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Control of cancer cell pathways key to halting disease spread, study shows

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Oncogenes are like friends who've gone off the deep end. Normally steady, reliable members of the cellular workforce, these genes become very bad influences when mutated or expressed at high levels -- urging a cell to divide uncontrollably and become cancerous.

Now scientists at the Stanford University School of Medicine and the University of Wuerzburg, Germany, have deciphered a part of the pathway used by a well-known oncogene called Myc to exert its malignant effect. Their findings confirm that at least some cancerous cells have within them the seeds to stop their own growth, if Myc can first be disabled.

They also show for the first time that the cancer cells' dependence on Myc -- a phenomenon called "oncogene addiction" -- is due to a pre-existing, self-regulatory pathway that, in the absence of the oncogene, drives out-of-control cells into a reproductive dead end called cellular senescence. Senescence is a fail-safe mechanism that prevents cells from being able to grow and divide.

"This strongly suggests that cancer cells set up circumstances that allow them to ignore their own internal cues," said Dean Felsher, MD, PhD, associate professor of medicine and of pathology and the leader of the Stanford Molecular Therapeutics Program. "If we can restore that cellular senescence pathway, the tumors stop growing." Felsher is also a member of the Stanford Cancer Center.

The researchers conducted their studies in mice and in cells grown in the laboratory on a specific type of blood-cell cancer called T-cell lymphoma. They found that interfering with an interaction between the Myc protein and another protein called Miz1 significantly limited the ability of the oncogene to cause lymphomas. Shutting off Myc expression restores this cellular senescence pathway and the tumors stop in their tracks. These findings may lead to new ways to fight lymphomas in humans.

The research will be published in the June 15 issue of Genes and Development. In an indication of the collaborative nature of the work, postdoctoral scholar Jan van Riggelen, PhD, from Felsher's lab, shares co-first authorship with graduate student Judith Muller from the University of Wuerzburg and Tobias Otto, PhD, presently at the Dana-Farber Cancer Institute in Boston. Felsher and Martin Eilers, PhD, professor of biochemistry at the University of Wuerzburg, are the senior authors of the study.

The concept of oncogene addiction is not new; in fact, Felsher and his lab members first showed in 2002 and 2004 that turning off Myc expression caused an abrupt and sustained regression in invasive bone and liver cancers in mice. Then, in 2007, they showed that cellular senescence was important to oncogene addiction. But until now no one knew that by shutting off Myc you could make cancer cells actually tell themselves to stop growing.

A clue came during a discussion Felsher had with Eilers, a German colleague and old friend. Members of Eilers' lab at the Theodor Boveri Institute had discovered that lymphoma cells produce and secrete high levels of a self-regulatory molecule called TGF-beta. This was interesting because TGF-beta is known to be an "anti-growth" signal for many types of cells. But it clearly wasn't working in the case of the Myc-expressing lymphoma cells.

"This strongly suggested that the Myc pathway may cause cancer by blocking the ability of TGF-beta to cause cellular senescence," said Felsher. Because a recent study by another lab also implicated TGF-beta in cancer progression, the researchers decided to investigate further to learn how Myc caused cancer and what role TGF-beta might play.

Van Riggelen found that Myc's cancer-causing ability was due to its ability to block the expression of genes that slow or stop a cell's progression through the cell cycle. Without these so-called checkpoint proteins, there's nothing to stop a cell from rushing headlong from one cycle of division to the next.

The researchers also found that Myc relies on Miz1, another protein, to steer it to the appropriate genes; a single mutation in the Myc protein that blocks its ability to bind to Miz1 increases the expression of these checkpoint genes and significantly impedes the protein's ability to cause cancer in laboratory mice. Cells from these lymphomas also displayed more signs of senescence than did cells from tumors with unmutated Myc. But what is it about TGF-beta?

The researchers found that shutting off Myc expression caused the cancer cells to begin to senescence and the tumors to regress -- consistent with the oncogene addiction model (without the Myc oncogene, the cells couldn't maintain their cancerous state). But when the TGF-beta pathway was blocked, the loss of Myc no longer triggered tumor regression.

"We've learned that in order for oncogenes to cause cancer, they have to first interfere with or block the cell's own self-regulatory, or autocrine, pathways," said Felsher. Because these pathways are simply turned off by some oncogenes, he explained, they tend to remain intact even as the cancer progresses. This means that shutting off the right oncogene can flip those pathways back on, or restore the cells' ability to hear their own signals, and may be a key step in fighting many types of cancer.

Felsher and his collaborators are now working with Stanford oncologist and lymphoma expert Ronald Levy, MD, to determine whether the results in mice hold true in human patients. Levy is the Robert K. and Helen K. Summy Professor in the School of Medicine and a member of the Stanford Cancer Center.

Clearly, TGF-beta is critically important in cancer progression. As long as its pathway is active, the cancerous cell remains poised to senesce. But Felsher and others also wonder if there's even more to the story. Might it be possible that the lymphoma cells make, and secrete, so much TGF-beta not to try to put the brakes on their own proliferation, but rather to block the division of other, non-cancerous cells around them? If so, TGF-beta may serve as a way for the cancer cell to clear the stage to allow unimpeded cell division.

"The idea that it's a secreted factor is very exciting," said Felsher. "It could function almost as a way to block other cells that compete with it for space or nutrients. But what it really tells us is that cancer development, and cancer therapies, don't occur in a vacuum. There's a lot of communication among and within cells that we need to understand."

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