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Stanford study prevents pancreatic tumor growth in mice by inhibiting key protein

STANFORD, Calif. — Researchers at Stanford University School of Medicine have identified a protein critical for the growth of pancreatic cancer. Blocking the expression of the protein slowed or prevented tumor growth in mice and made cultured cancer cells vulnerable to the conditions of low oxygen that occur in solid tumors.

"This research clearly shows that inhibiting the protein inhibits the tumor's ability to grow," said cancer biologist Amato Giaccia, PhD. "Ultimately, we'd like to be able to specifically knock out the expression of this protein in pancreatic tumors in humans."

Pancreatic cancer is a highly aggressive and deadly disease that accounts for more than 30,000 deaths in the United States annually, and current therapies are largely ineffective.

"Right now, we have very little to offer these patients," said Giaccia. He is the Jack, Lulu and Sam Willson Professor and professor of radiation oncology and the senior author of the research, which will be published Feb. 1 in the journal *Cancer Research*. Giaccia is also a member of the Stanford Cancer Center.

The researchers studied a protein called connective tissue growth factor, or CTGF. Also known as CCN2, the protein is involved in the abnormal growth of connective tissue in response to injury or disease. It was also thought to be involved in pancreatic tumor progression, although the exact role it played was unknown.

Giaccia and his collaborators found that human pancreatic cancer cells expressing high levels of CCN2 grew robustly when injected under the skin of mice. In fact, in the developing tumor these cells soon out-competed others that expressed lower levels of the protein. Conversely, pancreatic cancer cells in which CCN2 expression was suppressed were either less likely or unable to form tumors when injected into mice.

The researchers observed similar effects when the cancer cells were injected directly into the animals' pancreases. Cancer cells expressing high levels of CCN2 formed tumors that grew more rapidly and metastasized more aggressively than did those expressing lower levels, and the mice died sooner than others injected with cancer cells expressing less CCN2.

It's difficult for many types of rapidly growing solid tumors to recruit and build enough blood vessels to keep all the cancer cells adequately oxygenated. Normal cells undergo a process of programmed cell death when oxygen levels drop too far. Overcoming this response to low oxygen levels — a condition called hypoxia — is a critical step in tumor progression.

The researchers wondered if CCN2 played a role in keeping tumor cells alive in hypoxic conditions. If so, this might explain why CCN2-expressing cancer cells are favored during tumor growth. They found that blocking CCN2 expression in cultured pancreatic cancer cells made them significantly more sensitive to hypoxia-induced death than their peers. Additionally, CCN2 was more highly expressed in pancreatic tumor samples from human patients than in neighboring tissue and CCN2 expression seemed to correlate with the expression of another protein expressed by hypoxic cells. Finally, hypoxic conditions themselves cause the pancreatic cancer cells to make CCN2.

Many other cellular conditions can also kick-start CCN2 expression, including the presence of CCN2 itself. The activation of other pathways known to be involved in cancer also increases its expression. As a result, many of the events that occur in a developing tumor act as a kind of perfect storm to support the production of ever-larger amounts of CCN2, which then support additional tumor growth and metastasis.

Looking ahead, the researchers would like to know whether people with pancreatic cancer could benefit from therapies targeting CCN2. A phase-1 clinical trial testing the safety of an antibody that binds CCN2 and blocks its activity in a small number of patients began in December at Stanford and Dartmouth-Hitchcock Medical Center. Phase-1 clinical trials are not designed to determine whether a treatment works — only whether it is safe enough for further testing. Albert Koong, MD, PhD, an assistant professor of radiation oncology and a member of the Cancer Center, is the principal investigator for the Stanford arm of the trial.

"We saw a pronounced effect of CCN2 inhibition in these experiments in mice," said Giaccia. "Our hope is that one day a combination of standard therapy and antibody treatment will have an effect on tumor progression in human patients."

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Giaccia's Stanford collaborators on the research include former post-doctoral scholars Kevin Bennewith, PhD, who is now a research scientist at the British Columbia Cancer Research Centre in Vancouver; Janine Erler, PhD, who is now a group leader at the Institute of Cancer Research at Chester Beatty Laboratories in London; post-doctoral scholars Xin Huang, PhD; and Christine Ham, MD; assistant professor of radiation oncology Edward Graves, PhD; associate professor of pathology Neeraja Kambham, MD; assistant professor of surgery George Yang, MD, PhD ; and Albert Koong.

The research was supported by a grant from the National Institutes of Health, the Blue Dot Fund, and the Canadian Institutes of Health Research. The phase-I clinical trial is sponsored by San Francisco-based FibroGen, Inc. Amato Giaccia is a paid consultant for FibroGen; FibroGen did not contribute any reagents or intellectual input to the current study.

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