Possible New Colon Cancer Gene Found

Mutations in the gene may foster development of the cancer by removing one of the brakes that help to control colon cell growth

SLOWLY BUT SURELY IN THE PAST FEW YEARS researchers have been pinning down the gene changes that lead to cancer. Now, a group of researchers may have taken a big step toward understanding colon cancer, which is the second most common malignancy in the United States. On p. 1366, Kenneth Kinzler and Bert Vogelstein of Johns Hopkins University Medical School and their colleagues report that they may have found a key gene for colon cancer development, possibly the site of the mutation that causes a hereditary colon cancer susceptibility known as familial adenomatous polyposis (FAP). "It looks to me like a very hot candidate gene," says John Minna of the National Cancer Institute-Navy Medical Oncology Branch and the Uniformed Services University of the Health Sciences in Bethesda, Maryland, whose work focuses on the genetic basis of lung cancer.

Colon cancer, like the other common solid tumors, apparently develops by a stepwise accumulation of several mutations, some of which activate oncogenes that push cells toward the cancerous state while others inactivate genes that suppress tumor growth (also see *Science*, 15 December 1989, p. 1386). But researchers find the newly discovered gene, which appears to be a suppressor, particularly interesting because its mutations may come into play in the initial stages of the pathway leading to colon cancer. If so, it might eventually be possible to detect colon cancer at an early stage by identifying mutations in this gene. And in the longer term, it might be feasible to inhibit tumor growth with drugs that replace the biochemical activity lost as a result of the mutations.

What the Vogelstein group may have isolated is the colon cancer gene thought to reside at segment q21 on chromosome 5. Two lines of evidence originally pointed to the existence of such a gene. Genetic studies done 4 years ago by two groups, one including Ellen Solomon and Walter Bodmer of the Imperial Cancer Research Fund in London, and the other including Ray White and his colleagues at the Howard Hughes Medical Institute at the University of Utah Medical Center in Salt Lake City, mapped the FAP gene to 5q21. Meanwhile, analysis of nonhereditary colon cancers by several groups revealed that the same chromosomal region is deleted in up to 60%, a result suggesting that the region contains a tumor suppressor gene that normally keeps colon cells from growing out of control.

This gene and the one that is defective in the hereditary condition FAP may be the same. That, anyway, was the assumption on which the Johns Hopkins workers based their strategy for going after the 5q21 gene. Using the same DNA probes with which White and Yusuke Nakamura of the Cancer Institute in Tokyo mapped the FAP gene location, they scoured DNA from nonhereditary tumors, looking for abnormalities that might indicate the presence of the putative tumor suppressor gene.

This proved to be a Herculean task, Vogelstein says. Only large DNA alterations, such as gene deletions or rearrangements, can be detected in such screens, and the researchers had to examine several hundred tumors before one of the probes picked up an abnormality. "It's a numbers game combined with a lot of luck," Vogelstein says. After finally detecting the abnormality, however, the researchers were able to use it as a tag for zeroing in on their candidate FAP gene.

Early studies of the gene have been encouraging. In particular, the researchers found two colon cancers in which the gene had point mutations, each changing one amino acid. "Point mutations are a smoking gun," Vogelstein says. "Since they were present in all the cells of the tumors, it suggests they were associated with the selective outgrowth of the cells that caused the tumors."

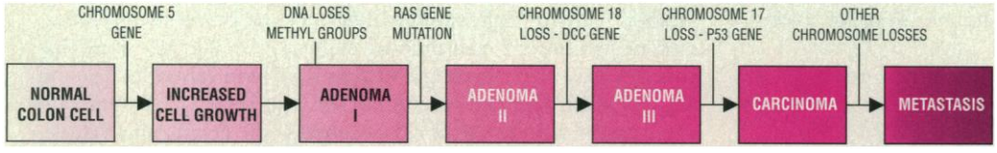
Also intriguing, Vogelstein says, is the structure of the protein encoded by the gene. The sequence of amino acids in one short segment suggests that the protein might be capable of binding to and regulating a G protein. That's significant because G proteins (so called because they bind guanosine nucleotides) are important intermediaries for transmitting signals in cells. Vogelstein speculates that the normal gene product suppresses cell growth by interacting with a G protein. That's how the recently discovered neurofibromatosis gene is supposed to work, he notes, and neurofibromatosis, like FAP, is characterized by numerous benign tumors, although in a different cell type.

But at the moment, no one knows what the new gene does, or indeed, if it really is the FAP gene. To prove it is, researchers need to show several things. For example, is the gene mutated in FAP patients? In preliminary work, White, for one, hasn't seen such mutations, but he says that he hasn't examined the entire gene, which is very large (more than 300 kilobases)—and so it is far too early to conclude that the Vogelstein group's candidate isn't the FAP gene. "We need to do the pick-and-shovel work at the [gene] locus to sort out what's happening," White says.

Another high priority is to find out whether the normal gene product has the postulated tumor suppressive effects, and, if so, how it produces them. If it does work through a cytoplasmic signaling pathway, that would be an encouraging development, says carcinogenesis expert Carl Barrett of the National Institute of Environmental Health Sciences. The reason: It might then be easier to design a drug to replace its activity than it would if the suppressor works in the nucleus, as one of the others implicated in colon cancer does. Researchers also want to know how the new gene might interact with the other genes that are already implicated in colon cancers.

Cancer researchers are generally pleased by the recent progress toward understanding the genetic underpinnings of colon cancer. "It's really exciting that we are beginning to get a molecular portrait of how a very important human cancer arises," Barrett says. A great deal of that progress has come from the Vogelstein lab. Indeed, according to *Science Watch*, five of the group's papers on the work have made the most cited paper list during the past 2 years—including the "hottest" paper in the biological sciences during 1990 (*Science*, 5 January 1990, p. 49). Will the new paper be next on the list?

■ JEAN MARX



In at the start. *Loss of a chromosome 5 gene appears to occur early in the development of many colon cancers, with other gene changes usually coming in later.*