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Hair on a man's head offers clues about prostate cancer

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Some of the drugs given to many men during their fight against prostate cancer can actually spur some cancer cells to grow, researchers have found. The findings were published online this week in a pair of papers in the *Proceedings of the National Academy of Sciences*.

The results may help explain a phenomenon that has bedeviled patients for decades. Hormone therapy, a common treatment for men with advanced prostate cancer, generally keeps the cancer at bay for a year or two. But then, for reasons scientists have never understood, the treatment fails in patients whose disease has spread – the cancer begins to grow again, at a time when patients have few treatment options left.

The new findings by a team led by Chawnshang Chang, Ph.D., director of the George Whipple Laboratory for Cancer Research at the University of Rochester Medical Center, help explain the process by showing that the androgen receptor, through which male hormones like testosterone work, is much more versatile than previously thought. Under certain conditions the molecule spurs growth, and at other times the molecule squelches growth – just like the same molecule does to hair in different locations on a man's head.

The new findings raise the possibility that under some conditions, some treatments designed to treat prostate cancer could instead remove one of the body's natural brakes on the spread of the disease in the body. The researchers stress that the results are based on laboratory studies and on findings in mice, and it's too soon to know yet whether the findings

apply directly to prostate cancer in men.

Understanding the effects of the androgen receptor gives physicians a toehold in efforts to develop more effective treatments for men with prostate cancer. That would be welcome news for the one of every six men who will get the disease during his lifetime. More than 28,000 men die from the disease in the United States each year, according to the American Cancer Society. Men's risk from prostate cancer is about equal to women's risk from breast cancer: Each year, about the same number of men get prostate cancer as women get breast cancer, and their risk of dying from the diseases is about equal, according to ACS.

Chang's findings are most relevant for patients with advanced prostate cancer, who typically receive hormone therapy after other treatments such as surgery or radiation. With hormone therapy, physicians blunt the effects of male hormones like testosterone to bring the disease in the prostate to a halt. One form of hormone therapy works by blocking the androgen receptor. Androgen deprivation therapy is generally very effective for a year or two, but for reasons that no one has understood, the cancer ultimately returns.

"When a man receives hormone therapy, initially the treatment works well, and his PSA (prostate specific antigen) level goes down," said Edward Messing, M.D., a urologist and an author of the paper. "But inevitably, the PSA will start climbing again, and that is usually the first sign that the treatment is beginning to fail. It's a sign that the cancer in the prostate is making a comeback."

In work funded by the National Cancer Institute, Chang's team found that blocking the receptor indeed prevents some cells in the prostate from growing, just as scientists expected. But Chang's team unexpectedly found that blocking the receptor actually spurs other prostate cells to grow.

"The androgen receptor acts differently in different cells in prostate tissue," said Chang. "It's always been assumed that blocking the androgen receptor will stop all prostate cells from growing, but we have found that that's not the case. Since current treatment acts non-specifically on all the cells having androgen receptors in the prostate, blocking the androgen receptor will give mixed results."

The team found that, as expected, the androgen receptor in prostate support cells known as stromal cells stimulates growth of cells, including cancer cells, in the prostate. He also found, surprisingly, that the receptor actually acts as a tumor suppressor in epithelial cells known as basal cells in the prostate.

Then Chang's team knocked out the androgen receptor in specific sets of prostate cells and studied the results. As expected, when the molecule is turned off in stromal cells, growth of cancer cells in the prostate slows. But when the molecule is turned off in the epithelial cells, it removes one of the body's natural inhibitors that prevents prostate cancer cells from spreading, making cells more likely to invade other tissues.

"While the androgen receptor is really driving prostate cancer, in another sense it appears that the receptor also normally inhibits the spread of cancer cells. It seems to have a dual role. Manipulating the androgen receptor can increase or decrease either of these actions depending on precisely how it's done," said Messing.

Chang says the molecule's versatility in the prostate should not come as a surprise, since the molecule's function elsewhere depends on its location.

"The effects of the androgen receptor on hair growth in men vary dramatically depending on where in the body the receptor is working," said Chang. "When the receptor is very active in the mustache area, more hair grows. When it's very active on the top of the skull, toward the

front, hair falls out and men become bald. And the hair on the back of the head is insensitive to the receptor. The effects of hormones depend on the location.

"We found that the same is true within the cells of the prostate itself," said Chang, who is a faculty member in the departments of Urology and Pathology and the James P. Wilmot Cancer Center.

Chang says it's likely that the androgen receptor works differently in different cells partly because the assortment of molecular colleagues it works with within the body changes from situation to situation. Like a foreman turning to a pool of employees to get certain jobs done, the androgen receptor taps different molecules in different situations, forming intricate complexes or groupings that then accomplish various tasks. The receptor works very quickly, assembling a team within seconds, accomplishing a task, then disbanding and making its helpers available to form a brand new team for another task.

Chang's team is working on ways to focus on these molecular "co-factors" as a way to target the androgen receptor differently in different cells, for instance, turning off the receptor in some cells while keeping it on in others, to fight prostate cancer. That type of cell-specific targeting is currently not possible.

The research in the laboratory involved tracking the disease in mice and also analyzing human prostate cancer cells in culture. Nevertheless, the work might include some hints for improving patient care. Possibilities include studying whether androgen suppression therapy might be used to target only specific cells within the prostate, as well as checking whether drugs designed to prevent cancer from spreading should be used in concert with hormone therapy.

Source: University of Rochester Medical Center