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Researchers identify nerve-guiding protein that aids pancreatic cancer spread

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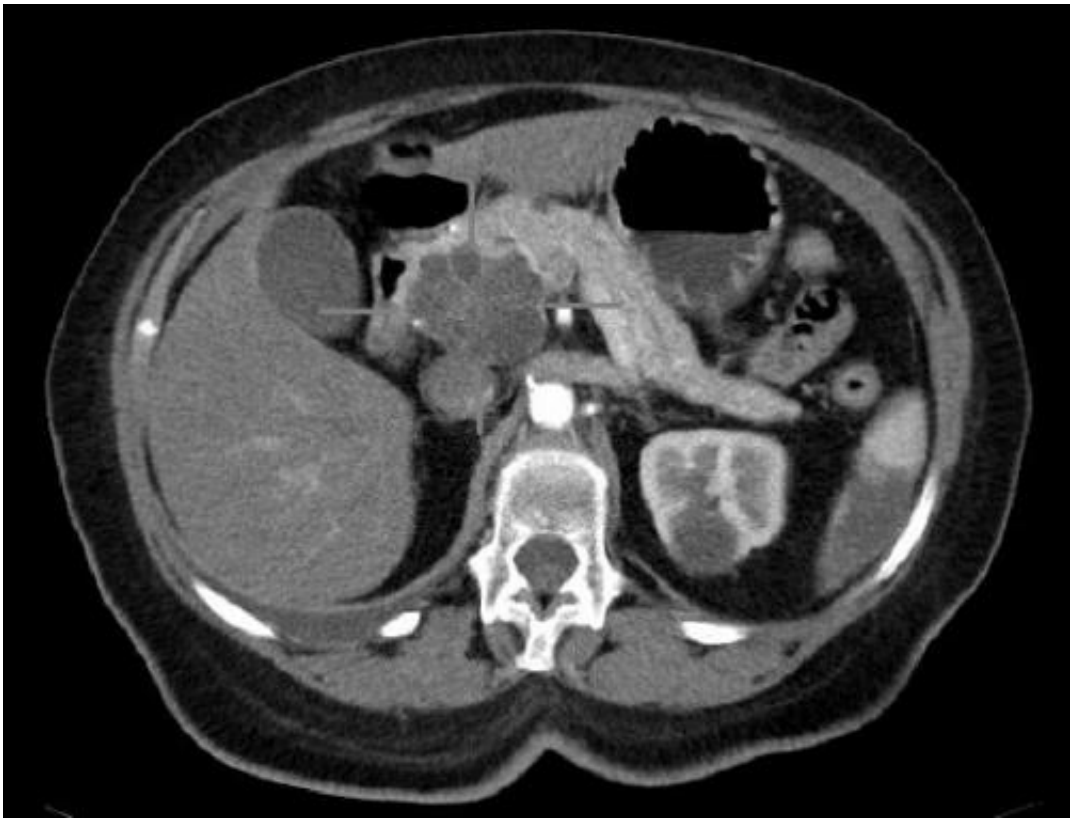

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Scientists at the Johns Hopkins Kimmel Cancer Center have identified a molecular partnership in pancreatic cancer cells that might help to explain how the disease spreads—metastasizes—in some cases. Their

findings reveal urgently needed new targets to treat pancreatic cancer, which strikes nearly 50,000 people in the U.S. each year and has only a 5 percent survival rate five years after diagnosis.

One of the molecular partners is annexin A2, a protein that scientists say was already linked to poor survival rates in these cancers. In a report published in the Aug. 4 issue of *Science Signaling*, Lei Zheng, M.D., Ph.D., and his colleagues show that annexin A2 helps usher a protein called Sema3D out of pancreatic cancer cells. Once outside the cells, Sema3D joins with another molecule to fuel the cancer's spread. Sema3D is a protein that guides the projecting arms of nerve cells, called axons, as the nerve cells grow and develop.

In experiments with mice, the researchers calculated a seventyfold drop in the amount of Sema3D secreted from mouse pancreatic cancer cells in animals that lacked annexin A2. In an experiment involving 23 mice, none of the annexin-free animals developed visible metastatic tumors. By contrast, 16 out of 17 mice that produced annexin A2 in their cells developed metastatic tumors in the liver, lungs or abdominal cavity.

In a second group of experiments using human tissue from patients with pancreatic ductal adenocarcinoma, which accounts for more than 90 percent of pancreatic cancers, Zheng and his colleagues also tracked down a link between the abundance of Sema3D in those tissues and the progression of metastatic pancreatic cancer.

The team reports that Sema3D was abundant in the main tumor tissue of only three of 13 (23 percent) patients who died after minimal cancer spread. But it was abundant in the main tumors of 14 of 22 (64 percent) patients who died with widely metastatic cancer, and also in the metastatic tumors of 17 of 23 (74 percent) patients.

The presence of Sema3D also seems to be associated with the recurrence

of pancreatic cancer in patients whose primary tumors were surgically removed, the scientists say. Sema3D was abundant in the primary tumors of 15 of 20 patients (75 percent) who lived free of the cancer for less than a year after their surgery, compared to only four of 15 (27 percent) patients who lived disease-free for more than two years after surgery.

With their new data in hand, the researchers are pursuing three possible therapeutic targets to stop pancreatic cancer metastasis driven by annexin A2 and Sema3D. "We are planning clinical trials with a recently developed vaccine to target annexin A2," says Zheng, an associate professor of oncology and surgery at the Johns Hopkins University School of Medicine. "But at the same time, we are also developing a therapeutic antibody targeting annexin A2, and we are looking for a small molecule that would inhibit Sema3D."

Zheng and colleagues emphasize they don't know precisely how the Sema3D encourages the spread of pancreatic cancer, but they think it may help cancer cells surround and track nerves to travel away from the main tumor.

This neural highway might be especially important in pancreatic cancer, they say, because it grows fewer blood vessels that can carry cancer cells to the rest of the body. "More so than some other cancers, pancreatic cancers are what we call neurotropic, meaning that they tend to invade nerves," explains Zheng.

It's also unclear at this point, he says, exactly how annexin A2 encourages pancreatic cancer cells to release Sema3D, but the researchers suspect annexin A2 may act like a bodyguard to Sema3D, sheltering and guiding the protein as it makes its way toward an exit at the cell surface. Or, they speculate, it may act more like a professional packer, helping to enclose Sema3D in tiny molecular bubbles called vesicles before it is secreted by the cell.

Zheng and his colleagues became interested in annexin A2's exact role in cancer spread after noting a curious effect in a trial of the pancreatic cancer vaccine GVAX, first developed by Johns Hopkins researchers.

In a 2011 vaccine trial of patients whose primary pancreatic tumors were surgically removed, "we found antibodies against annexin A2 in those who had received the vaccine and who also had demonstrated long-term, disease-free survival after receiving the vaccines," explains Zheng. "This suggested to us that we should study annexin's role in pancreatic cancer progression."

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Jaffee and Zheng hold a patent on annexin A2 as a target for cancer therapy, and Zheng has a pending patent on annexin A2 as an immunological target (U.S. Patent Application No. 14/249,534).

Provided by Johns Hopkins University School of Medicine