Researchers find prostate cancer drug byproduct can fuel cancer cells

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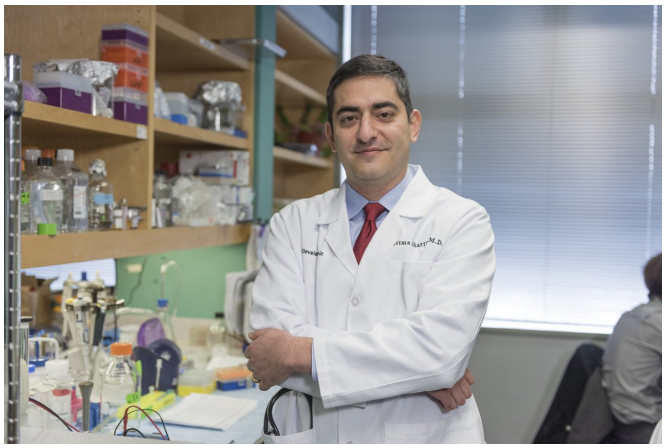

Nima Sharifi, MD, Cleveland Clinic Lerner Research Institute. Credit: Cleveland Clinic

A genetic anomaly in certain men with prostate cancer may impact their response to common drugs used to treat the disease, according to new research at Cleveland Clinic. The findings may provide important information for identifying which patients potentially fare better when treated with an alternate therapy.

In a newly published study in *Journal of Clinical Investigation*, researchers found that abiraterone, a common prostate cancer drug, yields high-levels of a testosterone-like byproduct in men with advanced disease who have a specific genetic variant.

The study's lead researcher, Nima Sharifi, M.D., Cleveland Clinic Lerner Research Institute Department of Cancer Biology, previously discovered that men with aggressive prostate cancer who have a specific variant in the HSD3B1 gene have poorer outcomes than patients without the variant. HSD3B1 encodes an enzyme that allows cancer cells to use adrenal androgens for fuel. This enzyme is overactive in patients with the variant HSD3B1(1245C).

In the new study, Dr. Sharifi and his team, including first author Mohammad Alyamani, Ph.D., found that men with the genetic anomaly metabolize abiraterone differently than men without the variant.

"We are hopeful these finding will lead to us being able to better tailor prostate cancer treatments based on a patient's specific genetic make-up," said Dr. Sharifi. "More studies are needed, but we have strong evidence that HSD3B1 status affects abiraterone metabolism and probably its effectiveness. If confirmed, we hope to identify an effective alternative drug that might be more effective in men with this genetic anomaly."

Traditional therapy for advanced prostate cancer—called androgen deprivation therapy (ADT) - blocks cells' supply of androgens (male hormones), which they use to grow and spread. While ADT is successful early on, cancer cells grow resistant, allowing the disease to progress to a lethal phase called castration-resistant prostate cancer (CRPC). In CRPC, cancer cells utilize an alternative source of androgens produced in the adrenal glands. Abiraterone blocks these adrenal androgens.

In the study, the researchers examined small molecule byproducts of abiraterone in several groups of men with CRPC and found that patients with the gene variant had high levels of a metabolite called 5?-abiraterone. The metabolite tricks androgen receptors into turning on dangerous pro-cancer pathways. Remarkably, this byproduct of abiraterone—which is designed to block androgens—may behave like an androgen and cause prostate cancer cells to grow. Investigating abiraterone's impact on clinical outcomes in CRPC patients will be an important next step.

"This study adds to our understanding of the deleterious effect of inherited variants of the

HSD3B1 gene and holds promise for precision medicine approaches in the management of men with advanced prostate cancer," said Eric Klein, M.D., chair of Cleveland Clinic Glickman Urological and Kidney Institute.

"This study helps to define a novel resistance pathway for abiraterone, a commonly used medication for patients with advanced prostate cancer. Dr. Sharifi's results could enable selection of different systemic therapies for patients who are carriers of certain genetic alterations in the HSD3B1 gene in order to prolong clinical response," said Howard Soule, Ph.D., executive vice president and chief science officer of the Prostate Cancer Foundation. "The Prostate Cancer Foundation is thankful to Dr. Sharifi for his continued investigations to improve therapy for advanced prostate cancer patients, and is proud to have funded this study."

Provided by Cleveland Clinic