Renegade Tumors

Does a protein steer cancer's course?

By KATHY A. FACKELMANN

A truck rumbles slowly down a mountain road. Suddenly, its brakes go out and it starts to accelerate. A few minutes later, the driver loses control and the 18-wheeler flies off the edge of the bluff.

The runaway truck illustrates what happens to cells that lose the function of a gene that helps "brake," or regulate, cell division. Rather than dividing in a slow, orderly fashion, these cells begin to divide faster and faster, eventually racing out of control.

What happens next? Cancer. This deadly proliferation of abnormal cells eventually afflicts about one in three Americans, according to the American Cancer Society.

Some cancer patients develop renegade tumors that do not respond to conventional treatment, notes Albert Deisseroth of the M.D. Anderson Cancer Center in Houston. The trouble is, oncologists can't always identify such patients.

New research suggests that a well-known braking gene, the retinoblastoma (RB) gene, plays a role in bladder cancer and a type of leukemia. Scientists believe progression of the cancer is caused when the gene's normal growth-regulating function is impaired or stopped. If confirmed, this finding might help researchers create a clinical test that would identify patients with very aggressive leukemia, bladder cancer and perhaps other malignancies as well. Armed with this information, oncologists could then provide such patients with the most powerful anticancer therapies available. "Now we have a marker [for these renegade tumors]," Deisseroth says.

The retinoblastoma gene is known to cause a ruthless eye cancer in children (SN: 1/5/85, p.10). Oncologists began to notice that some survivors of this cancer went on to suffer unrelated cancers, such as bone and bladder cancers, later in life. This observation raised the possibility that problems with the RB gene might help explain some cancers that strike the general population. Indeed, subsequent research showed a link between the RB gene and a number of common adult cancers, including lung, breast, prostate, bladder and bone cancer.

These intriguing findings led Deisseroth and William F. Benedict at the Baylor College of Medicine Center for Biotechnology in The Woodlands, Texas, to take a look at leukemia. People with leukemia, a cancer of certain white cells in the bloodstream and bone marrow, often experience fatigue and weight loss. The American Cancer Society estimates that the disease will strike 28,200 Americans in 1992 and kill 18,200.

The Baylor-M.D. Anderson team focused on 43 men and women with acute myelogenous leukemia (AML), a particularly severe form of leukemia. Rather than test for the retinoblastoma gene directly, the researchers looked for the telltale protein that cells produce when the gene is turned on. Scientists believe the RB protein is somehow involved in regulating cell growth.

The investigators discovered that 13 of the 43 patients (30 percent) showed either abnormally low or no detectable levels of RB protein in their leukemic white blood cells. This suggests that problems with the RB gene are common for people with AML.

More important, when the researchers homed in on a subgroup of 20 newly diagnosed AML patients, they discovered that the RB test accurately predicted the course and severity of their disease.

All 20 received the same regimen of anticancer drugs, yet some lived much longer than others.

For example, those whose blood cells showed little or no sign of the RB protein survived approximately 39 days from the time of diagnosis; patients whose cells contained high concentrations of RB protein lived an average of 333 days.

AML patients with lots of RB protein still had a fighting chance against the disease, speculates study coauthor Steven M. Kornblau of M.D. Anderson. The test showed that they still had functional RB genes helping cells crank out the growth-regulating protein.

The RB test may one day flag leukemia patients who will soon take a turn for the worse, suggests Benedict. He described the new findings on March 31 at the American Cancer Society's science writers' seminar, held in St. Petersburg, Fla. The study will appear in an upcoming issue of CANCER RESEARCH.

The healthy human body relies on cell division to replace aging or dead cells. Cancer strikes when this normal, restorative process runs amok.

How does it happen?

Molecular biologists believe the process starts when radiation, a virus or a chemical carcinogen damages the cell. That injury may activate a gene, a sequence of DNA that tells the cell to manufacture a specific protein. Cancer-causing genes, called oncogenes, can be involved at the genesis of a tumor. For example, the *ras* gene, when activated, may help cause colon and rectal cancer (see sidebar). The RB gene, on the other hand, causes trouble when it is shut off. In adult cancers, the impairment of this gene may trigger the molecular events that cause an existing tumor to turn nasty, a process that eventually leads to metastasis – the spread of tiny cancer cells to distant parts of the body.

Benedict believes another gene is responsible for setting off the process that causes leukemia. Later in the disease, something happens to inactivate the RB gene, he suggests.

Data from other studies provide some support for Benedict's hypothesis. One investigation, involving people with bladder cancer, suggests that the RB gene is involved in the progression of that disease.

Pathologist Carlos Cordon-Cardo of the Memorial Sloan-Kettering Cancer Center in New York City wanted to find a marker of a tumor's behavior. His team turned to the RB gene and its protein product.

They searched for the retinoblastoma protein in frozen tumor samples obtained from men and women who were diagnosed with bladder cancer at some time during the past 10 years. The samples from 13 of the 38 patients with invasive cancer (cancer that had spread from the lining of the bladder to the surrounding muscle) had little or none of this crucial protein. All 38 had died of the disease.

When the researchers went back to check these patients' medical records, they found that the 13 people with little or no RB protein fared worst. Those 13 survived only about a year after the biopsies were obtained, whereas the 25 people who had high levels of RB protein lived about eight years after diagnosis.

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noblastoma alteration associates with tumors that are more aggressive in nature," Cordon-Cardo told SCIENCE NEWS. His team's results have not yet been published.

Cordon-Cardo believes the RB gene is involved in a turning point – when bladder cancer changes from a relatively benign disease to one that spreads wildly and aggressively.

Another study, this one led by Benedict and Christopher Logothetis of the M.D. Anderson Cancer Center, adds weight to that belief. Logothetis and Benedict studied 43 men and women with bladder cancer who had been treated with surgery and cell-killing chemotherapeutic drugs. The researchers won't release the details of the study, which has not yet been published; however, Logothetis says that 37 percent of the patients showed altered RB functioning, as measured by the protein test. Those same individuals tended to deteriorate more quickly than people who showed high levels of RB protein in their tumor cells, he says.

Furthermore, the retinoblastoma test appeared as helpful as other indicators currently used to gauge disease severity, Logothetis says. Right now, pathologists look at a sliced section of tissue under the microscope to assess the tumor's aggressiveness. But that method is subject to error, notes Cordon-Cardo. He and others working with the RB protein test hope that it will provide oncologists with a more definitive marker of a rowdy tumor.

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> — Cordon-Cardo

Are tumors that lack the RB protein a nastier breed than tumors that retain this braking factor? If scientists can prove they are, oncologists could begin to use the protein test to guide their treatment strategies. For example, about 20 percent of early-stage bladder cancer patients show no sign that they will deteriorate quickly, yet many die within a year, Logothetis says. At present, oncologists have no foolproof way of identifying these high-risk cases.

If the RB marker works, oncologists could spot patients who need more aggressive therapy. In some early-stage bladder cancers, doctors remove the tumors but leave the bladder intact – an approach that works well for patients who have a slow-growing cancer. However, for patients on the verge of invasive disease, doctors could recommend removal of the entire bladder as well as chemotherapy to push back the attacking cancer, Logothetis says.

Similarly, says Kornblau, the RB test may identify people with leukemia who require all-out treatment to rout their cancer. Most patients with acute myelogenous leukemia initially receive anticancer drugs. Those who suffer a recurrence go on to receive a bone marrow transplant.

"One of the problems with AML is that you don't know when to do a bone marrow transplant," Kornblau says. Because the high-risk patient may die before transplantation is considered, the RB test would be particularly useful in determining who needs such intensive treatment

Genetic clues to colorectal tumors

Imagine a truck rumbling downhill with a stuck accelerator. The truck flies off the cliff. This time a diagnosis of the problem would focus on the accelerator, not the brakes.

Whereas the RB gene speeds cancer's progress when shut off, the *ras* gene causes trouble when a mutation turns it on. Like a racing accelerator, the activated *ras* gene tells the cell to keep on truckin'.

Scientists believe a mutation in this gene is involved in the very early stages of colon and rectal cancer, which will kill an estimated 58,300 people in the United States this year, according to the American Cancer Society. If diagnosed early, most people with colorectal cancer can expect to live at least five years. However, the disease can remain hidden, producing only mild symptoms such as a change in bowel habits.

Doctors searching for signs of this potentially lethal disease must rely on a test that detects blood in stool samples. The stool test is an inexact method that can miss some colorectal cancers while flagging certain noncancerous conditions such as hemorrhoids.

Now, researchers have developed a test that detects mutations in the *ras* gene and may one day help identify healthy people at risk of developing colorectal cancer.

In the April 3 SCIENCE, David Sidransky of Johns Hopkins University in Baltimore and his colleagues describe a stool test that detects mutations in the *ras* gene.

In theory, the notion of looking for the wayward gene sounds simple enough. In practice, however, the process is a little like looking for the proverbial needle in a haystack.

Stool is a mixture of undigested food, mucus and by-products of the digestive process. "We were trying to isolate cells that had sloughed off the human colon, which are only a small percentage of that mess," Sidransky says. The investigators had to find not just healthy colon cells but also cells from the tumor itself, a task that required a powerful molecular probe. The team turned to polymerase chain reaction (PCR), a technique that can identify trace amounts of genetic material.

To begin their experiment, they focused on 24 men and women who had either a malignant tumor or a polyp, a wart-like growth. Using PCR to analyze tumor tissue and polyps, the researchers found that nine of the 24 people had a mutation in the *ras* gene.

Then came the crucial part of the experiment. The scientists used PCR to test stool samples from the nine people with known mutations. They found that PCR identified the problem *ras* gene in eight of the nine cases, including two people who had only benign polyps.

The Hopkins scientists believe their method may one day provide physicians with a reliable way of screening stool samples for the earliest signs of colon and rectal trouble, perhaps even before a benign tumor or polyp turns malignant. If oncologists can find very tiny tumors, the chances of curing a patient with surgery are much better, Sidransky says.

For now, however, the technique remains experimental. Further testing with larger groups of people is needed to determine whether such an approach can accurately detect tiny tumors and polyps likely to become malignant. This particular method looks for mutations in the *ras* gene, which appears in less than 50 percent of all colorectal cancers.

What about people who lack this mutation? The team hopes to develop a screening method that would also spot other common genetic mutations that can lead to colon or rectal cancer. Sidransky believes such a test will reach the market in about five years.

– K.A. Fackelmann

at the time of diagnosis, he says.

The link between the retinoblastoma gene and leukemia remains tentative, and preliminary results need confirmation before doctors can make use of the findings, cautions Benedict. On the other hand, many researchers have evidence suggesting that the RB test can predict the course of bladder cancer. Benedict believes a test for aggressive bladder cancer will be available within the year.

Researchers still don't understand why the RB gene sometimes malfunctions. Has a toxic chemical or some other factor caused the gene to mutate, shutting off cellular production of the RB protein? Or does some other gene control the functioning of the RB gene?

If future studies implicate a mutation in the RB gene, researchers might turn to gene therapy in their search for cancer cures. Genetic engineers would have to devise a method of inserting a healthy RB gene into malignant cells. Once activated, the healthy RB gene would instruct the cells to crank out the growth-regulating protein, curbing cancer's spread, Deisseroth speculates.

"But that's in the future," Deisseroth cautions. Like truck mechanics struggling to fix a faulty brake system, researchers must first identify the molecular mechanisms underlying the cancer. "We have to find out what's wrong," he says, "before we can start to think about how to fix it." □