Understanding How Castration-Resistant Prostate Cancer Develops Resistance to Anti-Androgen Therapy

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Prostate cancer is the leading cancer in American males, and the third leading cause of cancer deaths among men of all ages. While common, it is generally a slow-growing disease and active surveillance or primary treatments - including surgery, radiation or hormone ablation - are sufficient for the majority of patients. However, development of castration-resistant prostate cancer (CRPC) is generally lethal and treatment options remain limited.

A novel drug, abiraterone, has recently been FDA-approved for men with CRPC. Abiraterone functions to block a key enzyme, CYP17A1, involved in steroidogenesis of androgens. Abiraterone treatment decreases circulating levels of testosterone and related androgens, which are important regulators of prostate cancer growth. While abiraterone has been associated with impressive responses in many men with CRPC, the duration of effect has been variable. Ultimately, most men will progress. The effects of abiraterone on prostate-tissue androgen levels and the mechanisms of resistance to abiraterone are not well characterized. To address these issues, Dr. Elahe Mostaghel of the Clinical Research Division and her collaborators treated mice bearing human CRPC xenografts with abiraterone to assess the effects on tumor growth, androgen concentrations, AR expression and steroidogenic gene expression.

Initial treatment of two different CRPC xenograft models resulted in tumor suppression and increased survival. Following initiation of abiraterone treatment, a rapid decrease in serum PSA and tumor-specific androgens was observed, leading to slower tumor growth and a survival advantage. However, extended abiraterone treatment activated multiple pathways to preserve AR-mediated gene expression in tumors. These pathways include increased expression of full length androgen receptor and ligand-independent splice variants that are constitutively active, as well as altering genes involved in steroid biosynthesis. As a result, dihydrotestosterone, the most potent form of the male androgens, is synthesized from adrenal androgens and its catabolism is impaired. Thus, while CYP17A1 inhibition suppresses tissue androgens and tumor growth, low-level androgens remain...
present, combined with elevated AR expression, to maintain sensitivity to low androgen levels. Overall, this study identifies mechanisms by which prostate tumors become resistant to abiraterone, and suggests that treatment of patients with higher dose levels of abiraterone, or potent AR blockade in combination with CYP17A1 inhibition may be of clinical benefit.