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Research: Single antibody shrinks variety of human tumors transplanted into mice

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Human tumors transplanted into laboratory mice disappeared or shrank when scientists treated the animals with a single antibody, according to a new study from the Stanford University School of Medicine. The antibody works by masking a protein flag on cancer cells that protects them from macrophages and other cells in the immune system. The scientists achieved the findings with human breast, ovarian, colon, bladder, brain, liver and prostate cancer samples.

It is the first antibody treatment shown to be broadly effective against a variety of human solid tumors, and the dramatic response — including some overt cures in the laboratory animals — has the investigators eager to begin phase-1 and -2 human clinical trials within the next two years.

"Blocking this 'don't-eat-me' signal inhibits the growth in mice of nearly every human cancer we tested, with minimal toxicity," said professor of pathology Irving Weissman, MD, who also directs Stanford's Institute of Stem Cell Biology and Regenerative Medicine and the Ludwig Center for Cancer Stem Cell Research at Stanford. "This shows conclusively that this protein, CD47, is a legitimate and promising target for human cancer therapy."

The antibody treatment also significantly inhibited the ability of the tumors to metastasize throughout the animals' bodies.

"This is exciting work and will surely trigger a worldwide wave of research designed to convert this strategy into useful therapies," said

Robert Weinberg, PhD, a professor of biology at the Whitehead Institute for Biomedical Research in Massachusetts who was not involved in the research. "Mobilizing the immune system to attack solid tumors has been a longstanding goal of many cancer researchers for decades."

The research will be published online March 26 in the *Proceedings of the National Academy of Sciences.* Weissman, who is the Virginia & D.K. Ludwig Professor for Clinical Investigation in Cancer Research at Stanford and a member of the Stanford Cancer Institute, is the senior author of the research. Postdoctoral scholars Stephen Willingham, PhD, and Jens-Peter Volkmer, MD, are the co-first authors of the study.

Previous work in Weissman's lab has shown that CD47 is normally expressed on the surfaces of circulating blood stem cells to protect them from immune cells called macrophages. Macrophages patrol the body looking for signs of trouble in the form of invaders or rogue cells, but they sometimes latch onto the wrong targets. CD47 prompts them to release cells they've grabbed by mistake.

Weissman and his colleagues also showed previously that some types of cancer cells — particularly those of blood cancers such as leukemia and lymphoma — have figured out a way to game the system and use this "don't-eat-me signal" to their advantage by expressing CD47 on their own surfaces. In 2010, they found that blocking CD47 with a specific antibody (plus adding another to further stimulate the macrophages' killing instinct) can cure some cases of human non-Hodgkin's lymphoma in mice. But it wasn't known until now how widespread or clinically important the phenomenon would be in human solid tumors.

In the current study, Willingham and Volkmer collected surgical samples of a variety of human tumors, including ovarian, breast, colon, bladder, brain, liver and prostate. To do so, they enlisted the help of clinical experts from across the School of Medicine, including those specializing

in oncology, urology, obstetrics and gynecology, radiation oncology, neurosurgery, hematology, pathology, otolaryngology and hepatology.

They showed that nearly every human cancer cell they examined expressed CD47 — usually at higher levels (on average, about three times more) than did non-cancerous cells. Furthermore, people whose cancer cells express a lot of CD47 tend to have shorter life spans than people with similar cancers that express less CD47. This suggests that an analysis of the levels of CD47 expression in some types of tumors could be a valuable prognostic tool for patients and their doctors.

Willingham and Volkmer then implanted the different human tumor cells into matching locations in the bodies of mice — breast cancer tumors into the mammary fat pads, and ovarian cancer tumors into the abdomen, for example. Once the tumors were well-established (after two weeks or more), they treated the animals with the anti-CD47 antibody.

The researchers saw that most of the established tumors begin to shrink and even, in some cases, disappear within weeks of treatment with the antibody. In one case, antibody treatment cured five mice injected with the same human breast cancer cells. When the tumor was gone, the treatment was discontinued; the mice were monitored for four months with no signs of recurrence.

"These results indicate that anti-CD47 antibodies can dramatically inhibit the growth of human solid tumors by blocking the ability of CD47 to transmit the 'don't-eat-me' signal to macrophages," concluded the authors.

"If the tumor was highly aggressive," said Weissman, "the antibody also blocked metastasis. It's becoming very clear that, in order for a cancer to survive in the body, it has to find some way to evade the cells of the innate immune system." The innate immune system is the body's first

line of defense against pathogens like bacteria and viruses. Unlike the adaptive immunity conferred by antibodies and T cells that recognize and battle specific molecules, cells of the innate immune system, like macrophages, respond non-specifically to a variety of threats.

The researchers' approach didn't work in every animal, though. A set of mice with breast cancer cells from a one human patient experienced no benefit from antibody treatment. "There's certainly more to learn," said Weissman. "We need to learn more about the relationship between macrophages and tumor cells, and how to draw more macrophages to the tumors." He suggested that reducing the size of a tumor with surgery or radiotherapy before antibody treatment could make the treatment more effective. Another option, he added, would be to use a second antibody in addition to CD47 that would further stimulate the ability of the macrophages or other immune cells to kill the cancer cells.

While treatment modifications may be beneficial, the findings about the effect of the single antibody are promising in their own right and set the stage for advancing the research. "We believe these results show that we should move forward quickly but cautiously into human clinical trials for many types of solid tumors," Weissman said.

More information: “The CD47-signal regulatory protein alpha (SIRPa) interaction is a therapeutic target for human solid tumors,” by Stephen B. Willingham, PNAS.

Provided by Stanford University Medical Center