# Researchers discover a gene that causes familial pancreatic cancer

December 12 2006

An international group of researchers has discovered that the mutated form of a gene called Palladin causes familial pancreatic cancer. The findings, published online today (Dec. 12) in the peer-reviewed journal PLoS-Medicine, may help explain why the disease is so deadly. The research project was led by Dr. Teri Brentnall, University of Washington associate professor of medicine, and supported by The Lustgarten Foundation, Canary Foundation, and other private sources.

Pancreatic cancer is usually a fatal diagnosis. One of the deadliest types of cancer, it is the fourth leading cause of cancer deaths overall, and third-leading cause of cancer deaths for people aged 40 to 60 in the United States. Most people with the disease die within a year of diagnosis; about 95 percent of patients die within five years. Researchers estimate that at least ten percent of all pancreatic cancer cases are inherited.

The discovery also reveals that the Palladin gene behaves abnormally in both the hereditary and non-hereditary, or sporadic, forms of pancreatic cancer. Previous studies by co-author Dr. Carol Otey, associate professor of physiology at the University of North Carolina, have revealed that when the Palladin gene is functioning properly, it gives a cell its shape and enables the cell to move. In the case of pancreatic cancer, a mutation in Palladin allows the cell to move much more quickly than normal, essentially invading the surrounding, healthy tissue.

Palladin, identified six years ago by Otey, is involved in the

cytoskeleton, the structural backbone of all human cells. Brentnall discovered that Palladin played a role in pancreatic cancer and began to collaborate with Otey. The team believes that the mutated Palladin causes cancer by causing the cytoskeleton to malfunction, which allowed the cells to move much more quickly than normal cells.

"A normal cytoskeleton holds up the cell wall, and gives it direction to sit down in its proper place and basically to behave," said Brentnall. "In cancerous cells, the cytoskeleton doesn't work correctly, and instead of sitting, the cells get up and invade areas where they don't belong, which is how the cancer spreads. This is a new way of thinking about cancer development in the pancreas."

"Brentnall and her colleagues' report of their fascinating discovery of a new cause of inherited pancreatic cancer provides us with important new insights into the mechanisms of pancreatic cancer development that will have a significant impact on future research," said Michael Goggins, MD, Associate Professor of Pathology, Medicine and Oncology at The Sol Goldman Pancreatic Cancer Research Center at Johns Hopkins.

Brentnall began her search for the pancreatic cancer gene in 1996 when one of her patients described his family's "curse." His grandfather, father, four uncles and three cousins had all died of pancreatic cancer, some at a very young age. Brentnall designated this family as "Family X" and set off to identify the source of the fatal inheritance. The puzzle took a decade to unravel.

Brentnall and her colleagues developed a surveillance program for the early detection of pancreatic pre-cancer in families who inherit the disease. "By performing surveillance on many of the Family X members, the research team identified which ones had the initial stages of pancreatic cancer" said Brentnall. "We then compared DNA samples from the family members with pre-cancer to those who did not have the

disease, and isolated the cancer-causing gene to an area of Chromosome 4."

Over the next two years, the researchers, led by Dr. Kay Pogue-Geile, associate professor of research at University of Pittsburgh School of Medicine, created a customized DNA microarray to help them isolate the gene responsible. They searched for the genes most abnormally expressed in that area on Chromosome 4, using pre-cancerous tissue from Family X pancreas and from 10 sporadic pancreatic cancers, comparing the results to normal pancreas tissue. The scientists hoped this approach would help them find the genes that were over-expressed in abnormal pre-cancerous and cancerous tissue.

"We finally found what we had so doggedly pursued -- a gene that was expressed 21 times more than any other," said Brentnall. "This gene, Palladin, was mutated in Family X and appeared to cause the fatal inheritance. Every one of the members of Family X who had the Palladin mutation got pancreatic cancer or pre-cancer, while the members of Family X who did not have the mutation were cancer-free."

By understanding the genes that cause pancreatic cancer in families, scientists can better understand why the disease forms sporadically in the general population. When Brentnall and her colleagues examined pancreas cells from cancer patients with no family history, they found that Palladin was also over-expressed in those cells. In fact, they found that in these non-hereditary cases, the gene became increasingly over-expressed as the pancreas tissue progressed through the pre-cancer stage and then to cancer.

Testing for a Palladin gene mutation may be possible in families that inherit pancreatic cancer (two or more affected family members). However, genetic testing is not likely to be useful for non-hereditary or sporadic pancreatic cancer (only one person affected in a family).

Brentnall and her team hope to develop a screening blood test for pancreatic cancer using the Palladin protein, as well as treatments that target mutations in Palladin.

In addition, early indications show that the study of Palladin may also shed light on how and why other cancers spread as well. Further information regarding genetic testing can be obtained at www.uwgi.org/ .

Source: University of Washington