Team discovers similarities between next-generation prostate cancer drugs

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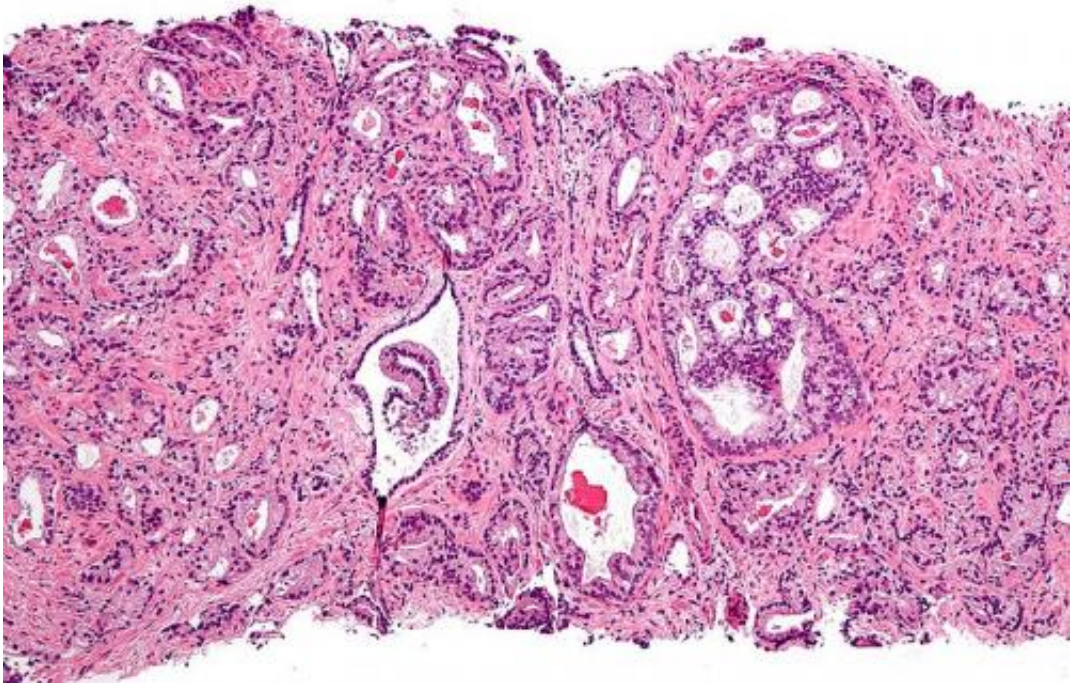

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

Cleveland Clinic researchers have shown for the first time how a class of advanced prostate cancer drugs are processed in the body and how their anti-tumor activity might change depending on how they are metabolized. Their pre-clinical findings, just published in *Cell Chemical Biology*, may lay the foundation for improving therapies for treatment-resistant, aggressive prostate cancer.

Next-generation anti-androgens are potent drugs that work by cutting off the prostate tumor's supply of androgens (male hormones), which fuel prostate cancer. The drugs, used in patients whose cancer has become resistant to hormone deprivation therapy, have been shown to improve survival in men with metastatic disease. Unfortunately, prostate tumors eventually become resistant to these drugs, highlighting the need for new therapies.

"Despite an array of improved treatment options that have become available over the past decade, prostate cancer remains the second leading cause of cancer mortality in men in the United States. There are few therapeutic options for men whose cancer has become resistant to all therapies," said Nima Sharifi, M.D., lead author on the study. "Our goal is to improve the use and role of these existing drugs and hopefully design new therapies that work better and longer."

Galeterone is a steroidal anti-androgen that was recently studied in a clinical trial. Dr. Sharifi's team in the Cleveland Clinic Lerner Research Institute's Department of Cancer Biology has shown that when galeterone is metabolized, it is converted to the intermediate molecule D4G, which blocks androgen synthesis and reduces the amount of androgens available to cancer cells. A pitfall is that galeterone is also converted to another molecule that may stimulate the tumor.

Dr. Sharifi previously found that another steroidal anti-androgen drug, abiraterone, is metabolized in a similar manner. He went on to show in landmark studies that abiraterone's metabolite D4A has greater anti-tumor activity than abiraterone alone and that other molecules stimulate tumor growth, suggesting that the drug should be fine-tuned to improve efficacy.

Dr. Sharifi's new findings suggest that effective steroidal anti-androgens share common metabolic activities and that their metabolites should be

closely examined for their effects on tumor survival. The findings may also guide medical decision making in the use of steroidal vs. nonsteroidal drugs for advanced prostate cancer.

"New agents and a clearer understanding of drug mechanisms are both urgently required to improve outcomes for treatment-resistant advanced prostate cancer," said Dr. Sharifi. "This work provides an important foundation that hopefully will lead to better treatment strategies for this disease."

Provided by Cleveland Clinic