune system, Felsher said.

"There is a growing sense of tremendous excitement in the field of cancer immunotherapy," said Felsher. "In many cases, it's working. But it's not been clear why some cancers are more sensitive than others. Our work highlights a direct link between oncogene expression and immune regulation that could be exploited to help patients."

The research is an example of Stanford Medicine's focus on precision health, the goal of which is to anticipate and prevent disease in the healthy and precisely diagnose and treat disease in the ill.

More information: "MYC regulates the antitumor immune response through CD47 and PD-L1," DOI: 10.1126/science.aac9935

Provided by Stanford University Medical Center