CAG spells out course of prostate cancers

From a boy's first whiskers to the first sparse hair follicles on his chest, hormones known as androgens spur the development of sexual characteristics that signal approaching manhood. Decades later, these hormones may fuel the growth of prostate cancer.

Researchers are beginning to understand why. A new study demonstrates that a peculiar pattern of DNA in the genes that encode androgen receptors may govern whether a man's cancer turns deadly or stays relatively benign.

The pattern is a short, repetitive DNA sequence, a so-called CAG repeat, named for the three DNA building blocks that form it. Investigators had previously found CAG repeats in androgen receptor genes on a man's X chromosome.

Researchers have long recognized that the interplay between androgens and their receptors on cell surfaces powerfully influences cell function. When an androgen latches onto a receptor on a prostate cell, for instance, the receptor reacts by prompting the cell to divide. If the cell is a cancer cell, replication may accelerate wildly.

In most men, prostate tumors grow almost imperceptibly, erupting into metastatic monsters in just 10 percent of cases.

Researchers have now found that men with 18 or fewer CAG repeats on their androgen receptor genes are more likely to get prostate cancer than men with stretches of 26 or more. In addition, the tumors of men with fewer repeats are more than twice as likely to turn into deadly malignancies as the tumors of men with more CAG repeats.

"This, to me, is a very fascinating thing biologically," says Philip W. Kantoff of Harvard Medical School in Boston. "As the CAG sequences get shorter and shorter, your risk of developing prostate cancer gets higher and higher. And they are a determinant of how aggressive [the cancer] will be."

Kantoff and his colleagues used blood samples collected from 1,175 men in the Physician's Health Study. About half of the men had developed prostate cancer between 1982 and 1995. The remainder served as a control group. "Men with shorter repeats were at particularly high risk for . . . metastatic and fatal prostate cancer," the scientists conclude in the April 1 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES. Kantoff also presented the results at a June 1996 meeting of the American Society for Clinical Oncology in Philadelphia.

Kantoff says that his interest in CAG repeats was sparked when researchers investigating an inherited neuromuscular disorder, Kennedy's syndrome, discovered the repeats in a coding region of the androgen receptor gene. "It's unusual to see DNA repeats in coding regions," he says.

Further study showed that men with Kennedy's syndrome had an unusually large number of CAG repeats, which seemed to render the men slightly less sensitive to the masculinizing effects of androgens. Investigators found they could increase the receptors' sensitivity to androgens in the laboratory by knocking out some repeats.

Two years ago, Kantoff and his colleagues began wondering whether CAG repeats played a role in prostate cancer, which is diagnosed in more than 300,000 men each year. "It's an obvious question, since these receptors modulate androgen function and androgen has something to do with prostate cancer development."

Earlier studies had shown that prostate tumors shrink temporarily if their androgen supply is cut off and that lower concentrations of the hormone reduce the likelihood of prostate cancer.

Last year, in a study of 104 prostate cancer patients, researchers at Memorial Sloan-Kettering Cancer Center in New York found that men with fewer CAG repeats were likely to get cancer at a younger age. "These data suggest that CAG repeat length can affect the risk of developing prostate cancer," the team concluded, cautioning that their findings were tentative.

Howard I. Scher, an author of that study, called Kantoff's report "very nice work" and added, "you can almost look at [CAG repeats] as the throttle or the accelerator. You know the gene to be active. CAG repeats determine how active." Other regulatory factors probably play a role as well, Scher says.

Several major questions remain. For instance, black men—who have fewer CAG repeats on average than white men—are also more prone to prostate cancer, but no one knows yet whether the two factors are related. Kantoff's team could not examine this issue because only 5 percent of the participants in the study were black. He and other colleagues plan to design a study that will permit a closer look. —*S. Sternberg*

Ink jets not just for the printed page

Desktop publishing is graduating quickly to the next level—desktop manufacturing. Using the technology of ink jet printers, researchers have devised a way to make pills by printing them in three dimensions. In this way, scientists can design and manufacture pills much as engineers create machine parts.

Instead of placing drops of ink on a piece of paper, the 3-D printer builds up a pill by repeatedly layering small amounts of powder and liquid binder on top of each other. "We use the same materials they use in normal drug manufacturing, except we put them together in a different way," says Michael J. Cima of the Massachusetts Institute of Technology.

Cima described the 3-D technique this week at a meeting of the Materials Research Society in San Francisco.

In a desktop printer, droplets of ink emerge from a tiny nozzle and are given an electric charge. Electrodes steer the ink drops to precisely controlled locations, forming letters at high resolution. Similarly, the 3-D printer lays down the pill's ingredients to create a microstructure inside the finished tablet. For example, tiny chambers inside the pill can be filled with one or more drugs in different concentrations.

Pills made in this way can carry very small doses of exceptionally potent drugs. "With this kind of technology, we can accurately deposit one 60 [micrometer-size] droplet in each pill, so the dosage control is much better than what you can get with conventional processing," Cima says.

Custom-designed pills also provide new ways to time the release of drugs after ingestion. For example, a printed antihistamine tablet made by Therics of Princeton, N.J., contains two binders that dissolve at different rates. This allows the tablet to release some of the drug right away for immediate relief and a second dose later. MIT is collaborating with Therics to refine the technology.

Pills could be designed to deliver a wide variety of drugs, says Mark G. Scher, Therics' vice president for business development. The company has tested the tablets in the laboratory and plans trials in animals later this year.

The process is a spin-off of technology being developed to make prototype machine components in polymer, ceramic, and metal. Instead of using costly and time-consuming molding techniques, researchers can print a 3-D sample part in a few days, or even a few minutes.

"It saves a lot of time at the front end of manufacturing," says Harris L. Marcus of the University of Connecticut in Storrs. The 3-D technique is best for making prototypes and small batches of components, he says, although it could be used for making the molds used in mass production.

Cima disagrees, saying that researchers must start viewing 3-D printing not just as a way to make prototypes but as a method of manufacturing large numbers of objects. Printers with thousands of nozzles could manufacture 100 million pills a year, assembly-line-style, he says. —*C. Wu*