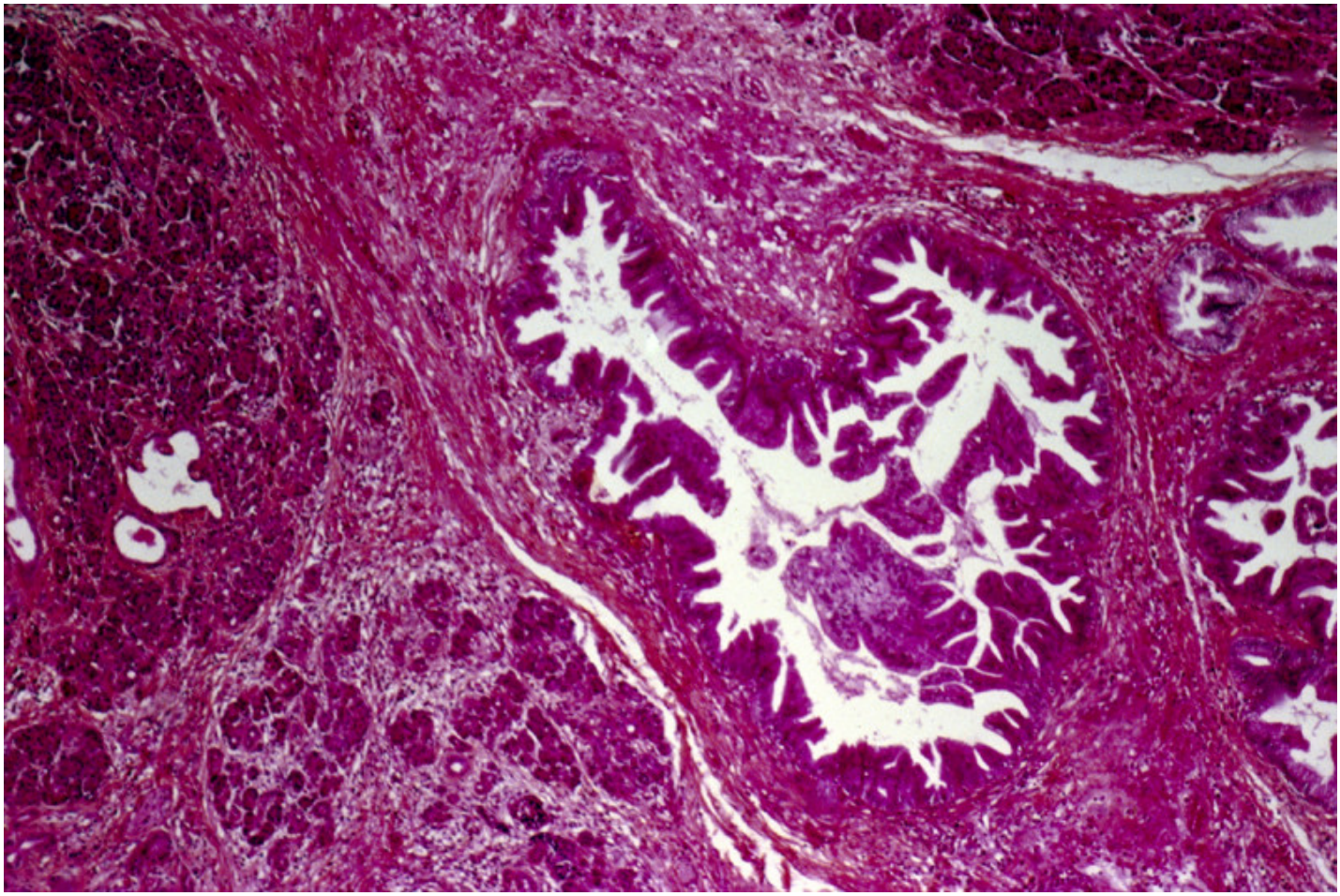
Studying a Forerunner of Pancreatic Cancer Reveals New Clues about How the Disease Develops

By Julie Grisham, **Monday, September 3, 2018**



Researchers are studying the genetic changes that occur early in the development of a pancreatic tumor, like that shown above. Source: CNRI/Science Source.

Summary

Understanding how pancreatic cancer develops is important for developing better drugs and screening methods. Researchers are finding new clues by studying abnormal pancreas cells that sometimes turn into cancer.

One universal truth about cancer is that the later it's detected, the harder it is to treat. **Pancreatic cancer** is one form of the disease that is almost always found when it's advanced, making it an exceptional challenge. Because it's rarely caught early in its development, this also means that researchers know less about what drives its formation and spread than they do with many other kinds of tumors.

Understanding how a cancer develops and grows, however, has important implications. It allows researchers to create better targeted therapies and develop better detection and screening methods. Now a study led by Memorial Sloan Kettering physician-scientist **Christine Iacobuzio-Donahue** is shedding new light on a phenomenon that sometimes leads to pancreatic cancer. The **results were published** September 3, 2018, in *Nature*.

A Possible Lead-Up to Cancer

When surgeons remove a cancerous pancreas, they often find groups of abnormal cells called pancreatic intraepithelial neoplasias (PanINs) in other parts of the organ. PanINs are also common in older people who do not have pancreatic cancer.

Pancreatic intraepithelial neoplasias are common in older people and don't always turn into pancreatic cancer.

Although they are not cancer, some PanINs eventually become cancer. Experts aren't sure how often that happens. "I think of them sort of like moles on the skin," says first author **Alvin Makohon-Moore**. "It may not turn into anything serious, but it's clear that some sort of change has taken place that could further transform into cancer." Dr. Makohon-Moore is a postdoctoral fellow in Dr. Iacobuzio-Donahue's lab.

In the new study, the investigators identified eight people who had undergone surgery for early-stage pancreatic cancer who also had PanINs in other parts of their pancreas. The patients were treated at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Medicine, where Dr. Iacobuzio-Donahue and her colleagues

worked when this research began. Several investigators from Johns Hopkins also contributed to the *Nature* paper.

The Search for Genetic Similarities — and Differences

The pancreas tissue was dissected under a microscope, and the cells from each PanIN were separated from the tumor cells in a very precise way. The DNA from each PanIN was then extracted, and the researchers conducted whole exome sequencing. This involves sequencing all the sections of the genome that are known to encode proteins. The tumors were also sequenced. For both types of cells, the investigators sorted out which mutations were likely to be directing cancer growth (called driver mutations) and which were just along for the ride (called passenger mutations).

"The goal of this research was to find mutations that the tumors and PanINs had in common and other mutations that the PanINs and tumors had acquired independently," Dr. Makohon-Moore explains. "Based on this, we could create evolutionary trees for each patient, to figure out how their tumors had evolved."

> "Eventually, we hope this research will give us a framework for interpreting the events that happen early in the development of pancreas tumors."

Alvin Makohon-Moore
researcher

Based on the driver mutations found in the PanINs and tumors, the team was able to determine which cancer-causing mutations led to invasive cancer and which were acquired later. Unexpectedly, they also found that the PanINs could move through the system of ducts in the pancreas.

Potential for Further Research

There are several important next steps in the research. One is to look at a greater number of PanINs and tumors to determine if there are any repeated genetic

patterns. That's difficult to do with samples from only eight people.

Another step is to look for attributes beyond the DNA that may be driving the formation of tumors. This will include studies of the cells around the PanINs. This area is called the microenvironment. Researchers will also look for changes in gene expression that are not reflected in the DNA sequence — called **epigenetic** changes.

"Eventually, we hope this research will give us a framework for interpreting the events that happen early in the development of pancreas tumors," Dr. Makohon-Moore says.

He adds that this inquiry may provide an explanation for why pancreatic cancer comes back so often after surgery. Even for people with early-stage disease whose tumors are completely removed, the disease returns in 60 to 70% of them. "It could be that these tumors are not as localized as we think they are and that they have the ability to move around within the pancreas," he says. "Our research may help provide a biological context for why this cancer is so aggressive."

Comments

> Commenting is disabled for this blog post.

Marcia Miller-Hjelle,. PhD

Sep 17, 2018 • 2:56 PM
Pancreatic mucinous cyst can have a propensity to become cancerous. Are the muryl nodules actually PanIns or reflect epigenetic changes. Why has it been so hard to ID biomarkers for those cysts that will become cancerous.... doesn't seem many are researching the problem. Why does an isolated cyst in uncinate process require a Whipple Procedure if caught early? Thank you. MAM-H

Memorial Sloan Kettering

Sep 18, 2018 • 12:28 PM
Dear Marcia, we forwarded your question to the researchers on this study, who replied, "In our study, all lesions were reviewed histologically and were either pancreatic cancer (adenocarcinoma) or pancreatic intraepithelial neoplasia (PanIN). There was no evidence of a cystic lesion or neoplasm in any of the tissues we examined. While our study does shed light on the evolutionary relationships of PanINs and pancreatic cancer, these data do not explain the nature of coexistent cystic neoplasms, as these differ from PanINs in their pathological features."