

New pancreatic cancer gene identified

Investigators have discovered a gene whose inactivation appears to contribute to the deadly transformation of pancreatic cells into cancer cells.

Cancer of the pancreas ranks as the fifth deadliest cancer in the United States, killing more than 25,000 people a year. The newfound gene probably plays a role in about half of those deaths, says Scott E. Kern of Johns Hopkins University Medical Institutions in Baltimore.

Although genes on other chromosomes have been linked to pancreatic cancer, investigators suspected that a gene on chromosome 18 was also involved: In about 90 percent of cases, pancreatic tumor cells lack part of one of the cell's two copies of that chromosome. "Chromosome 18 stood out as an unexplained and important player," says Kern.

To narrow the region in which a cancer gene might exist, the investigators began to determine the parts of chromosome 18 missing from patients' cancer cells. Four of their patients lacked the same small region on both copies of their chromosome 18.

"If you get hit with lightning four times, you're probably standing near a tree or lightning pole. We quickly realized we were in the right area," says Kern.

Within that small region, the investigators unearthed a gene they call *DPC4*. The exact function of the protein encoded by *DPC4* remains a mystery, although it resembles proteins identified in fruit flies and earthworms, the researchers report in the Jan. 19 *SCIENCE*. Those proteins appear to belong to a family of molecules active in controlling the proliferation of cells, they say.

That possible function, and the observation that both copies of the gene are deleted in many patients' cancer cells, led the researchers to conclude that *DPC4* is a new member of a growing class of genes called tumor suppressors.

Researchers have learned that if chromosomal deletions or other genetic alterations rob a cell of the function of a tumor suppressor gene, that cell can ignore the strict regulations on cell growth and division that the body ordinarily imposes. This cancerous transformation can only occur if both copies of the tumor suppressor gene are silenced.

After determining the DNA sequence of *DPC4*, Kern and his colleagues discovered that some pancreatic cancer patients who were obviously missing one copy of the gene had small mutations in the other copy.

Yet not every person with cancer of the pancreas had *DPC4* problems. "There seem to be other pathways by which this cancer occurs," says Kern. He also suggests that other types of cancers, such as bladder and colorectal, may result from the loss of *DPC4*.

To determine whether *DPC4* is indeed a tumor suppressor, investigators need to add a functioning *DPC4* gene back into cancer cells that are missing both copies of the gene and see if the cells return to a noncancerous state, says Nick R. Lemoine of the Imperial Cancer Research Fund in London.

Both he and Kern suggest that the discovery of *DPC4* will someday help physicians battle what is one of the most aggressive and untreatable forms of cancer. By the time most patients have been diagnosed with pancreatic cancer, notes Lemoine, the disease has already spread to other parts of the body.

"The more [genes involved in pancreatic cancer] we identify, the better position we will be in for screening, diagnosis, and, ultimately, therapy," says Lemoine.

— J. Travis