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PROSTATE CANCER

Targeting metabolism

Enzalutamide resistance in castration-resistant prostate cancer (CRPC) could be inhibited by targeting aberrant corticosteroid metabolism, according to new data published in *eLife*. Subsequent resensitization of castration-resistant tumours to enzalutamide treatment could improve the outcomes of men with advanced disease.

Resistance to enzalutamide can be mediated through an upregulation of glucocorticoid receptor (GR) expression in the context of androgen receptor (AR) inhibition. However, as GR signalling is essential to many biological processes, direct targeting of this receptor is problematic. Thus, Li and colleagues hypothesized that a tumour-specific GR metabolic mechanism could provide a pharmacological target that avoided the adverse effects caused by systemic GR blockade.

The researchers observed that prolonged exposure to enzalutamide impedes the conversion of cortisol to inactive cortisone *in vitro* and *in vivo*. To elucidate the mechanism of inhibition, the investigators analysed the expression of 11-β-HSD2 — which catalyses the conversion of cortisol into cortisone. In AR-expressing cells, 11-β-HSD2 expression was reduced compared with AR-negative cells; however, *HSD11B2* expression was unaffected. Furthermore, 11-β-HSD2 was not directly antagonized by enzalutamide and loss 11-β-HSD2 was not attributable to GR stimulation. The conversion of cortisol to cortisone was reinstated in enzalutamide-treated cells that stably or transiently expressed 11-β-HSD2.

The researchers reported that 11-β-HSD2 overexpression inhibits the growth of xenograft tumours exhibiting enzalutamide resistance, reduces corticosterone concentrations, and prolongs progression-free survival in mice. Clinically, nine of 11 biopsy samples from patients treated with enzalutamide exhibited 11-β-HSD2 loss, and a subset of these samples also demonstrated upregulation of the GR.

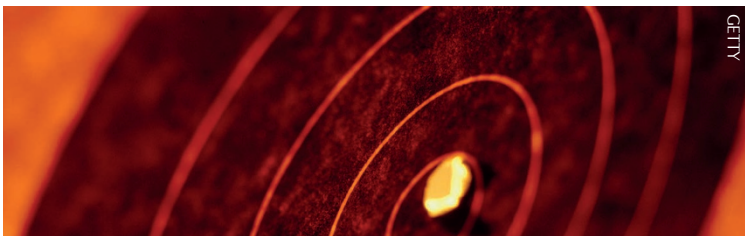
The investigators then further analysed the mechanism of action of 11-β-HSD2 loss in the context of enzalutamide resistance. The E3 ubiquitin ligase AMFR is known to associate with 11-β-HSD2, and the team hypothesized that it might be required for enzalutamide-induced 11-β-HSD2 loss. AMFR expression was not increased by enzalutamide treatment; however, Erlin-2 — which is involved in the AMFR-associated endoplasmic-reticulum-associated degradation pathway — was upregulated in patient samples. Silencing *AMFR in vitro* caused an increase in 11-β-HSD2 protein expression, but had no effect on transcript levels, and induced the conversion of cortisol to cortisone. *In vivo*, enzalutamide resistance was inhibited and 11-β-HSD2 levels were maintained in xenografts in which AMFR was knocked down.

Together these data suggest that cortisol metabolism could represent a therapeutic target in enzalutamide-resistant CRPC that could avoid the issues associated with systemic glucocorticoid ablation and improve the outcomes of men with advanced tumours.

Louise Stone

> “Silencing *AMFR in vitro* caused an increase in 11-β-HSD2 protein expression”

ORIGINAL RESEARCH PAPER Li, J. *et al.* Aberrant corticosteroid metabolism in tumor cells enables GR takeover in enzalutamide resistant prostate cancer. *ELife*. http://dx.doi.org/10.7554/eLife.20183.001 (2017)



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