Nabbing a gene for colorectal cancer

With much fanfare last week, two separate research teams announced the discovery of a gene that underlies a common type of colon and rectal cancer. The advance may lead to a blood test that would identify people who have inherited the mutant form of this gene, the researchers say.

"The discovery of a cancer gene is a textbook example of the kinds of payoffs we can expect when we invest in basic research," says Health and Human Services Secretary Donna E. Shalala.

The gene in question appears to cause hereditary nonpolyposis colorectal cancer (HNPCC), one of the most common inherited diseases in humans. The hunt for a gene responsible for some cases of HNPCC intensified last spring when a team led by Bert Vogelstein of the Johns Hopkins University School of Medicine in Baltimore reported that the gene was located on a specific stretch of DNA along chromosome 2, one of the 23 pairs of human chromosomes (SN: 5/8/93, p.292).

Now, Vogelstein and his colleagues report they've zeroed in on the guilty gene, which resides on the short arm of chromosome 2. A second team, led by Richard Kolodner of the Dana-Farber Cancer Institute in Boston and Richard Fishel of the University of Vermont Medical School in Burlington, reports it has linked that gene to HNPCC. What's more, the gene is the human version of the MSH2 gene Kolodner had been studying in yeast. Those studies showed that MSH2 plays an important role in ensuring the fidelity of DNA replication.

Kolodner, Fishel, and their colleagues described their findings in the Dec. 3 CELL. Vogelstein's group will detail its work in the Dec. 17 issue of the same journal.

People with HNPCC, also known as Lynch syndrome, inherit the tendency to develop colorectal cancers, as well as stomach, uterine, and some other malignancies. Those who carry the mutant gene have about an 80 percent chance of getting such cancers, often before they reach the age of 50.

For Henry T. Lynch, the oncologist who first described this syndrome, the discovery of a gene for HNPCC represents a dream come true. Lynch's theory that HNPCC is inherited met with much skepticism when presented at a scientific meeting in 1964, he recalls. But he never gave up, telling his patients: "One of these days, we're going to get the gene."

That day has finally dawned, says Lynch, who is at Creighton University School of Medicine in Omaha, Neb. Lynch is a coauthor of the Dec. 17 paper, along with Vogelstein, Stanley R. Hamilton, also of Johns Hopkins, Jeffrey M. Trent of the National Center for Human Genome Research in Bethesda, Md., and others.

Trent says the team began its search by snipping out the region of DNA that had been targeted in May. They then compared DNA sequences from this crucial segment to genes known to reside in that area of chromosome 2. The researchers ruled out several genes before hitting pay dirt with the MSH2 gene. When they examined tumor cells taken from patients with HNPCC, the researchers discovered mutations in the MSH2 gene.

A number of scientists working with yeast and bacteria have shown that the gene directs the production of a protein that homes in on errors that arise when a cell divides and copies its DNA. When working properly, this protein flags the mistakes and alerts the cell's repair machinery to fix any errors in the base pairs that make up each DNA molecule.

MSH2's function fits with another finding, also reported by Vogelstein's group last May. They had shown that the DNA obtained from HNPCC tumor samples exhibited a curious series of errors, indicating that the cellular DNA repair mechanism may have gone awry.

That finding electrified Fishel and Kolodner, who had already started to focus on the human version of the MSH2 gene, believing that it might cause human disease. They knew that mutations in the MSH2 gene result in the same kinds of DNA errors in yeast that Vogelstein's group found in human tumor tissue.

"We switched into high gear," Kolodner says. Rather than laboriously hunt through the DNA looking for candidate genes, Fishel and Kolodner's group started with the hypothesis that a flaw in the MSH2 gene causes Lynch syndrome in humans. Indeed, they found that people with HNPCC have a mutation in the MSH2 gene on chromosome 2.

Eventually, researchers hope to use the information about the MSH2 gene to develop a therapeutic approach to ward off inherited cancers. For the near future, however, the research may bring some HNPCC family members relief in the form of a blood test, Lynch says.

With a blood test, doctors could rule out this syndrome in people who have not inherited the flawed gene. For people who do have the mutant gene, knowledge of that cancer risk should lead to frequent screens for cancer, including a procedure that identifies precancerous changes in the colon, says Francis Collins, director of the National Center for Human Genome Research. That should help prevent this "terrible disease" for many people with the mutant gene, he adds.

– K.A. Fackelmann

A new twist on bacterial rotary engines

Like tiny submarines, some bacteria move by spinning their tails rather than flailing them about like whips.

In such cases, the tails – stiff, helical flagella that resemble elongated corkscrews – hook on to a primitive driveshaft, which is spun by what biologists call a "rotary engine."

At a recent meeting of the Materials Research Society in Boston, Howard C. Berg, a biologist at Harvard University, described his group's efforts to show how rotary motors propel bacteria forward. While they know that protons moving through the cell membrane power the engine, the scientists seek the mechanism that "causes a rotor to go around and turn a crank," Berg says.

Berg and his colleagues first "tethered" the tails of *Escherichia coli* cells to a sapphire base, then spun the cell bodies around in two directions, at various speeds, with a rotating electric field. Finally, they calculated the twisting power, or torque, of the bacterium's tiny motor.

Two new findings emerged, Berg reports. First, when spun forward, the engines produced a steady force at a wide range of speeds. "This finding is very unusual," Berg says. "Most engines don't behave that way." Second, when spun backward, the driveshafts first resisted, then slipped and broke. "This, too, was interesting," Berg adds. "It's like a ratchet mechanism."

While many theoretical models seek to explain how bacterial motors turn, these results point strongly to a "tightly coupled" model, notes Berg. That model suggests that a fixed number of protons, moving through the bacterial membrane, causes each rotation.

"These ion-driven machines are a marvel of nanotechnology," says Berg. "That nature could invent such an engine at all is utterly fascinating. People are amazed by little nanotechnology gears, but these engines are so small that 1,000 could fit on a man-made motor."

Details of Berg's experiment, carried out with Linda Turner, a biologist at the Rowland Institute for Science in Cambridge, Mass., appear in the November BIOPHYSICAL JOURNAL. *– R. Lipkin*