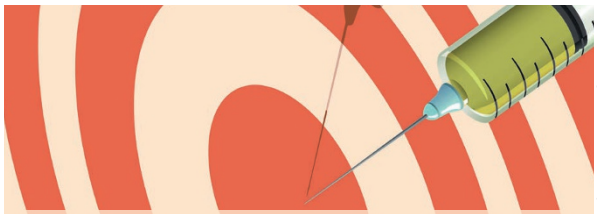
Nature Reviews Urology | Published online 14 Feb 2017; doi:10.1038/nrurol.2017.23



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PROSTATE CANCER

Cholesterol homeostasis — a target for treatment

> “cholesterol levels in 27HC-treated cells were significantly depleted”

New research published in *Cancer Research*, has identified a potential mechanistic link between prostate cancer progression and dysregulated cholesterol homeostasis. Targeting this mechanism could provide a new therapeutic approach for treating this disease.

The investigators initially observed that prostate cancer cells cultured using lipoprotein-deficient serum had reduced growth compared with cells grown using normal serum. Furthermore, addition of low-density lipoprotein to lipoprotein-deficient serum restored the growth capacity of these cells.

Using a bioinformatic approach, the researchers identified cholesterol-related genes whose expression levels correlated with aggressive prostate cancer. In total, expression levels of 176 genes were assessed relative to three clinical features of prostate cancer — T stage, Gleason score, and presence of lymph node metastasis — that were extracted from TGCA. Only *CYP27A1* expression was significantly associated with all three clinical features.

Further investigation showed that *CYP27A1* expression levels were significantly lower in tumour samples than benign tissue and also reduced in metastatic samples compared with primary tumour. *In vitro*, prostate cancer cells that were engineered to stably overexpress *CYP27A1* under the control of a doxycyclin-inducible promoter had significantly reduced growth. Moreover, *in vivo*, *CYP27A1*-overexpressing cell-line-derived xenograft tumours were significantly smaller than control xenografts.

To investigate the mechanism by which CYP27A inhibits prostate cancer cell growth, the investigators treated prostate cancer cells with 27HC (the product of CYP27A1 conversion of cholesterol). Treatment with 27HC inhibited prostate cancer cell growth, even in antiandrogen-resistant cell lines; in addition, cleaved PARP and p27 levels both increased. Furthermore, cholesterol levels in 27HC-treated cells were significantly depleted and levels of the precursor form of SREBP2 (which is involved in cholesterol homeostasis) were also decreased. The effects of 27HC were reversed by adding exogenous cholesterol or the active nuclear form of SREBP2. Moreover, overexpression of SREBP2 or LDLR (a major target of SREBP2) reduced the sensitivity of cells to 27HC treatment.

These data provide a mechanism by which dysregulation of cholesterol homeostasis via the CYP27A1–27HC axis in prostate cancer cells promotes tumour growth, and provide novel therapeutic targets for treating this disease.

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ORIGINAL ARTICLE Alfaqih, M. A. *et al.* CYP27A1 loss dysregulates cholesterol homeostasis in prostate cancer. *Cancer Res.* http://dx.doi.org/10.1158/0008-5472.CAN-16-2738 (2017)