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PROSTATE CANCER

A new tARget

The progression to castration-recurrent prostate cancer (CRPC) is generally believed to involve the androgen receptor (AR) in most patients. Current treatments target the AR ligand-binding domain (LBD) but these all eventually fail. Marianne Sadar and colleagues have identified a new compound that targets the amino terminal domain (NTD) of AR, and provide in vivo evidence that this new drug could be effective at treating CRPC owing to its ability to attenuate downstream AR signalling.

AR is activated by androgen or by other factors when androgen is removed, resulting in the transactivation of the AR NTD and AR binding to androgen response elements (AREs) in the promoters of androgen-regulated genes. The authors screened a library of extracts from marine sponges for an inhibitor of AR NTD transactivation and identified the small molecule EPI-001, which inhibited transcriptional regulation of androgen-regulated genes, but not those regulated by the related progesterone and glucocorticoid steroid receptors. Importantly, EPI-001 was effective at inhibiting both ligand-dependent and ligand-independent transactivation of AR, as well as inhibiting constitutively active AR lacking its LBD.

What is the mechanism of action? Chromatin immunoprecipitation analyses showed that EPI-001 reduced the interaction of AR with the AREs of target genes, including *PSA* and *TMPRSS2*. EPI-001 bound the NTD of AR and inhibited the recruitment of the transcriptional cofactors CBP and RAP74, suggesting that EPI-001 functions by blocking protein–protein interactions at the NTD. EPI-001 reduced androgen-dependent and androgen-independent proliferation of LNCaP prostate cancer cells that express AR and had no effect on cells that do not require AR activation for growth.

To determine whether EPI-001 inhibits CRPC tumour growth, male mice bearing LNCaP subcutaneous xenografts were castrated when the tumours were approximately 100 mm in size. Treatment of these mice by intravenous injection of EPI-001 resulted in a greater than 50% reduction in tumour volume in 2 weeks compared with vehicle-treated animals. The major organs of the mice treated with intravenous EPI-001 showed no signs of toxicity. Long-term treatment of mice with EPI-001 by intratumoral injections resulted in a 62% reduction in tumour growth. Castrated mice bearing orthotopic LNCaP xenografts exhibited similar reductions in tumour growth in response to intravenous EPI-001. In addition, mice with subcutaneous xenografts of PC3 cancer cells, which do not express AR and are not responsive to androgen, were not responsive to EPI-001 treatment.

These studies have identified a specific inhibitor of AR-dependent tumour growth that does not exhibit toxicity at a therapeutic dose range. EPI-001 has a new mode of action, as it targets the transactivation of AR regardless of the presence of androgen, and is a promising therapy to delay the progression of CRPC.

Mhairi Skinner, Consulting Editor, NCI–Nature Pathway Interaction Database

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ORIGINAL RESEARCH PAPER Andersen, R. J. *et al.* Regression of castrate-recurrent prostate cancer by a small-molecule inhibitor of the amino-terminus domain of the androgen receptor. *Cancer Cell* **17**, 535–546 (2010)

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