

APRIL 02, 2002

Gene Alteration Spurs Growth of Colon Cancer

Researchers have discovered a novel gene alteration that causes an abnormal cellular “off-switch” that contributes to the growth of colon cancer. Identification of the gene alteration, which appears to contribute to tumor malignancy in about 40 percent of patients with colon cancer, may permit researchers to better understand how tumors become malignant and invasive.

Howard Hughes Medical Institute investigator Sanford D. Markowitz and colleagues at Case Western Reserve University, University Hospitals of Cleveland, and four other institutions have shown that inactivation of the *helicase-like transcription factor* (*HLTF*) gene contributes to transforming normal colon cells into cancer cells. The gene is a member of a family of genes that removes the proteins that coil around DNA, thus exposing individual genes to the cell’s gene-expression machinery. HLTF proteins help stabilize DNA and regulate the production of other proteins in the cell.

"Understanding what this gene does in the cell will help us comprehend how colon cancer gets started and could be a new target for drug intervention."

— Sanford Markowitz

“HLTF belongs to a pathway that is just beginning to be appreciated in the development of cancer,” said Markowitz. “This is the first time a protein in this family has been implicated as a participant in a major, common form of cancer.” Markowitz and his colleagues reported their findings in the April 2, 2002, edition of the *Proceedings of the National Academy of Sciences* .

“This is a new colon cancer suppressor gene whose inactivation appears to contribute to malignancy in about 40 percent of cases,” said Markowitz. “Understanding what this gene does in the cell will help us comprehend how colon cancer gets started and could be a new target for drug intervention.”

In the study, the scientists examined colon cancer cells and normal cells from 63 colon cancer patients and 34 colon cancer cell lines grown in the laboratory. They discovered that production of the HLTF protein had been

shut down by a mechanism called DNA methylation.

“This type of methylation produces an abnormal ‘off switch’ that in this case inappropriately shuts down production of a tumor suppressor protein,” said Markowitz. The methylation process has also been implicated in turning off other tumor suppressor genes and is recognized as a contributor to the development of cancer.

When the scientists introduced a functional copy of the *HLTF* gene into the colon cancer cell lines that lacked the gene, the cells stopped growing. This finding suggests that the *HLTF* gene is itself a tumor suppressor gene that can stop tumors from growing.

Markowitz said that the studies also hint that drugs that reverse methylation may be a new type of cancer treatment. These drugs are now in the early stages of development. In the short term, however, Markowitz believes the finding may help doctors diagnose colon cancer and perhaps differentiate aggressive, invasive tumors from less aggressive forms of colon cancer.

When Markowitz and his colleagues looked in lung and breast cancer cells, they found the *HLTF* gene was normal. Based on this result, they concluded that the *HLTF* gene may be involved specifically in colon cancer progression. Furthermore, the scientists had previously detected abnormal methylated DNA in the blood of some colon cancer patients, suggesting that if the findings hold for the commonly methylated *HLTF* gene, it could be a target for a new diagnostic test for colon cancer. Markowitz cautioned that the result needs to be duplicated and other cancer cells need to be tested.

Markowitz is optimistic, and he cites recent work by HHMI investigator Bert Vogelstein at The Johns Hopkins University School of Medicine that demonstrates a new targeted, non-invasive test for finding about half of colon cancers using the *APC* tumor suppressor gene.

“What has limited the development of a simple diagnostic test for colon cancer previously has been finding the right target that can catch close to all the cases,” said Markowitz. “What we describe in this paper is a test that can catch 40 percent of colon cancers. A screen that searches for *APC* and *HLTF* mutations may be able to catch more than 90 percent of cancers, making blood or stool sampling practical.”

The development of a simple, non-invasive colon cancer diagnostic test could greatly increase early detection of the second leading cause of cancer death among adult Americans, said Markowitz. A blood or stool test is seen as a way of significantly increasing the number of people whose colon cancer is detected in the early stages of growth when the prognosis for full recovery is good. By contrast, colonoscopy, the current standard for detection, is invasive, so people tend to put off or avoid having the test.

The scientists also found that those tumors with the silenced *HLTF* gene were actually less likely to spread to adjacent tissues. The results suggest that tumors with *HLTF* turned off may grow more slowly than other tumors.

“In the patient group we studied, the patients with abnormal HLTf seemed to do somewhat better,” he said. “This suggests testing for HLTf mutations may have some prognostic value in determining how aggressive the cancers are.”

Markowitz added that the combination of applying modern molecular techniques and identifying key targets such as HLTf should make colon cancer diagnosis and treatment easier, as well as providing more information about the severity of the disease.