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# Building a better mouse model to understand pancreatic cancer

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Cancer of the pancreas is usually not detected until it's too late to cure. But precursor lesions that form in the pancreas and its ducts can signal the disease before it strikes, and when caught early enough, they can be prevented from progressing to become cancer.

In a new study, researchers led by a molecular biologist at the University of California, San Francisco (UCSF), report two breakthroughs in understanding those lesions and their role in pancreatic cancer: the development of the first mouse model that simulates a precursor lesion called intraductal papillary mucinous neoplasia (IPMN), and the identification of an enzyme, Brg1, that appears to help cause the formation of IPMN lesions while also suppressing another precursor lesion.

A University of Utah co-author on the study says the research proves that epigenetics – changes in genetic activity caused by forces other than modifications in the DNA sequence, such as when genes are turned on or off – play a role in pancreatic ductal adenocarcinoma (PDA), the most common type of cancer of the pancreas. "These findings may provide an avenue for intervention in PDA, if we can understand the epigenetics," says Matthew A. Firpo, Ph.D., research associate professor of surgery.

Mathias Hebrok, Ph.D., of UCSF School of Medicine, led the study published on Sunday, Feb. 23, 2014, in *Nature Cell Biology*. Sean J. Mulvihill, M.D., University of Utah professor of surgery, associate vice president for clinical affairs and CEO of the University of Utah Medical

Group, is also a co-author on the paper. He and Firpo have banked human samples of IPMN for many years and shared some with Hebrok for his research.

"This study not only represents a longstanding collaboration between the University of Utah and UCSF but also is a reflection of the transition in research from single investigators working on their own to highly collaborative studies with experts in many fields from different institutions," says Mulvihill, who is also a pancreatic cancer surgeon and an investigator with the University of Utah's Huntsman Cancer Institute.

With a five-year survival rate of just 4.4 percent, cancer of the pancreas is the fourth leading cause of cancer deaths. In 82 percent of cases, the disease is found when it's too late to remove the tumor. Tumors that are smaller than 2 centimeters and haven't metastasized are considered the best cases for surgery. When tumors are operable, the five-year survival rate approaches 40 percent, according to Firpo.

IPMN is one of three classes of pancreatic cancer precursor lesions. Pancreatic Intraepithelial Neoplasia (PanIN) and mucinous cystic neoplasm (MCN) also are lesions that precede pancreatic cancer. PanINs are the lesions most commonly thought to lead to PDA.

Brg1 is an enzyme that regulates gene expression by altering DNA structure in the nucleus of a cell, a process known as chromatin remodeling. Hebrok found that when the Brg1 gene is knocked out in mice that are predisposed to PanIN development and subsequent PDA, lesions form that are similar to human IPMN. He confirmed that through the human IPMN samples from Mulvihill and Firpo.

But in addition to Brg1's role in forming IPMN lesions, Hebrok discovered that when the gene is knocked out in mice that have an activated gene called KRAS, whose role is to help regulate cell division,

PanIN lesions occur less frequently. This indicates that Brg1 protects against PanIns but also helps cause IPMN lesions.

"As someone who researches pancreatic cancer, I think this discovery is significant because it defines mechanisms that lead to this cancer in ways that we didn't know about before," says Firpo, who's also a member of the Pancreas Cancer Research Program and Experimental Therapeutics Program at the University of Utah's Huntsman Cancer Institute. "It illuminates an area that were just guessing at before."

It's also significant because people with IPMN, which has been more frequently diagnosed in recent years, have a much better prognosis for survival than those with PanINs. The symptoms of IPMN usually become noticeable before cancer develops, meaning the lesions can be treated before a cancerous tumor forms. PanINs, however, typically don't show symptoms before an inoperable tumor has formed.

That's why it is so important to find the disease as early as possible, according to Mulvihill. "Better understanding of the beginnings of pancreatic cancer gives us much more hope for both prevention and cure."

Provided by University of Utah Health Sciences

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