Metastasis of pancreatic cancer in action

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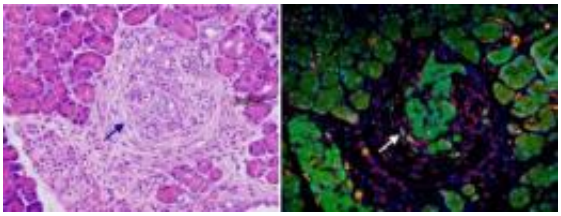

Pancreatic cells spread by blending in. The left panel shows an inflammed pancreatic duct surrounded by what appear to be fibroblasts (blue arrow). Lineage tagging allowed the researchers to see that some of these fibroblast-like cells are actually invading pancreatic epithelial cells in disguise (left panel, white arrow). Such cells have undergone a process of epithelial-to-mesenchymal transition and are able to enter the bloodstream. Credit: Andrew Rhim, PhD, Perelman School of Medicine, University of Pennsylvania; Cell Press

Ben Stanger, MD, PhD, assistant professor of Medicine in the Division of Gastroenterology at the Perelman School of Medicine, University of Pennsylvania, and Andrew Rhim, MD, a Gastroenterology Fellow in the Stanger lab, discovered that pancreatic cancer cells in an animal model begin to spread before clinically obvious tumor tissue is detected. What's more, they showed that inflammation enhances cancer progression in part by facilitating a cellular transformation that leads to entry of cancer cells into the circulation. They report their findings this week in *Cell*.

Metastasis has been difficult to study because it involves a series of unpredictable events. To capture these events, the team developed a sensitive method to tag and track pancreatic epithelial cells in a mouse

model of pancreatic cancer. Tagged cells invaded and entered the bloodstream unexpectedly early, before overt malignancy could be detected by rigorous analysis of tissue slides.

Pancreatic cancer is among the most lethal of cancers, with no real treatments, and at the time of diagnosis up to three-quarters of patients have metastatic disease, says Stanger. Little is known about how pancreatic cancer cells spread, "What leads to this are rare events that are hard to catch in tissues. Small numbers of cells break off tumors and move, but how can we find them?"

These wandering cells are associated with a phenomenon called the epithelial-to-mesenchymal transition (EMT). This change in cell motility is an important process during the development of embryos. But when the transition is aberrantly reactivated in adults it can have dire physiological consequences, leading to cancer metastasis as well as other disease processes. Epithelial cells form a covering or lining of a body surface and are the type of cell from which most solid tumors arise. However, when a molecular switch is turned off or absent, epithelial cells acquire characteristics of another cell type, called mesenchymal cells, and gain the ability to migrate and move away from the primary tumor site.

Using a mouse model of pancreatic cancer developed at Penn in 2005, the team delivered mutations in an oncogene and a tumor suppressor protein, K-ras and p53 respectively, in the pancreas. A green marker was also induced in the embryos' still-forming pancreas. At about one to two months, the juvenile mice developed pre-malignant lesions, and at about four to five months full blown pancreatic cancer.

During this time, the mouse pancreatic epithelial cells lost their epithelial characteristics and became more like mesenchymal cells, blending in and making their way to the bloodstream. True epithelial cells are sticky,

keeping linings tightly connected, but these imposter epithelial cells changed identity, becoming less sticky.

With the green stain, the researchers were able to detect the transition from epithelial cell to mesenchymal cell in a tissue slide, showing many green cells that had undergone EMT. "We are now able to see what was before before unseeable – the pancreas cells that have taken on a disguise," says Stanger.

What spurs the EMT in first place? The team surmised that it was inflammation, so they blocked inflammation with an immunosuppressant, and at about eight to ten weeks, the green cells undergoing EMT disappeared. Conversely, when they induced pancreatitis- associated inflammation, the EMT green cells increased.

In trying to relate these findings to metastasis, they looked for green EMT cells outside of the pancreas and found them in the blood and distinct tissues such as the liver at eight to ten weeks of age, long before a pathologist would recognize it as cancer.

"These results provide new insight into the earliest events of cellular invasion and suggest that inflammation enhances cancer progression by giving cells increased access to the bloodstream," says Stanger.

The team plans to use the methodology used in this study to enhance the detection of spreading cells in human patients at an early timepoint, when therapy could have a greater impact.

Both the development of the pancreatic cancer mouse model and Dr. Stanger's current work were partially funded by research grants from the Pancreatic Cancer Action Network. "We are highly encouraged by Dr. Stanger's recent results," said Lynn Matrisian, PhD, vice president of Scientific and Medical Affairs at the Pancreatic Cancer Action Network.

"A deeper understanding of the disease biology, and in particular metastasis, will move us closer to our goal of doubling the survival rate of pancreatic cancer by the year 2020."

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