MedicalXpress

New 'don't eat me' signal may provide basis for cancer therapies

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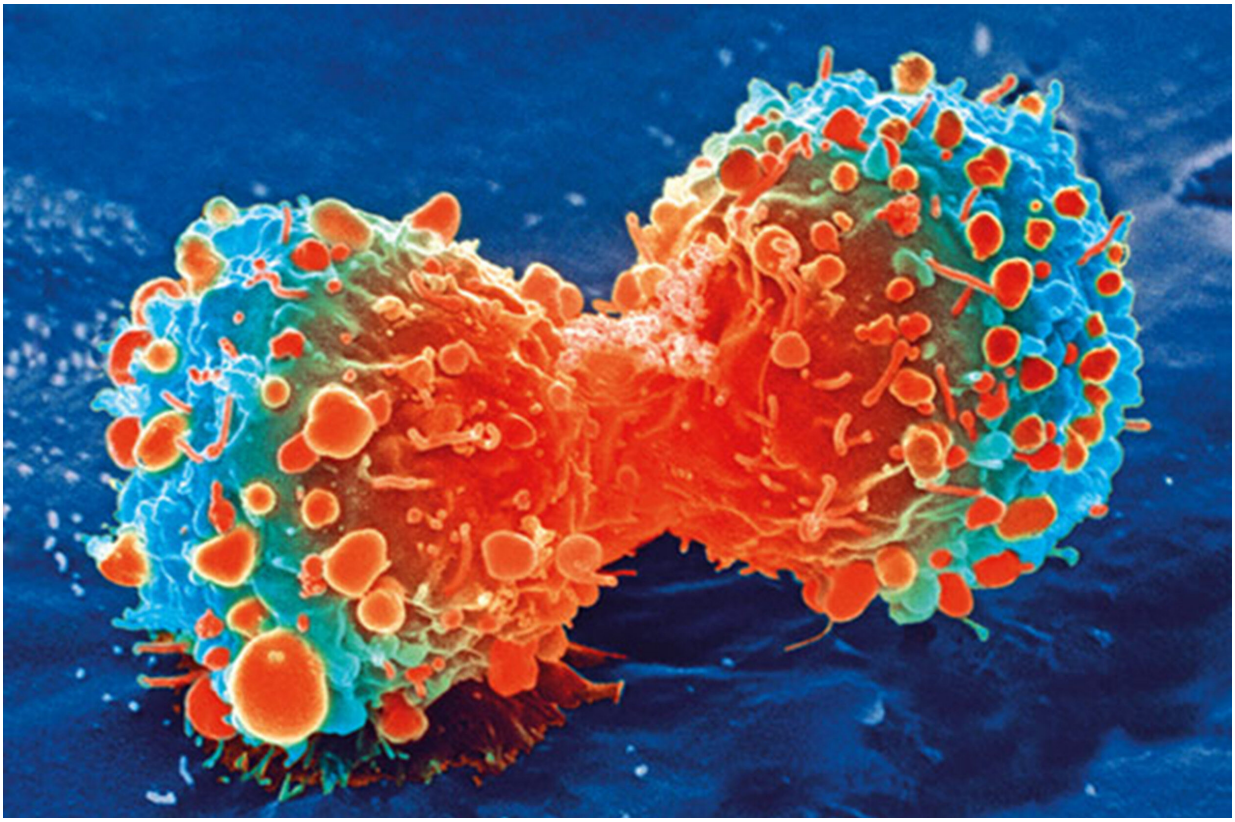

Cancer cell during cell division. Credit: National Institutes of Health

Researchers at the Stanford University School of Medicine have discovered a new signal that cancers seem to use to evade detection and destruction by the immune system.

The scientists have shown that blocking this signal in mice implanted with human cancers allows immune cells to attack the cancers. Blocking other "don't eat me" signals has become the basis for other possible anti-cancer therapies.

Normally, immune cells called macrophages will detect cancer cells, then engulf and devour them. In recent years, researchers have discovered that proteins on the cell surface can tell macrophages not to eat and destroy them. This can be useful to help normal cells keep the immune system from attacking them, but cancer cells use these "don't eat me" signals to hide from the immune system.

The researchers had previously shown that the proteins PD-L1, CD47 and the beta-2-microglobulin subunit of the major histocompatibility class 1 complex are all used by cancer cells to protect themselves from immune cells. Antibodies that block CD47 are in clinical trials. Cancer treatments that target PD-L1 or the PDL1 receptor are being used in the clinic.

The Stanford researchers now report they have found that a protein called CD24 also acts as a "don't eat me" signal and is used by cancer cells to protect themselves. A paper describing the research will be published July 31 in *Nature*. Amira Barkal, an MD-Ph.D. student, is the lead author. Irving Weissman, MD, professor of pathology and of developmental biology and director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine and director of the Ludwig Center for Cancer Stem Cell Research, is the senior author.

"Finding that not all patients responded to anti-CD47 antibodies helped fuel our research at Stanford to test whether non-responder cells and patients might have alternative 'don't eat me' signals," said Weissman, who holds the Virginia and D.K. Ludwig Professorship for Clinical Investigation in Cancer Research.

Looking for additional signals

The scientists began by looking for proteins that were produced more highly in cancers than in the tissues from which the cancers arose. "You know that if cancers are growing in the presence of macrophages, they must be making some signal that keeps those cells from attacking the cancer," Barkal said. "You want to find those signals so you can disrupt them and unleash the full potential of the immune system to fight the cancer."

The search showed that many cancers produce an abundance of CD24 compared with normal cells and surrounding tissues. In further studies, the scientists showed that the macrophage cells that infiltrate the tumor can sense the CD24 signal through a receptor called SIGLEC-10. They also showed that if they mixed cancer cells from patients with macrophages in a dish, and then blocked the interaction between CD24 and SIGLEC-10, the macrophages would start gorging on cancer cells like they were at an all-you-can-eat buffet. "When we imaged the macrophages after treating the cancers with CD24 blockade, we could see that some of them were just stuffed with cancer cells," Barkal said.

Lastly, they implanted human breast cancer cells in mice. When CD24 signaling was blocked, the mice's scavenger macrophages of the immune system attacked the cancer.

Of particular interest was the discovery that ovarian and triple-negative breast cancer, both of which are very hard to treat, were highly affected by blocking the CD24 signaling. "This may be a vulnerability for those very dangerous cancers," Barkal said.

Complementary to CD47?

The other interesting discovery was that CD24 signaling often seems to operate in a complementary way to CD47 signaling. Some cancers, like blood cancers, seem to be highly susceptible to CD47-signaling blockage, but not to CD24-signaling blockage, whereas in other cancers, like ovarian cancer, the opposite is true. This raises the hope that most cancers will be susceptible to attack by blocking one of these signals, and that cancers may be even more vulnerable when more than one "don't eat me" signal is blocked.

"There are probably many major and minor 'don't eat me' signals, and CD24 seems to be one of the major ones," Barkal said.

The researchers now hope that therapies to block CD24 signaling will follow in the footsteps of anti-CD47 therapies, being tested first for safety in preclinical trials, followed by safety and efficacy clinical trials in humans.

For Weissman, the discovery of a second major "don't eat me" signal validates a scientific approach that combines basic and clinical research. "CD47 and CD24 were both discovered by graduate students in MD-Ph.D. programs at Stanford along with other fellows," Weissman said. "These started as fundamental basic discoveries, but the connection to cancers and their escape from scavenger macrophages led the team to pursue preclinical tests of their potential. This shows that combining investigation and medical training can accelerate potential lifesaving discoveries."

More information: CD24 signalling through macrophage Siglec-10 is a target for cancer immunotherapy, *Nature* (2019). DOI: 10.1038/s41586-019-1456-0 , nature.com/articles/s41586-019-1456-0

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