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PROSTATE CANCER

Revealing mechanisms of resistance

New research has revealed possible mechanisms by which castration-resistant prostate cancer (CRPC) becomes resistant to the androgen receptor (AR)-targeted therapies abiraterone and enzalutamide.

Blood was collected from 36 patients with CRPC for circulating tumour cell (CTC) enumeration and isolation at baseline and at 4, 6, and 12 weeks after beginning treatment and at the time of disease progression. Time to progression was significantly shorter in men with ≥5 CTCs per 7.5 ml of blood at baseline.

Sequencing revealed novel AR mutations, including deleterious frameshift and early truncation mutations in the androgen-binding domain that could facilitate escape from AR-targeted therapies. Notably, no significant increases in AR-variant 7 (AR-V7) levels were observed between drug-sensitive and drug-resistant samples and high baseline AR-V7 status did not predict poor response to treatment.

Differential gene expression analysis of grouped drug-sensitive and grouped drug-resistant CTCs showed that ~2,100 genes were differentially regulated. Furthermore, ingenuity pathway analysis identified several altered pathways between drug-sensitive and drug-resistant CTCs. Specifically, TGFβ signalling, *SMAD3*, and *CCND1* were significantly upregulated in drug-resistant CTCs.

In vitro, knockdown of *SMAD3* in enzalutamide-resistant LNCaP cells reduced cell viability. Overexpression of *CCND1* in LNCaP cells increased cell proliferation and treatment of *CCND1*-overexpressing cells with cyclin-dependent kinase (CDK) inhibitors inhibited proliferation. Combined treatment of enzalutamide-resistant LNCaP cells with enzalutamide and CDK inhibitors also reduced proliferation. Moreover, treatment of another, independent, enzalutamide-resistant LNCaP cell line that overexpressed *CCND1* with CDK inhibitors also hampered cell growth.

These results reveal novel potential mechanisms of resistance and provide new targets for treatment of men with CRPC.

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ORIGINAL ARTICLE Pal, S. K. *et al.* Identification of mechanisms of resistance to treatment with abiraterone acetate or enzalutamide in patients with castration-resistant prostate cancer (CRPC). *Cancer* https://doi.org/10.1002/cncr.31161 (2017)