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Some pancreatic cancer treatments may be going after the wrong targets, study finds

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New research represents a significant change in the understanding of how pancreatic cancer grows – and how it might be defeated.

Unlike other types of cancer, pancreatic cancer produces a lot of scar tissue and inflammation. For years, researchers believed that this scar tissue, called desmoplasia, helped the tumor grow, and they've designed treatments to attack this.

But new research led by Andrew D. Rhim, M.D., from the University of Michigan Comprehensive Cancer Center, finds that when you eliminate desmoplasia, tumors grow even more quickly and aggressively. In the study, mice in which the desmoplasia was eliminated developed tumors earlier and died sooner.

"This flies in the face of 10 years of research," says Rhim, assistant professor of gastroenterology at the U-M Medical School. "It turns out that desmoplasia is a lot more complex than previously thought. Components of this complex scar tissue may be the body's natural defense against this cancer, acting as a barrier or fence to constrain cancer cells from growing and spreading. Researchers who have been trying to target desmoplasia to kill tumors may need to reevaluate their approach."

Several drugs targeting desmoplasia are in clinical trials and one was recently stopped early because of poor results. "Our study explains why this didn't work," Rhim says.

The researchers were able to arrive at this surprising conclusion by using a better mouse model. Previous models have used mice with compromised immune systems injected with human pancreatic cancer cells, producing tumors that don't closely resemble human pancreatic cancer. The current model utilizes mice that are genetically engineered to express the two most common genetic mutations seen in pancreatic cancer. The mice developed cancer spontaneously, and the cancer closely resembled human pancreatic cancer.

Results of the study appear in *Cancer Cell*. The work represents a collaboration among teams at the University of Pennsylvania, Columbia University, Johns Hopkins University, Memorial Sloan Kettering Cancer Center and Mayo Clinic.

Using genetically engineered mice, the researchers blocked desmoplasia by knocking down the signaling pathway that produces it. They discovered that desmoplasia prevents the formation of blood vessels that fuel the tumor. When it's suppressed, the blood vessels multiply, giving the cancer cells the fuel to grow. The researchers next wondered: What if you then target blood vessels with treatment?

What they found in this study was that a drug designed to attack blood vessels, called an angiogenesis inhibitor, significantly improved overall survival in the mice who had desmoplasia blocked. Angiogenesis inhibitors already exist on the market with approval from the U.S. Food and Drug Administration.

Another key finding of the study is that eliminating desmoplasia created tumors that resembled undifferentiated pancreatic cancer in humans. Undifferentiated tumors lack desmoplasia, have abundant blood vessels and grow and spread quickly. About 10 percent of pancreatic cancers in patients are undifferentiated.

This suggests that angiogenesis inhibitors may be effective in patients with undifferentiated tumors.

This study suggests that patients with highly aggressive, undifferentiated pancreatic cancer may be good candidates for treatment with an angiogenesis inhibitor, a drug that is already approved by the U.S. Food and Drug Administration for other cancers. Researchers are moving toward developing a clinical trial. Plans for such an approach are currently underway.

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