

# SWI/SNF protein complex plays role in suppressing pancreatic tumors: study

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A well-known protein complex responsible for controlling how DNA is expressed plays a previously unsuspected role in preventing pancreatic cancer, according to researchers at the Stanford University School of Medicine.

Technological advances in the way researchers can compare normal and tumor DNA showed that the gene for at least one subunit of the multi-subunit SWI/SNF [protein complex](#) was either deleted, mutated or rearranged in about a third of the 70 human pancreatic cancers that the Stanford team examined. Additionally, the researchers found that restoring the expression of one of the missing genes slowed the growth of [pancreatic cancer](#) cells in the laboratory and caused them to enter an arresting state called senescence.

"This is really strong [genetic evidence](#) that this complex plays a role in pancreatic cancer," said associate professor of pathology Jonathan Pollack, MD, PhD, "and it suggests the influence of the SWI/SNF complex is on par with that of other well-known tumor suppressors, such as p53."

Pollack is the senior author of the research, which will be published online Jan. 9 in the [Proceedings of the National Academy of Sciences](#). Graduate student Hunter Shain is the first author.

The tumor-suppressing role of the SWI/SNF complex had not been previously discovered because the disabling changes were spread among

five of the complex's protein subunits. In other words, one person's pancreatic cancer might have a mutation or deletion in one protein subunit, while another's could have a change in a different subunit. Considered individually, each variation occurs relatively infrequently.

Shain and Pollack used a technique called array comparative genomic hybridization, or CGH, to pinpoint places in the genome that differed among normal and cancerous pancreatic epithelial cells. The procedure relies on the ability of single-stranded DNA to seek out and bind to its [mirror image](#). By comparing the relative amounts of tumor and normal DNA that bind to a panel of reference sequences, the researchers can tell whether the cancer cell contains amplifications or deletions of genetic material in specific regions throughout the genome. These copy-number variations often occur in genes or regions important in regulating uncontrolled cell growth.

The researchers examined about 70 different pancreatic cancers, including specimens provided by their co-authors at the Sol Goldman Pancreatic Cancer Research Center at the Johns Hopkins University School of Medicine. Forty-eight of the cancers were primary samples from human patients that had been coaxed to grow in immune-deficient mice; 22 had been maintained as laboratory-grown cancer cell lines. Shain used high-density arrays of reference DNA sequences for the CGH, which allowed him to identify amplified or deleted regions at a much higher resolution than previously possible — narrowing the areas of interest to just a few thousand nucleotides rather than larger stretches of DNA.

When the researchers looked at the results of the array CGH analysis, they found many genes known to be involved in pancreatic cancer, and also some new candidates. In particular, they noticed that the genes for individual subunits of the SWI/SNF complex were altered in about 5 to 10 percent of the cancer samples — an interesting finding, but not

prevalent enough to spark further immediate investigation under normal circumstances. However, when considered together, Shain and Pollack realized that more than a third of the cancer samples contained a deletion, mutation or rearrangement in the gene for at least one of the five subunits.

"Our intention was to identify new genes involved in pancreatic cancer," said Pollack. "The discovery that SWI/SNF plays a role was exciting because we never would have found it any other way. It really validates the use of genome-wide analysis."

The researchers then experimented with artificially increasing the expression of the gene for one of the subunits in cancer cells in which it was deleted. They found that, in the laboratory, these pancreatic [cancer cells](#) engineered to re-express the missing protein slowed their growth and even began to senesce, or enter a permanently arrested state, rather than dividing uncontrollably.

The involvement of SWI/SNF in pancreatic cancer is both exciting and challenging because of its global effect on gene expression. DNA is normally packaged tightly around bundles of protein called histones, and the combination of DNA and proteins is called chromatin. SWI/SNF works by repositioning histones on DNA to make it available for transcription factors that govern DNA's use as a template for the synthesis of RNA, which goes on to serve as a template for the proteins to do the work of the cell.

"We're becoming more and more aware that chromatin modification and remodeling play an important role in cancer," said Pollack, pointing out that several other recent studies have also zeroed in on proteins controlling the architecture of the genome. "What we'd like to learn now is specifically how altering this particular complex affects cancer progression. The major effect is likely to be through changes in the

expression of genes."

The researchers are now working to pinpoint exactly which genes are important to drive the growth of human pancreatic cells by artificially overexpressing or blocking the expression of genes coding for various SWI/SNF subunits.

Provided by Stanford University Medical Center

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