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Therapy sneaks into hard layer of pancreatic cancer tumor and destroys it from within

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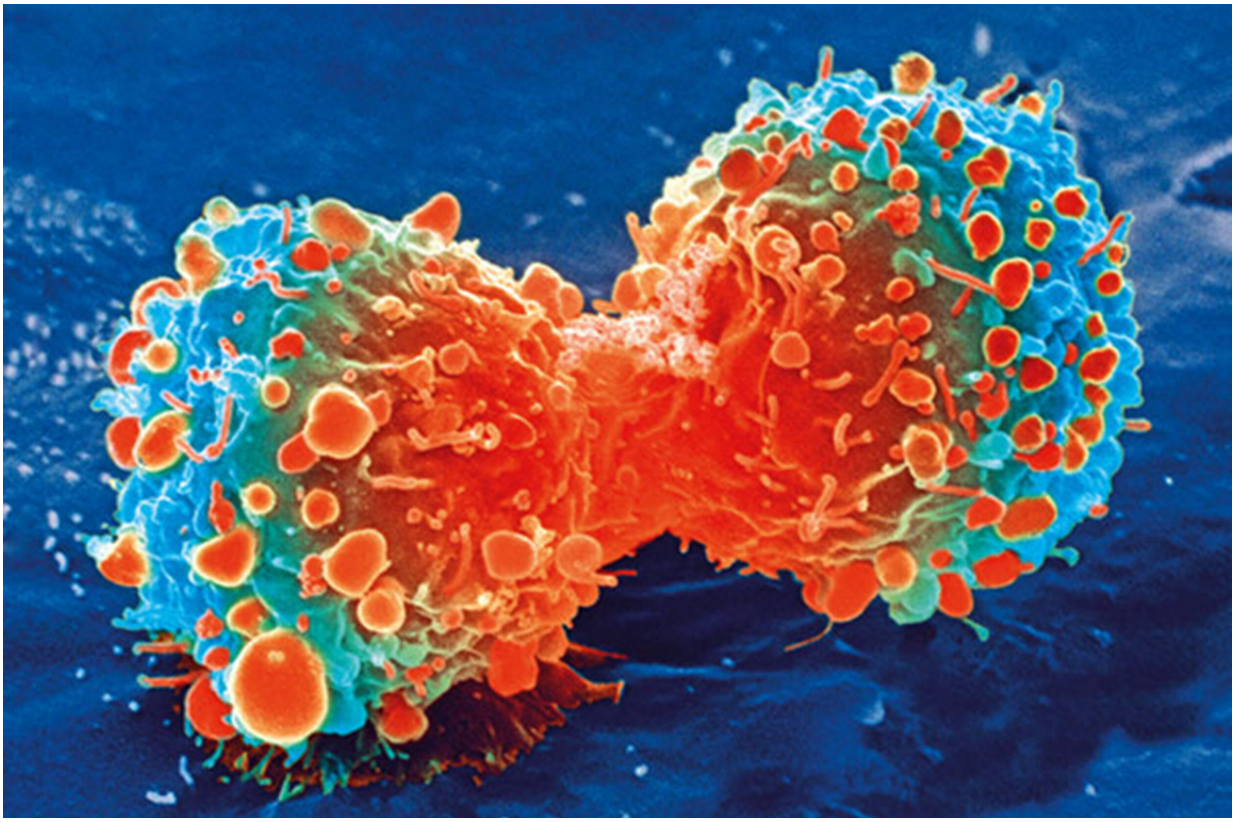

Cancer cell during cell division. Credit: National Institutes of Health

Every 12 minutes, someone in the United States dies of pancreatic cancer, which is often diagnosed late, spreads rapidly and has a five-year survival rate at approximately 10 percent. Treatment may involve

radiation, surgery and chemotherapy, though often the cancer becomes resistant to drugs.

Researchers at University of California San Diego School of Medicine and Moores Cancer Center, in collaboration with Sanford-Burnham-Prebys Medical Discovery Institute and Columbia University, demonstrated that a new tumor-penetrating therapy, tested in animal models, may enhance the effects of chemotherapy, reduce metastasis and increase survival.

The study, published online March 9, 2021 in *Nature Communications*, showed how a tumor-targeting peptide, called iRGD, can sneak inside the armor that the tumor built to protect itself and use the fibrous tissue as a highway to reach deeper inside, destroying the tumor from within.

The pancreas is a large gland located behind the stomach. It makes enzymes that aid digestion and hormones that regulate blood-sugar levels. Pancreatic ductal adenocarcinoma (PDAC) is a subtype of pancreatic cancer that is highly drug-resistant due, in part, by the hard shell-like outer layer surrounding the tumor.

"This type of tumor is made up of a dense fibrous tissue that acts as a barrier to drugs trying to get through. Many drugs can reach the vessels of the tumor, but they are not able to get deep into the tissue, making treatment less effective, and that is one reason why this type of cancer is so challenging to treat," said Tatiana Hurtado de Mendoza, Ph.D., first author of the study and assistant project scientist at UC San Diego School of Medicine and Moores Cancer Center.

"Our study found that the tumor-penetrating peptide iRGD is able to use this fibrous network to deliver chemotherapy drugs deep into the tumor and be more effective."

The research team examined the microenvironment of PDAC tumors in a mouse model. They found that after targeting the tumor blood vessels, iRGD binds to high levels of β5 integrin, a protein produced by cells known as carcinoma-associated fibroblasts (CAFs) that produce much of the tumor's protective fibrous cover.

"We were able to closely replicate human disease in our mouse model and found that when iRGD was injected with chemotherapy in mice with high levels of β5 integrin, there was a significant increase in survival and a reduction in the cancer spreading to other organs in the body compared to chemotherapy alone. This could be a powerful treatment strategy to target aggressive pancreatic cancer," said Andrew Lowy, MD, co-corresponding author of the study, professor of surgery at UC San Diego School of Medicine and chief of the Division of Surgical Oncology at Moores Cancer Center at UC San Diego Health.

"What is also exciting about this finding is the iRGD therapy did not produce any additional side effects. This is critically important when considering treatments for patients."

The researchers said next steps include a national human clinical trial. They estimate the trial could begin in one year.

"The knowledge gained from our study has the potential to be directly applied to patient care. We also believe that the levels of β5 integrin within a pancreatic cancer could tell us which patients would benefit the most from iRGD-combination therapy," said Lowy.

More information: Tatiana Hurtado de Mendoza et al, Tumor-penetrating therapy for β5 integrin-rich pancreas cancer, *Nature Communications* (2021). DOI: 10.1038/s41467-021-21858-1