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How advanced prostate cancer becomes resistant to androgen-deprivation therapy

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For the past 70 years the treatment of choice for advanced, metastatic prostate cancer has been androgen-deprivation therapy. That is, the suppression of circulating testosterone – the hormone that fuels prostate-cancer growth – via surgical castration (orchiectomy) or medical castration with testosterone-blocking drugs. While such therapy buys time for patients, it is not a cure, as inevitably the cancer becomes resistant to the androgen deprivation and continues to grow.

A team of researchers led by Peter Nelson, M.D., and Elahe (pronounced EL-ah-hay) Mostaghel, M.D., Ph.D., of Fred Hutchinson Cancer Research Center; and R. Bruce Montgomery, M.D., and Paul Lange, M.D., of the University of Washington School of Medicine, in collaboration with other colleagues at UW and Oregon Health Sciences University, has uncovered what may be the key to understanding how prostate tumors eventually become resistant to androgen-deprivation therapy.

“We found that despite the suppression of circulating androgen levels to very low or castrate levels, metastatic prostate tumors are themselves able to maintain significant levels of testosterone, which fuels the growth of the cancer,” said Mostaghel, a clinical-research associate in Nelson’s laboratory, which is based in the Human Biology Division of the Hutchinson Center.

The researchers found that testosterone levels were four times higher in metastatic tumors from castrate men (collected immediately after death

via rapid autopsy) than in benign and cancerous prostate tissue in men with normal circulating androgen levels (collected at the time of prostate surgery).

This finding, reported in the June 1 issue of Cancer Research, could lead to the development of better drugs to treat metastatic disease – cancer that has spread beyond the prostate to distant sites throughout the body, such as bone, lymph nodes and internal organs.

“So far we’ve targeted systemic, or circulating, androgens in men with advanced prostate cancer,” Mostaghel said. “What these findings suggest is that we really need to target the metastatic prostate-tumor tissue itself as the source of tumor androgens.”

In addition to measuring androgen levels in distant tumor sites, the researchers analyzed gene-expression patterns in the metastatic tissue to confirm the presence of genetic pathways that control testosterone production. The researchers indeed found within the metastatic tissue the genetic transcripts necessary for making the proteins that produce testosterone and other androgen hormones.

“We not only found that metastatic-tumor tissues have high enough androgen levels within them to support continued growth of the tumor cells, but also a critically important reason behind why those androgens are there – the discovery that the gene pathways for synthesizing androgens from cholesterol appear to be present in the distant tumor sites. This finding will allow us to start honing in on the specific source of those androgens and how we can eliminate them,” Mostaghel said. “As we develop new drug targets, we will need to focus on enzymes that seem to be active in the tumor tissue itself. This offers a new way of looking at hormone suppression. In addition to systemic suppression, it suggests we also need to target hormone suppression much more specifically, inside the tumor itself.” Doing so could improve treatment

for patients with all stages of prostate cancer, she said, from men with metastatic disease to men with high-risk, localized tumors in which there is concern that small amounts of cancer may have escaped the prostate.

Mostaghel and colleagues feel the most promising drug targets will be inhibitors of CYP17 enzymes, which disrupt the conversion of progesterone to testosterone precursors, as well as inhibitors of enzymes that perform subsequent steps in testosterone production: AKR1C3 and 17BHSD3.

For the study, the researchers examined soft-tissue prostate-cancer metastases obtained from eight medically or surgically castrated men via the University of Washington rapid-autopsy program, one of a handful of such programs in the nation. For control purposes, the researchers also examined benign and cancerous prostate tissue from eight men who underwent radical prostatectomy for early-stage, localized prostate cancer, and prostate tissue from two men whose prostates were removed for reasons unrelated to prostate cancer.

The researchers also examined metastatic human prostate-cancer cells, obtained from androgen-deprived men, which had been engrafted and allowed to grow in both castrated and non-castrated mice, a process called xenografting.

Androgen levels in the xenograft tumors in the castrated mice, which had no circulating androgen, were actually higher than in the xenograft tumors in the mice that had not been castrated. The researchers found a particularly striking difference in levels of DHT. “We found DHT levels to be twice as high in the castrated mice,” Mostaghel said. “That tells us that the tumor is making testosterone and hanging on to it somehow and is further evidence that metastatic tissue has the capacity to make its own testosterone.”

Each year, approximately 200,000 U.S. men are diagnosed with prostate cancer. While the majority of cases are early-stage, localized disease – due in large part to the widespread use of PSA, or prostate-specific antigen screening – an estimated 50 percent of patients diagnosed and treated for clinically localized prostate cancer will progress to more advanced disease, which kills an estimated 30,000 American men annually.

Source: Fred Hutchinson Cancer Research Center