Androgen blockade therapy for men with advanced prostate cancer often yields only a temporary fix or respite, not a permanent cure. Now, researchers at Johns Hopkins have discovered critical differences in the hormone receptors on prostate cancer cells in patients who no longer respond to this therapy. The findings, reported in the Jan. 1 issue of *Cancer Research* , could lead to a way to track disease progression, as well as new targets to fight prostate cancer.

Prostate cancer cells rely on androgens, male hormones that include testosterone, to survive and grow, explains Jun Luo, Ph.D., an assistant professor at Johns Hopkins' James Buchanan Brady Urological Institute. Since 1941 , doctors have taken advantage of this dependency to battle prostate cancer by depriving patients of androgens, either by surgical castration or by means of injectible drugs or by means of estrogen. For most patients, androgen deprivation therapy causes tumors to shrink, sometimes dramatically. However, it's never a cure—unless the patient is elderly and dies of some other condition before his prostate cancer becomes hormone refractory, eventually his PSA will rise, signalling that the cancer is resurging in a stronger form, now resistant to the standby treatment.

Seeking the reason why this therapy eventually fails, Luo and his colleagues at the Johns Hopkins University School of Medicine, the University of Washington and Puget Sound VA Medical Center looked to a key player: the androgen receptors on prostate cancer cells.

Using a large database, the researchers searched for variations of the nucleic acid RNA that prostate cells use to create androgen receptors, eventually identifying seven RNA sequences different from the "normal" androgen receptor already known to scientists. When they looked for these sequences in cells isolated from 124 prostate cancer patients, they found over-production of these outlaw variants in prostate cancer cells taken from patients whose disease had become resistant to androgen deprivation therapy. One variation—known as AR-V7, was also prevalent in a select group of patients who had never taken hormone therapy, but whose cancer aggressively regrew after surgery to remove their tumors.

To see how androgen receptors made from AR-V7 differ from others, the researchers forced lab-grown prostate cancer cells to produce only the AR-V7 sequence. Unlike cells with other androgen receptors, those with only AR-V7 receptors acted as if they were continually receiving androgens—turning on at least 20 genes that rely on androgens for activation—even though no androgens were present.

The results suggest that hormone therapy might encourage prostate cancer cells to overproduce the AR-V7 receptors over time, leading them to survive and grow aggressively

even without androgens, explains Luo. In some patients, he adds, AR-V7 receptors might already be prevalent even without hormone therapy, predisposing them to an already-aggressive form of prostate cancer that won't respond as well to hormone deprivation therapy.

"We may eventually be able to develop an assay to test for this androgen receptor variant, giving us a way to test which patients are good candidates for hormone deprivation therapy and providing a way to monitor disease progression in patients already on this therapy," Luo says.

Examining the differences between AR-V7 and other androgen receptor variants may also provide researchers with new ideas to develop prostate cancer-fighting pharmaceuticals, he adds.

Other researchers who contributed to this study include Rong Hu, Thomas A. Dunn, Shuanzeng Wei, Sumit Isharwal, Robert W. Veltri, Elizabeth Humphreys, Misop Han, Alan W. Partin, William B. Isaacs and G. Steven Bova, all of the Johns Hopkins University School of Medicine; and Robert L. Vessella of the University of Washington and Puget Sound VA Medical Center.

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Although this diagram at nature.com of Androgen-receptor signaling in prostate cancer does not include the newly discovered androgen receptor types, it does show how hormone-dependent androgen signaling takes place through dihydrotestosterone stimulation of the androgen receptor and how hormone-refractory prostate cancer cells survive through stimulation of multiple signaling pathways.

Researchers Identify Molecular Cause of Drug-Resistant Prostate Cancer

December 21, 2003.