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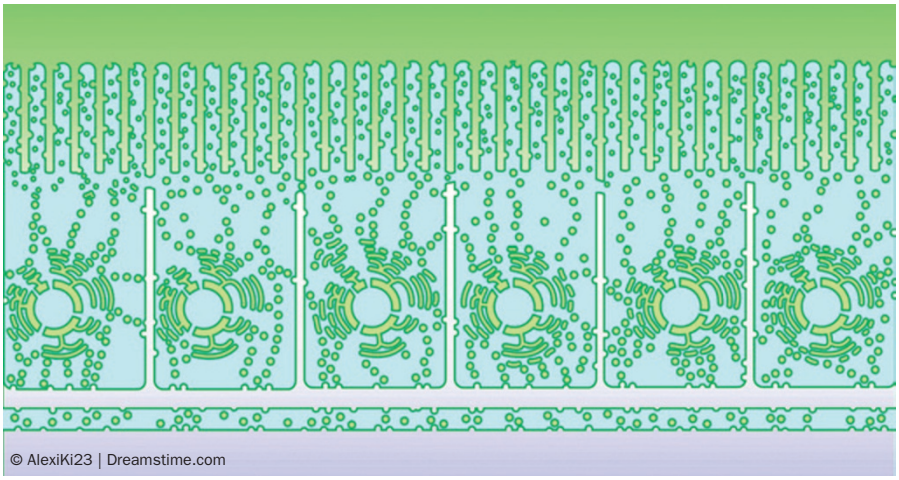
PROSTATE CANCER

Androgen deprivation causes EMT in the prostate



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Androgen deprivation causes epithelial–mesenchymal transition (EMT) in both healthy and cancerous prostate tissue, according to a team of researchers from San Francisco, USA. This process is thought to be mediated by a negative feedback loop between the androgen receptor and Zeb1.

In the first set of experiments, Sun *et al.* evaluated the gene expression profiles of intact and castrated mouse prostates. 3 days postcastration, *N-cadherin*, *Twist1* and *Slug* expression levels were upregulated. These increases were reversed upon testosterone replenishment. Similar changes were observed in tumor biopsies from patients and *SLUG* was one of the top-ranking genes for expression status 14 days after chemical castration.

In further work, xenografts of LuCaP35—derived from a lymph node metastasis of prostate cancer—were transplanted onto mice. Those with established grafts were castrated, and regressed tumors were isolated 4 weeks later. Gene expression profiling revealed activated TGFβ signaling in regressed cancers, as well as increased expression of several EMT-inducing genes and two 'stemness' markers (WNT5a and WNT5b). '*In vitro* castration'—achieved by depriving LNCaP cells of hormones—produced slow-growing cells that formed spheres and adhered poorly to plates.

In all studies, androgen deprivation resulted in increased *ZEB1* expression, suggesting a key role for this gene in EMT. Androgen receptor and Zeb1 expression are mutually exclusive of each other and the group identified a bidirectional negative feedback loop that mediates castration-induced EMT.

These findings could have significant implications for prostate cancer therapy as EMT has been linked to therapeutic resistance and a poor prognosis. Thus, patients receiving androgen deprivation therapy might benefit from concomitant treatment with an EMT inhibitor. In support of this theory, a novel drug targeting N-cadherin has been shown to delay the onset of castration resistance.

"The monoclonal antibodies targeting N-cadherin are encouraging, though toxicity may ultimately limit their utility," says Leisa Johnson, who coordinated the work done by Sun *et al.* "Many of the most attractive players are transcription factors (for example, *ZEB1*, *TWIST1*, and *SLUG*) that have notoriously proved difficult to target therapeutically. RNAi-based therapeutics hold promise, though successful delivery still remains their biggest challenge. Whether targeting *ZEB1* could resensitize castration-resistant prostate cancer to androgen deprivation therapy remains to be determined."

Melanie Clyne

Original article Sun, Y. *et al.* Androgen deprivation causes epithelial-mesenchymal transition in the prostate: implications for androgen-deprivation therapy. *Cancer Res.* doi:10.1158/0008-5472.CAN-11-3004