Pancreas Cells Move Out Before Tumors Form

Researchers at the University of Pennsylvania have discovered one explanation for why pancreatic cancer usually remains undetected until after it has metastasized: At least in mice, the cancer cells start spreading even before they form primary tumors. The investigators also found that inflammation helps drive that process by encouraging the transformation of epithelial cells into mesenchymal cells that can enter the bloodstream.

Led by Ben Stanger, MD, PhD, a developmental biologist and assistant professor of medicine, the researchers bred mice with mutations in Kras and p53, genes often mutated in human pancreatic cancers. They also introduced an allele that tagged pancreatic epithelial cells with a green marker, allowing them to see how the cells developed and changed over time.

After about 1 to 2 months, the mice began to develop premalignant lesions, which progressed to pancreatic cancer after 4 to 5 months. But even before actual tumors formed, the pancreatic epithelial cells began adopting characteristics of mesenchymal cells and traveled to other sites, including the liver.

Hypothesizing that inflammation spurred the epithelial-to-mesenchymal transition (EMT), the scientists blocked inflammation by treating the mice with the immunosuppressant dexamethasone when the animals were 8 to 10 weeks old. The green cells undergoing EMT disappeared. Conversely, when the researchers induced pancreatitis with an agent that kills pancreatic duct cells, the number of green cells undergoing EMT increased.

The researchers also looked for these cells outside of the pancreas and found them seeding the liver and circulating in the blood of mice at 8 to 10 weeks of age, long before they would form actual tumors at the primary site. That discovery lends credence to the theory that inflammation may enhance metastasis by giving cells increased access to the bloodstream, says Stanger.

Although the study did not demonstrate whether such disseminated cells can directly lead to tumor formation or metastatic disease, “Knowing that the pancreas is shedding cells early in the disease process may give us a way to determine who is at risk,” explains Stanger. “Perhaps the presence of circulating cells in the bloodstream could be used as a marker for pancreatic cancer.”

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