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## Loss of Tumor Suppressor Gene Triggers Colon Cancer

Researchers have found the first connection between the loss of a tumor suppressor gene and activation of a cancer-promoting oncogene, a scenario thought to be prevalent in the initiation of many cancers but which has never been proven.

The newfound link also helps to explain the genesis of most cases of colon cancer, the second leading cause of cancer deaths in the United States.

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The scientists found that mutated *APC* genes, regarded as one of the body's master brakes on cell growth, switch on c-*MYC*, a gene long associated with cancers of various sorts in both animals and humans.

"This connection is fascinating and we hope it leads to further understanding of this pathway," says Bert Vogelstein, an HHMI investigator at The Johns Hopkins Oncology Center. The report by Vogelstein and Johns Hopkins colleagues, Kenneth Kinzler and HHMI associate Tong-Chuan He, appears in the September 4, 1998, issue of the journal *Science*.

For Vogelstein, who has studied the genetic basis of colon cancer for nearly 20 years, "this ends one chapter of the *APC* story," but begins many more. "Master genes such as *p53*, another tumor suppressor, or *APC* usually don't work on just one pathway. So c-*MYC* is probably not the only gene whose expression is controlled by *APC*. We are working to find the others," he said.

The discovery also offers hope of finding new ways to treat colon cancer. Knowing that the c-*MYC* oncogene is one final link in the colon cancer chain "brings up an obvious and potentially powerful way to disrupt that interaction," Vogelstein says. Vogelstein's team plans to begin screening

compounds that can block expression of the *c-MYC* oncogene through interference with the transcription factors regulated by APC.

In 1991, investigators including the Vogelstein-Kinzler team first identified *APC* (adenomatous polyposis coli), and linked mutations in that gene to colon cancer. Mutations in the *APC* gene were found in the hundreds of polyps that populate the colons of patients with an inherited disease, familial adenomatous polyposis (FAP). Similar mutations were found in about 85 percent of all colon cancers, including patients who had no family history of colon cancer.

By 1993, the researchers showed that APC interacts with the protein  $\beta$ -catenin, a cell adhesion molecule commonly found in stomach tissue. That finding later helped to explain why nearly 10 percent of colon cancer cases develop with normal *APC* genes; the mutations are in  *$\beta$ -catenin*.

Next it was shown that  $\beta$ -catenin associates with the TCF family of proteins that activates gene transcription, and that APC regulates this association. This led to the hypothesis that APC,  $\beta$ -catenin and Tcf-4 collaborate to regulate gene activity in colon cells, although the precise targets of that complex remained unknown. Finding those targets might tell the researchers how the protein complex promotes errant cell growth.

The break came when the team used a powerful screening procedure to sort out the genes that are turned on or off by APC. They found that the *c-MYC* gene quickly shut down after APC was applied, giving them direct evidence linking *APC* to *c-MYC*, a known oncogene.

Summarizing the results, Vogelstein explains that normal APC prevents  $\beta$ -catenin from binding to Tcf-4, which, in turn, foils *c-MYC* expression. If APC or  $\beta$ -catenin is mutated, however, the *c-MYC* oncogene is unchecked and promotes cell growth.

While Vogelstein says it is too early to speculate whether this pathway may be shared by a number of other cancers, he notes that "*c-MYC* is a powerful growth promoter, and this study should stimulate a lot of new work in this area."