CANCER RESEARCH

New Tumor Suppressor Found In Pancreatic Cancer

On the scale of public attention, pancreatic cancer ranks far below breast cancer or prostate cancer. One reason is that it affects far fewer people—tens rather than hundreds of thousands in the United States and Europe. But few cancers are more dangerous. Most pancreatic cancers have already metastasized by the time they are diagnosed, making curative surgery an option for just 1 in 500 patients. Half the patients die within 6 weeks, and the 5-year survival rate is less than 1%. Recently, however, cancer researchers have begun to understand just what makes this cancer so aggressive.

The latest clue comes from a team led by Scott Kern of Johns Hopkins University School of Medicine. On page 350, the researchers report that they have identified a new tumor suppressor gene, whose loss or inactivation may contribute to the development of pancreatic cancer.

This is not the first tumor suppressor gene to be linked to the cancer. Early on, the *p53* gene, which has been implicated in a wide range of human cancers, was found to be frequently mutated in pancreatic tumors. And more recently, the cancer has proved to be a useful hunting ground for additional tumor suppressors, aiding the search for the breast cancer susceptibility gene *BRCA2* and helping confirm the importance of the *p16* gene as a tumor suppressor.

And the new gene, which the Johns Hopkins team calls *DPC4* (for *Deleted in Pancreatic Cancer, locus 4*) appears to be at least as important as the others for pancreatic cancer. Kern's team finds *DPC4* is lost or mutated in about 50% of the pancreatic tumors examined. "It looks like a big player in pancreatic cancer," says molecular geneticist Alexander Kamb of the Salt Lake City biotech firm Myriad Genetics, who was a member of the team that linked *p16* to cancer development. Initial results suggest that *DPC4* loss is also implicated in other cancers, including some colon, bladder, and biliary tumors.

What's more, *DPC4*'s sequence provides an intriguing hint about what its normal role might be. It may be a part of a well-known system for inhibiting cell growth. If so, that could explain how its loss could contribute to the runaway cell growth of cancer and might also provide a new approach to more effective therapies for pancreatic cancer, if drugs could be developed to restore its missing suppressive effects.

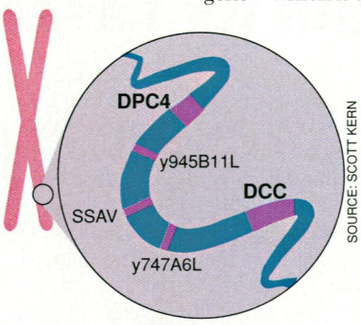
Kern and his colleagues had been tracking the *DPC4* gene, which is located on the long arm of chromosome 18, for about a year and a half. They thought that region might harbor a tumor suppressor for pancreatic cancer because the vast majority—about 90%—of the tumors show deletions in the area in at least one of the two chromosome 18 copies, and such deletions often mark the locations of tumor suppressor genes. In fact, one candidate for the gene had already been identified in the area by Bert Vogelstein's group, also at Johns Hopkins: a gene called *DCC* (for *Deleted in Colon Cancer*), which is implicated in colon cancer development.

Because the chromosome 18 deletions found in colon cancer cells often overlap with those seen in pancreatic cancer cells, *DCC* might also be involved in the pancreatic tumors. But that was by no means certain, as the deleted regions are big enough to contain thousands of genes. "Chromosome 18 has losses which are immense; therefore it's very hard to pick out which are the sensitive sites," Kern says.

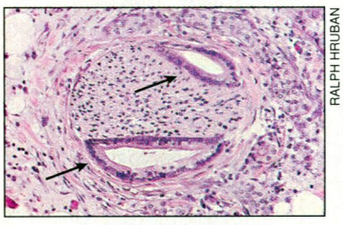
To home in on the pancreatic cancer gene, Kern and his colleagues took advantage of the fact that both copies of a tumor suppressor must be inactivated for cancer to develop. Usually, one copy is lost as part of a large deletion, while the other is inactivated by a smaller mutation. Finding the critical mutation is one way to pinpoint the gene, but that entails trawling through the DNA looking at point mutations. A minority of tumors, however, lose the two gene copies through small deletions on both chromosomes. Such "homozygous deletions," which are easier to find than point mutations but more specific than large deletions, have helped identify other tumor suppressor genes, including *p16*.

And the strategy paid off again in the pancreatic tumors. Of 31 tumor samples screened, four showed evidence of the same homozygous deletions within the target area. "We got as lucky as a person could get," says Kern. "We knew we were in a hotspot of homozygous deletions right then."

By screening additional samples of human pancreatic cancer cells, they eventually narrowed the chromosome 18 segment lost to a small region containing only one DNA sequence capable of encoding a protein. This gene—which is different from *DCC*—proved to be missing from 25 of 84 pancreatic cancers. And six of 27 cancer samples without homozygous deletions had mutations that inactivated the gene. That is "exactly what you'd expect for a mutation in a tumor suppressor gene....It's as good evidence as you can get at this stage," says molecular geneticist Mike Stratton, of the Institute of Cancer Research in Sutton, U.K., whose team identified *BRCA2*.



SOURCE: SCOTT KERN



RALPH HRUBAN

Gene link. *DPC4* and *DCC* are neighbors, but it's *DPC4* loss that helps pancreatic cancers grow aggressively, as in these metastases (*arrows*) in a nerve bundle.

The new work rules out *DCC* as a tumor suppressor for pancreatic cancer, but it was also important to establish whether *DPC4* is implicated in colon cancers. In unpublished work, Kern and Vogelstein find that some homozygous deletions in colon cancer include *DPC4*, raising the possibility that it might be. However, other deletions include *DCC*, but exclude *DPC4*, so "they appear to be two different loci," says Vogelstein.

Exactly what *DPC4* normally does in the cell remains to be established, but its sequence provides some tantalizing clues. The DPC4 protein resembles a fruit fly protein called Mad, which is thought to be a member of the pathway by which another protein known as DPP transmits its signals to the cell interior. DPP, which controls several aspects of fruit fly development, is in turn closely related to transforming growth factor β (TGF-β), a mammalian protein that acts as a growth suppressor for many cells. If DPC4 is part of the TGF-β signaling path, then its loss might well contribute to excessive cell growth. Such a possibility "is quite provocative [because] the TGF-β pathway is so clearly involved in cell growth," Vogelstein says.

And that is not the only provocative issue raised by the new work. Deletions in chromosome 18 are seen in some 90% of pancreatic tumors, but only 50% show *DPC4* loss or inactivation. "There may be another [tumor suppressor] gene nearby to account for the other 40%," Kern says. Finding it, and other pancreatic tumor suppressor genes that researchers think may be lurking in the genome, may finally explain why pancreatic cancer growth is so unstoppable.

–Claire O'Brien

Claire O'Brien is a writer in Cambridge, U.K.