Study finds genetic mutation in castration-resistant prostate cancer

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The mutation occurs in the androgen-synthesizing enzyme 3βHSD1 in castration-resistant prostate cancer (CRPC), according to research published online today in *Cell*. This mutation enables the tumor to make its own supply of androgens, a hormone that fuels the growth of the prostate cancer.

Prostate cancer requires a constant supply of androgens in order to sustain itself. The current standard of care for patients with metastatic prostate cancer is medical castration, the ability to interfere with the body's production of testosterone (androgens) using medications that disrupt the process. Oftentimes, metastatic prostate cancer flourishes despite the lack of testosterone in the bloodstream, creating CRPC. These tumors are able to exist without the body's supply of testosterone by creating androgens within the tumor cell; however, increased androgen synthesis has not yet been attributable to any known mutations. The Cleveland Clinic discovery shows that the 3?HSD1 mutation makes this enzyme hyperactive to create androgens.

"This discovery gives us the ability to identify molecular subtypes of prostate cancer known to resist treatment. By finding the mutated enzyme, we can now investigate treatments that block it. This kind of strategy is the crux of personalized medicine which is currently used as the standard of care for some forms of lung cancer and melanoma," said Nima Sharifi, M.D., Kendrick Family Chair for Prostate Cancer Research at Cleveland Clinic, who led the research.

The 3?HSD1 mutation can occur within CRPC tumors and it can also come from germline DNA, which is inherited from maternal and paternal sources.

The research found that laboratory models of human prostate cancer fall into two categories of androgen synthesis: those that make androgens slowly and those that do so rapidly. Next, they found that the 3?HSD1 mutation explains the difference between these two categories and that DNA from some patient tumors also contains this mutation. The mutation works by opening the floodgates to androgen synthesis, essentially throwing fuel on the fire that promotes tumor progression.

In an era of personalized cancer care, there is increased focus on defining and treating cancer by its genetic abnormalities. Tumor-promoting enzyme mutations in several cancers have been identified and, subsequently, have led to the development of targeted drug therapies, improving outcomes for patients.

"The past decade has seen an explosion of molecularly targeted therapies that are matched to specific mutations in a given patient's tumor," says Dr. Sharifi. "However, no drug-targeting based on enzyme mutations exists for the standard treatment of metastatic CRPC. With this finding, we have the opportunity for matching a mutant disease-driving biomarker with a pharmacologic inhibitor."

Prostate cancer is the most common cancer in men, with nearly 240,000 new cases diagnosed each year in the United States. According to the American Cancer Society, there will be an estimated 30,000 deaths due to prostate cancer in 2013. Almost every man who dies of prostate cancer dies with castration-resistant prostate cancer.

Provided by Cleveland Clinic