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Scientists discover link between inflammation, pancreatic cancer

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Solving part of a medical mystery, researchers at the University of California, San Francisco have established a link between molecules found in an inflamed pancreas and the early formation of pancreatic cancer – a discovery that may help scientists identify new ways to detect, monitor and treat this deadly disease.

Scientists have known for many years that pancreatitis, a painfully inflamed pancreas, is a common risk factor for pancreatic cancer – along with things like smoking and diet. But nobody knew exactly why.

Now the UCSF team, led by Matthias Hebrok, Ph.D., has discovered at least part of the connection. In an article appearing in the journal *Cancer Cell* this week, they show that two molecular "signals" produced abundantly in the pancreas during inflammation – a protein named Stat3 – helps initiate the early stages of pancreatic cancer, while another protein, called MMP7, appears to affect metastasis.

In laboratory experiments, Hebrok and his colleagues showed that blocking these proteins in mice shrunk the number of lesions that can lead to cancer and reduced the extent of cancer metastasis. They also showed that one of these molecules, MMP7, may be a clinical indicator of cancer stage, possibly making it useful as a marker for more aggressive disease. The research could also help identify new ways to target pancreatic cancer with drugs.

"If you are able to down-regulate inflammatory signals at an early stage

of the disease, you may be able to curb the formation of early lesions," said Hebrok, who directs the UCSF Diabetes Center and is the Hurlbut-Johnson Distinguished Professor in Diabetes Research.

Inflammation and Pancreatic Cancer

Pancreatic cancer in the United States is all too common and far too deadly. According to the National Cancer Institute, there were some 43,140 new cases of pancreatic cancer diagnosed in the United States in 2010 and 36,800 deaths from the disease last year. Overall, fewer than one in 20 people diagnosed with pancreatic cancer this year will be alive five years from now.

One of the problems with the disease is that there are no reliable, sensitive screens that allow doctors to catch it early. By the time it is detected, the cancer often is so advanced it cannot be surgically removed or easily treated.

Like many scientists who study diabetes, Hebrok is very familiar with pancreatic cancer, because diabetes onset often precedes the cancer diagnosis and may be one of the warning signs. Part of his research in the past few years has involved looking at the microscopic changes that take place in the pancreatic organ when cancer emerges.

The pancreas is a 6-inch-long gland sandwiched between the stomach and the backbone. Inside are tiny cavities called "acini" in which enzymes are produced that drain through ducts into the stomach to help digest food. Pancreatic cancer may start in these cavities or in the ducts when the cells lining them undergo transformations and begin multiplying, forming cancerous lesions – a process often kick-started by inflammation.

Hebrok and his colleagues have discovered that the molecule Stat3 is a

key player in this process. It is produced in the pancreas and induces the cells of the pancreas to proliferate as part of a normal healing process in response to inflammation. Sometimes this process goes awry, however, and leads to the transformation of normal cells into cancerous ones. Stat3 also increases the amount of MMP7, which contributes to cancer metastasis.

The UCSF team showed that blocking MMP7 in mice blocks metastasis and reduces the size of cancer tumors. Collaborating with a group at the University of Utah, they examined blood samples taken from people with pancreatic cancer, and they found that those with more MMP7 in their blood were more likely to be at an advanced stage of cancer.

This suggests that MMP7 might be a useful marker to guide treatment for people with pancreatic cancer. And the new insight into the overall process of how inflammation is linked to pancreatic cancer might help scientists identify new targets for cancer therapy – if ways of interfering in the process can be found and if those approaches prove effective in clinical trials

"As with many things, timing is critical," Hebrok said. "We will need to understand in more detail during which stage of the disease therapeutic targets are activated to efficiently inhibit their function and thus cancer formation and progression."

Provided by University of California, San Francisco