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# Scientists find one reason why bladder cancer hits more men

Scientists have discovered one of the reasons why bladder cancer is so much more prevalent in men than women: A molecular receptor or protein that is much more active in men than women plays a role in the development of the disease. The finding could open the door to new types of treatment with the disease.

In an article in the April 4 issue of the Journal of the National Cancer Institute, Chawnshang Chang, Ph.D., of the University of Rochester Medical Center and colleagues show that the androgen receptor, which is central to the action of testosterone and other hormones that are much more plentiful in men than women, appears to play a key role in the disease.

In experiments reported in the journal, mice without the receptor had dramatically lower rates of bladder cancer compared to normal mice with the receptor, and human cancer cells with the receptor were much more aggressive than those without it. Mice develop bladder cancer for many of the same reasons people do, and the molecular signals that control cancer development in mice mirror those in humans.

The disease hits about three times as many men as women, including estimates of 50,000 men and 17,000 women in the United States in 2007, according to the American Cancer Society. Some scientists have suspected that male hormones working in concert with the androgen receptor might play a role, but hard evidence has been minimal until now, said Edward Messing, M.D., a bladder cancer expert and chair of Urology. Instead, scientists have suspected that factors like greater exposure of men to cigarettes and industrial chemicals has been responsible.

"For many years, people have recognized that men are more likely than women to get bladder cancer," said Messing, one of the authors of the paper. "More and more women are smoking and working with chemicals in the workplace, yet their bladder cancer rates have not really

changed much. There is no longer any question that the androgen receptor is playing a role in bladder cancer."

The work by a team of collaborators from Rochester and from Yokohama City University Graduate School of Medicine in Japan was led by Chang, director of the George Whipple Laboratory for Cancer Research at the University of Rochester Medical Center and a faculty member in the departments of Urology and Pathology and the James P. Wilmot Cancer Center.

Chang is an expert on the androgen receptor, which is central to many diseases and conditions, most notably prostate cancer. For that disease, hormone therapy to block the supply of hormones that turn on the receptor is a staple of treatment for men with advanced disease. The new findings open the possibility that perhaps someday, drugs that target male hormones, like those used against prostate cancer, might help men with bladder cancer.

The strongest evidence for the involvement of male hormones in bladder cancer was what happened when Chang's team disabled the androgen receptor in mice. While their normal counterparts with the androgen receptor got significant levels of bladder cancer when exposed to a carcinogen ‚92 percent of the males and 42 percent of the females ‚not a single mouse whose androgen receptor was knocked out developed bladder cancer. The mice without the receptor also had significantly fewer premalignant changes in their bladder.

Besides opening the door to possible new treatments, Chang says the findings could help doctors decide which cases of bladder cancer are most likely to re-occur. His team found a correlation between the frequency of the androgen receptor in tumor cells and the recurrence of the tumor ‚tumors more likely to re-appear had more of the protein. If the finding holds up in wider testing in human tumors, it would help doctors know which patients to treat aggressively right from the start.

The JNCI paper is the latest installment in a body of research Chang has compiled that shows that the story of the androgen receptor and male hormones like testosterone is much more complex than was once thought. For years it's been widely thought by doctors and scientists that all male hormones, and only male hormones, work through the androgen receptor.

But he felt there was more to the story. If anyone would know, it would be Chang, who in 1988 was the first person to clone the androgen receptor, and was the first to discover that the protein needs molecular allies called co-factors to accomplish many of its tasks. Now more than 80 co-factors are known, offering many new targets to stop conditions like male-pattern baldness and diseases like prostate cancer.

Nearly a decade ago, Chang showed that molecules other than male hormones like testosterone are able to activate the androgen receptor. That finding isn't simply gathering dust in textbooks; it likely explains why hormone therapy for men in the advanced stages of prostate cancer ultimately fails. His work explained a long-baffling phenomenon in these patients, where drugs that work well for a few years suddenly make the cancer grow again late in the course of the disease.

In the recent paper, Chang continued this line of work, only in bladder cancer instead of prostate cancer. He took a closer look at the nearly disease-free male mice that didn't get bladder cancer despite exposure to a carcinogen. Some of those mice then received a drug known as DHT, a male hormone. In theory, such a drug only works if the androgen receptor is present, so the drug should not have had an effect. But 25 percent of these mice then got bladder cancer, clear evidence that the hormone is able to somehow side-step the traditional, receptor-mediated, pathway and still have an effect.

The work shows starkly that simply cutting off the supply of hormones like testosterone will have only a limited effect. The androgen receptor can still play a crucial role in the development of cancer, even without the hormones. The team has shown in other studies that even female hormones such as estrogen can turn on the androgen receptor.

"The activity of the androgen receptor is different from the activity of hormones that target the receptor," said Chang. "We've shown very clearly that even without these hormones, the receptor is still active in the development of cancer. This is crucial information as doctors seek to develop treatments for diseases like prostate or bladder cancer in men."

To knock out the androgen receptor, the team used a compound known as ASC-J9, a synthetic chemical compound that is loosely based on a compound found in curcumin. Chang's laboratory, in collaboration with San Diego-based AndroScience Corp., has screened hundreds of compounds for their activity involving the androgen receptor. Just last month, the team showed that ASC-J9 offers promise against a rare neuromuscular disease known as Kennedy's disease.

The compound is now being tested as a cream to treat acne in a clinical trial run by AndroScience, a biotech company founded by Chang, Charles C-Y Shih, and Por-Hsiung Lai in 2000. The University owns a stake in the company, which has licensed several of Chang's research findings.

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The first author of the paper is Hiroshi Miyamoto, M.D., Ph.D., who was a post-doctoral researcher in Chang's laboratory and is now a medical resident in the Department of Pathology and Laboratory Medicine. Miyamoto was joined by several of his former colleagues at Yokohama City University Graduate School of Medicine in Yokohama, Japan, who did much of the work with the human bladder cancer cell lines and analyzed levels of the androgen receptors. Collaborators there include Hitoshi Ishiguro, Hiroji Uemura, Yoshinobu Kubota, and Yoji Nagashima.

Other authors of the paper, in addition to Chang and Messing, are Zhiming Yang, a former graduate student now at Zhejang University and 2nd Hospital in Hangzhou, China; Yei-Tsung Chen and Yueh-Chiang Hu, former graduate students and now researchers at Harvard; Yu-Jia Chang, formerly a post-doctoral researcher with Chang, now an assistant professor at Taipei Medical University and Hospital in Taipei, Taiwan; former graduate student Meng-Yin Tsai, now at Chang Gung Memorial Hospital in Kaohsiung, Taiwan; and Shuyuan Yeh, associate professor of Urology.