

Cancer cells revert to normal at specific signal threshold, researchers find

Cancer starts when key cellular signals run amok, driving uncontrolled cell growth. But scientists at the Stanford University School of Medicine report that lowering levels of one cancer signal under a specific threshold reverses this process in mice, returning tumor cells to their normal, healthy state. The finding could help target cancer chemotherapy to tumors while minimizing side effects for the body's healthy cells.

The researchers identified a precise threshold level of the signaling molecule Myc that determined the fate of tumor cells in a cancer of the immune system in mice. Above the threshold, high levels of Myc drove immune cells to grow too large and multiply uncontrollably. When the researchers lowered Myc levels below the threshold, the same cells shrank to normal size, stopped multiplying and began dying normally.

"This is a new concept," said Catherine Shachaf, PhD, an instructor in microbiology and immunology who shared lead authorship of the study with colleague Andrew Gentles, PhD, a research associate in radiology. Previous research demonstrated that turning Myc and other cancer signals all the way off can kill a tumor, but this is the first time scientists have demonstrated a specific midway point at which a cancer signal reverted to a healthy level, Shachaf said. The findings will be published in the July 1 issue of *Cancer Research*.

Identifying the threshold was important because Myc functions in both healthy and cancerous cells as a transcription factor, a protein signal that binds DNA to turn genes on or off. Excess Myc contributes to about 50 percent of human cancers, including malignancies of the immune system and lung.

But Myc is essential, at lower levels, for normal cell function. So, switching Myc all the way off is not an option for treating cancer.

"I wanted to figure out, if we had a drug to turn off Myc, how could we give it to people without hurting them?" said Dean Felsher, MD, PhD, associate professor of oncology and of pathology. Felsher and Sylvia Plevritis, PhD, associate professor of radiology, are the study's senior authors and are both members of the Stanford Cancer Center.

In the past, scientists have shown that cancer signals such as Myc are "like light switches," Felsher said. "Now we know that, in some cases, you don't need to turn the light completely off."

"The real significance of this paper is that it demonstrates that there is a defined amount of Myc that switches the balance between normal cell growth and tumorigenesis," said Bill Tansey, PhD, a professor and expert on cancer-gene regulation at Cold Spring Harbor Laboratory in New York, who was not involved in the research. "The idea that this is a threshold is really not the way we were all thinking."

Using mice that were genetically engineered to develop Myc-driven tumors in response to a chemical in their drinking water, the researchers slowly lowered Myc from an elevated, cancer-causing level to the precise point at which tumor cells returned to normal. Near the threshold, they examined many aspects of cell metabolism to obtain a detailed picture of how the cancer cells changed as Myc dropped. They measured changes in gene activity, protein levels, protein activation inside the cells and the appearance of cell-labeling proteins on the exterior surface of the cells. The scientists wrote a new piece of computer software to help them see how these different types of data fit together into detailed metabolic pathways.

"At the Myc threshold, there is a big change: Programmed cell death becomes dominant over growth," said Gentles.

The threshold was characterized by both a return of normal controls on the cell's life cycle, which stopped inappropriate growth, and re-activation of the pathways that prompt normal cell death, Gentles said.

"We were able to experimentally prove that we can turn Myc off a little bit, or for a little time, and that's enough to have a profound effect on cancer," Felsher said.

The multidisciplinary research team that conducted the work included 14 scientists from seven different Stanford departments.

The study's results will be used to design future cancer treatments, the team said. At present, no drugs target Myc. Understanding the Myc threshold will make it easier to design new drugs that focus on Myc itself or target other key signals required to switch from tumor to healthy cells. Armed with a detailed profile of cellular changes near the Myc threshold, researchers now have a much better idea of where to look for new cancer treatments. "It allowed us to narrow down the hunt," Felsher said.

Source: Stanford University

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