

Developing an Easier Screen for Colon Cancer

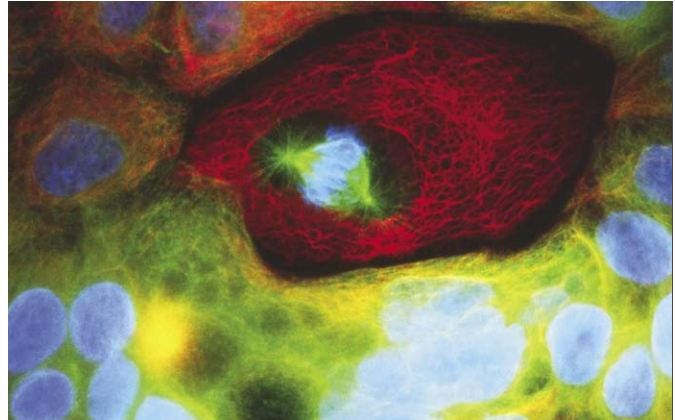
A noninvasive and inexpensive test might soon displace colonoscopies.

COLORECTAL TUMORS TAKE THE LIVES OF MORE ADULT Americans than any other cancer except lung cancer, even though colon cancer is almost always curable by surgery if detected early enough.

Yet most people never undergo a colon cancer screening test, says HHMI investigator Sanford Markowitz of Case Western Reserve University. Colonoscopy can detect more than 90 percent of colon tumors. But the procedure is expensive and unpleasant, and carries some degree of risk. Meanwhile, the fecal occult blood test (FOBT), the standard noninvasive screen that detects blood in the stool, catches only 15 percent of colon cancers.

Markowitz and his colleagues have now developed a noninvasive test, 3 times more sensitive than the FOBT, that relies on a telltale chemical signature in a gene called *vimentin*. While the gene in cancerous colon cells displays chemical modifications called methylations, it is rarely, if ever, methylated in healthy cells. On this basis, Markowitz's lab devised a biochemical assay that can detect the aberrant gene modification in as few as 15 cancer cells—a sensitivity that allows the test to be performed on DNA shed in a stool sample. In a clinical trial, the test detected *vimentin* methylations in 46 percent of colon cancer patients, and it caught early-stage tumors as effectively as it did late-stage tumors.

New progress toward a comprehensive noninvasive screening test for colorectal cancer has also been made by HHMI



UNDER A MICROSCOPE, COLON CANCER IS CHARACTERIZED BY IRREGULARLY SHAPED CELLS WITH LARGE NUCLEI AND EVIDENT CELL DIVISION. HERE, NUCLEI ARE BLUE, TUBULIN SPINDLES ARE GREEN, AND MUSCLE FIBER (MYOSIN) IS RED.

NANCY KEDERSHA / PHOTO RESEARCHERS, INC.

investigator Bert Vogelstein and his colleagues at the Sidney Kimmel Cancer Center at the Johns Hopkins Medical Institutions. The researchers recently reported that they could detect DNA fragments of mutant forms of a key cancer gene, called APC, in blood plasma from patients with certain types of colon cancer. “The test we developed for plasma DNA mutations can also be used to study fecal DNA mutations,” says Vogelstein. “We are working with Sandy Markowitz’s group to develop the optimal combination of DNA markers to use for this purpose.” ■

- Paul Muhlrud -

IN BRIEF

lab to lack Nova-2, they found that the protein is indeed required for LTP of slow inhibition. It is not, however, necessary for LTP of excitation. “It was totally surprising to us, but it’s really intriguing that there could be controls at that level,” Lily Jan says.

GENETIC CLUE TO TOURETTE’S SYNDROME REVEALED

Researchers have identified the first gene mutation associated with Tourette’s syndrome (TS), opening a new avenue for understanding the complex disorder that causes muscle and vocal tics. Until now, causes of TS, which afflicts as many as 1 in 100 people, have eluded researchers because the disease appears to be caused by subtle mutations in many genes.

The researchers published their findings in the October 14, 2005, issue of the journal *Science*. Matthew W. State of the Yale University School of Medicine was senior author of the paper. His research was supported by an HHMI institutional award to support early

research by promising scientists at Yale. Other coauthors at Yale included HHMI investigator **Richard P. Lifton**, and neurobiologists Nenad Sestan and Angeliki Louvi from the Yale Child Study Center.

State and his colleagues searched near the breakpoints of an inversion on chromosome 13 discovered in a TS patient. They identified one gene, called *SLITRK1* (for Slit and Trk-like family member 1), that is expressed in the brain in the regions implicated in TS, and is associated with the growth and interconnection of neurons. The gene was then confirmed to be linked to TS in other patients.

Lifton points out that State’s approach is somewhat different from his own strategy of analyzing rare genetic abnormalities that tend to run in families. “The idea of looking for clues from chromosomal anomalies is a very powerful one that has paid off in this case,” says Lifton. “The findings point for the first time to a pathway that appears to contribute to the pathogenesis of TS and enables further

studies not only from a genetic perspective, but also from a pathophysiologic one.”

NEW VIEW OF THE BIOLOGICAL LANDSCAPE

A new technique for analyzing the network of genetic interactions promises to change how researchers study the dynamic biological landscape of the cell. The technology, called epistatic miniarray profiles (E-MAP), has already been used to assign new functions to known genes, to uncover the roles of previously uncharacterized proteins, and to define how biochemical pathways and proteins interact with one another. E-MAP will enable new understanding of how genes and proteins function in the cell, says **Jonathan S. Weissman**, an HHMI investigator at the University of California, San Francisco, and leader of the team that developed the technique. The work was published in the November 04, 2005, issue of *Cell*.