



Anti-Androgens Can Trigger Prostate Cancer Growth

The drugs commonly given to help men beat prostate cancer may actually help the cancer grow under some conditions, a University of Rochester Cancer Center team shows in a study published in the June 23 issue of the *Proceedings of the National Academy of Sciences*.

The work provides a possible explanation for why most forms of hormone therapy, a common treatment for prostate cancer, almost always lose effectiveness after one or two years.

The team showed that drugs known as anti-androgens, often given to men to shrink the prostate and kill the cancerous cells within, can trigger the protein that makes the prostate and its cancer grow.

"It's a real shocker, and it's still quite controversial, but our experiments show that this happens," says Chawnsiang Chang, lead investigator and George Whipple Professor of Pathology and Urology. "These compounds are capable of stimulating what they're supposed to be preventing."

He stresses, though, that much more research is needed to confirm the results, and that it's too early to consider altering the standard treatment patients receive today.

The prostate is a peach-sized organ between the bladder and rectum that contributes fluids to semen. Prostate cancer, which strikes slightly more often in men than breast cancer does in women, kills about 39,000 men in the U.S. each year.

The growth of the prostate and cancerous cells there rely on the androgen receptor, the protein turned on by testosterone and other "male" hormones, known as androgens. The receptor triggers genes that give men facial hair, deep voices and other masculine traits, including prostate growth.

In women, estrogen hormones are responsible for developing female characteristics. While both are present in everyone's bodies, scientists have long thought that the two groups of hormones turn on very distinct sets of genes.

For several decades physicians have treated men with advanced prostate cancer with castration therapy, anti-androgens, or estrogen-like compounds to shrink the prostate. But within a couple of years the treatments lose effectiveness and the prostate starts growing again, mysteriously.

Since the therapy usually comes after doctors have tried other treatment options, such as surgery, brachytherapy, or radiation, its failure often marks a turning point in the spread of the disease.

In the PNAS paper Chang and colleagues show that anti-androgenic compounds can cross the line and turn on the androgen receptor. Working with human prostate cells in a cell culture, the scientists showed that anti-androgens, including hydroxyflutamide, bicalutamide (casodex), and cyproterone acetate, can trigger the androgen receptor, which in turn spurs the growth of the prostate and its cancerous cells.

In another PNAS paper last month the team showed that estrogen can also turn on the androgen system and even seems to play a critical role in the formation of the male reproductive system.

In partial-androgen-insensitivity syndrome, a person has both an X and a Y chromosome and is genetically a man, but because of a single mutation in the androgen receptor the person has severe genital abnormalities and lives as a woman. A few thousand people in the U.S. have the disease. The team showed that the mutation contributes to the syndrome by knocking out estrogen's ability to turn on the androgen receptor.

Chang, a well-known expert on the androgen receptor, was the first to clone the protein back in 1988. Last month he showed that another molecule must be present for estrogen to turn on the receptor. That molecule, known as co-factor AR70, offers a new target against prostate cancer, Chang says. AR70 is one of several androgen receptor co-factors that the team has identified as working with other molecules to turn on the androgen receptor.

"The goal is to develop a tissue-specific anti-androgenic compound," says Chang, "so that we can turn on or off the androgen system selectively. For instance, perhaps we can stimulate hair growth but not damage the reproductive system. Identifying these co-factors is a step toward such specificity."

Also working on the project, which was funded by the National Institutes of Health, were postdoctoral researchers Hiroshi Miyamoto and Shuyuan Yeh of the University, and medical oncologist George Wilding of the University of Wisconsin. - [Tom Rickey](#)

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UR scientist finds cancer mystery clue

■ He suspects that a drug therapy may accelerate the course of prostate disease.

BY STAFF WRITER

CORYDON IRELAND

A common drug therapy for prostate cancer may, in fact, make the condition



Chang 傳祥

worse, according to researchers at the University of Rochester.

"It's a real shocker," said lead investigator Chawnshang Chang, a UR professor of biochemistry, pathology and urology. "These compounds are capable of stimulating what they're supposed to be preventing."

Doctors have known for a while that drugs used to block the male hormones that aggravate prostate cancer stop working after about two years.

The UR research — which Chang admits is "controversial" — offers the first real explanation: a molecule called ARA70 that accelerates the formation of male hormones.

Future drugs, said Chang, must target not only male hormones, but enabling compounds like ARA70.

The six-page study appears in today's issue of the prestigious *Proceedings of the National Academy of Sciences*.

Chang cautioned that more research is needed, including animal and human studies.

And he said that it is too soon to change current hormone drug therapies for prostate cancer, the most common malignancy affecting

American men. The disease afflicts 200,000 men a year and kills another 39,000.

The prostate is a muscular, walnut-size organ seated between the rectum and the bladder.

It contributes fluid to semen and is a high-risk cancer site for men over 50.

In a few years, the Rochester work could lead to a new generation of hormone-based drugs for treating the disease.

"As a scientist, I'm never sure when," said a cautious Chang, who has studied the biochemistry of prostate cancer for 18 years.

But negotiations with an undisclosed drug company for more research are already under way, he added.

Current prostate cancer treatments include surgery, radiation and — in its last stages — "antiandrogens."

These drugs block male hormones that prompt facial hair, deepen voices — and in prostate cancer, speed up the production of cancer cells.

Using cell cultures from both cancerous prostate tissue and yeast, the UR team showed that some commonly prescribed antiandrogens can trigger the protein that makes the prostate — and its cancer — active again.

Last month, another study by Chang reported that estrogen, a female hormone, sometimes mimics androgen, the primary male hormone.

That might explain why prostate cancer cells may continue to thrive, even when androgen is blocked by drugs. □

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Los Angeles Times

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Therapy May Spur Prostate Cancer, Study Finds

■ Artificial hormones can begin mimicking the ones they are supposed to stop, researchers say. However, treatment is effective for a few years at least, they add.

By SARAH YANG
TIMES STAFF WRITER

Hormones commonly used to treat advanced stages of prostate cancer can eventually help the cancer grow, offering the first explanation of why hormone therapy almost always fails after two to three years, according to a study published this week in the Proceedings of the National Academy of Sciences.

Researchers at the University of Rochester Cancer Center found that the drugs used to block the supply of androgens—natural steroid hormones such as testosterone that signal prostate cancer cells to grow and multiply—can actually begin mimicking the very hormones they are supposed to stop.

The switch, observed in lab-grown prostate tumors,

occurs when a protein molecule in the prostate cancer cells, called ARA70, binds with an androgen receptor, said lead investigator Chawnsang Chang, a professor of pathology and urology at the University of Rochester. This interaction somehow induces the anti-androgen drugs to stimulate the hormone receptors rather than block them.

“Once these two proteins interact, the anti-androgens start behaving like androgens,” Chang said.

Testosterone makes up 98% of androgens feeding the cells. Intervention typically involves surgical or medical castration, the latter using chemicals to prevent the body from making testosterone.

Anti-androgen drugs such as bicalutamide and flutamide, also known by their respective brand names Casodex and Eulexin, are then used to block the remaining androgens produced by the adrenal glands that lie on top of the kidneys.

One of the mysteries that has long puzzled clinicians is why androgen levels and cancer tumors, after years of shrinking with anti-androgen drugs, suddenly start growing again. Dr. Arie Belldegrun, professor of urology and chief of the division of urologic oncology at the UCLA Jonsson Cancer Center, said the study

helps explain this mystery. He also said the findings could be used to help develop more effective drugs.

“Once you know that this molecule is the problem, you can design blockers that block ARA70,” he said. “You can focus on something more specific.”

Prostate cancer is the leading form of cancer among men in the United States. Every year, nearly 40,000 die from prostate cancer, making it the No. 2 cause of cancer death in the nation. Hormone therapy is one of the last lines of defense for prostate cancer patients, used only when the disease has spread to other parts of the body.

“At least a third of all patients, maybe even half, diagnosed every year will get this therapy,” said Belldegrun.

Chang cautions that prostate cancer patients should not stop hormone therapy because the findings are limited to cell cultures in the laboratory and tests on animals or humans are still to come. He adds that there is still “no better method” available for treating the advanced stages of prostate cancer, and that it is at least effective for the first few years of treatment.