Gene copying aids prostate tumor growth

Even severe prostate tumors usually shrink after an initial treatment with drugs. Yet many of these cancers advance again, resisting all attempts to rein them in.

Until now, nobody knew why. But a report published this month suggests that some prostate tumors may outwit therapy by generating extra copies of a gene that promotes cell growth. Recurrence of tumors greatly increases the risk of dying.

The prostate gland, the walnut-size male sex gland located below the bladder, produces some of the fluid that goes into semen. The American Cancer Society estimates that more than 40,000 men in the United States will die of prostate cancer this year.

For men with advanced prostate cancer, doctors recommend drugs or surgical removal of the testes to stanch the flow of androgens, the male sex hormones, including testosterone, that fuel the growth of malignant prostate cells.

That strategy can work for months or even years. But if the cancer springs back, it does so despite hormone-blocking therapy.

Tapio Visakorpi of the National Center for Human Genome Research in Bethesda, Md., and a team of U.S. and Finnish colleagues wanted to find out how that deadly resistance works.

They started their experiment by analyzing 23 recurrent prostate tumors taken from men who had been treated with hormone-blocking therapy. The research team discovered that 7 of 23 tumors (30 percent) had extra copies of a gene known as the androgen receptor gene. This gene codes for a protein receptor that interacts with androgens and somehow tells prostate cells to divide.

On average, tumor cells in the study contained from 4 to 22 androgen receptor genes. In one case, a tumor cell had 40 receptor genes. Healthy prostate cells contain only one such gene, which resides on the X chromosome.

The gene copying appears to take place as a result of treatment: When the team looked at 16 prostate tumor samples taken from the same patients prior to therapy, they found no such gene amplification. Visakorpi and his coworkers describe their findings in the April NATURE GENETICS.

The findings indicate that some prostate tumors may adapt to, or even thrive in, the environment created by hormone-blocking therapy. Such treatment curbs the body's supply of androgens by targeting the testes' production of these hormones. The adrenal glands still secrete a small amount, however.

In response to the decreased androgen production, tumor cells multiply the androgen receptor gene. Such malignant cells probably crank out lots of the gene's protein product and thus can efficiently make use of even low concentrations of androgen, Visakorpi speculates.

"I think it's an exciting result," comments oncologist Rosalind Eeles of the Institute of Cancer Research & Royal Marsden Hospital in London, England. If confirmed by other studies, the findings suggest new treatment avenues for men who have recurrent prostate tumors. At present, doctors give such patients standard doses of hormone-blocking therapy, says Eeles. But the new study suggests that oncologists should increase the dose — if it can be done safely — thus creating a more effective androgen blockade, she says.

The findings may also lead to better treatment for men with newly diagnosed prostate cancer, Visakorpi says. If researchers could identify those tumors most likely to copy the androgen receptor gene, oncologists might start off with a therapy aimed at complete blockage of androgen.

That drastic approach just might stop prostate cancer in its tracks, he adds.

— K. Fackelmann

World War II vets: Physical backlash

World War II combat veterans who grew up in privileged households and attended an elite university developed relatively few symptoms of post-traumatic stress disorder (PTSD), a debilitating stress reaction observed in a substantial minority of Vietnam vets, according to a 50-year study.

However, veterans from the same group who survived heavy fighting in World War II developed more chronic physical illnesses and died sooner than those who experienced little or no combat, report George E. Vaillant, a psychiatrist at Brigham and Women's Hospital in Boston, and his coworkers.

Even though the incidence of PTSD in this group is relatively low, the data "confirm that severity of trauma is the best predictor of who is likely to develop PTSD," the scientists conclude in the April AMERICAN JOURNAL OF PSYCHIATRY. Moreover, the study suggests that PTSD symptoms do not necessarily prove incapacitating.

Vaillant's group drew on physical and psychological data gathered between 1939 and 1944 from 249 male sophomores at Harvard University. Of that number, 152 served abroad for at least 1 month and completed further testing shortly after their return; six men died in World War II. These 152 veterans completed questionnaires every 2 years thereafter. A final questionnaire and a physical examination were administered in 1988 to 107 of the surviving participants.

This study has the advantage of tracking men throughout much of their lives, beginning before combat exposure. It also largely excludes several predispositions for PTSD, such as poverty, poor education, low military rank, and long-standing behavior problems. These influences have clouded the exact role of combat on Vietnam-era cases of PTSD, the researchers hold.

PTSD symptoms include recurring memories of and nightmares about combat, sleep difficulties, overreactions to sudden noises or other startling events, and a numbing of emotions.

Upon returning to civilian life in 1946, 17 of the 152 veterans — 12 of them survivors of heavy combat — reported two or more PTSD symptoms. Only 1 of the 17 suffered from full-blown PTSD, as defined in 1988; another four nearly qualified for PTSD.

Of those five veterans, two eventually killed themselves, one was murdered, one still suffered from PTSD symptoms in 1988, and one refused to participate in the follow-up.

In 1988, a total of eight veterans, including five who survived heavy combat in World War II, reported one or more PTSD symptoms. These eight had reported no marked signs of anxiety or emotional disorder as undergraduates, the investigators say. Students scoring high on a measure of psychological distress tended to cite comparable distress at age 65, regardless of combat exposure.

Still, intense fighting exacted a physical toll on World War II veterans. Thirty of 54 heavy-combat survivors — including 16 of 27 who faced heavy combat and cited one or more PTSD symptoms in 1946 — developed a chronic physical illness or died by age 65. A much lower rate of disease and death occurred in the remaining vets.

Stable family backgrounds may have prepared vets in this sample to master wartime traumas, suggests John C. Nemiah, a psychiatrist at Dartmouth Medical School in Hanover, N.H., in an accompanying editorial.

Extroverted, athletic men were more likely to engage in heavy combat, Nemiah notes. These individuals may be less inclined to reflect on trauma-related emotions and more apt to suffer damaging physiological stress responses, he theorizes.

— B. Bower