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PROSTATE CANCER

Conserved lipid synthesis drives castration resistance

> lipid biosynthesis genes were restored to a level similar to or greater than *PSA* and *TMPRSS2*

Androgen receptor (AR)-regulated lipid biosynthetic pathways could drive the progression towards castration-resistant prostate cancer (CRPC), according to data recently published in *Oncogene*.

Alterations in the AR cistrome during prostate cancer development are well established, with the co-opting of several new oncogenic targets, as well as changes in AR chromatin binding. AR splice variants (AR-Vs) might be a potential mechanism by which this reprogramming occurs, as these can be constitutively active and bind to different enhancer sites from the full-length AR (AR-FL).

Han *et al.* used a VCaP cell-line-derived xenograft model, which — like naturally occurring human prostate tumours — eventually develops castration resistance and demonstrates increased levels of AR, AR-Vs, and steroidogenesis genes. By extracting cells from these resistant tumours, they developed a cell-line model of CRPC, named VCS2. AR ChIP-seq analysis using an antibody against the AR N-terminal region showed a marked overlap in binding peaks between the two cell lines. Examination of AR-binding sites close to genes activated by dihydrotestosterone (DHT) treatment identified a number of AR-binding sites, and gene ontology analysis showed similar enrichment of pathways, including lipid metabolism. Further analysis identified 32 androgen-stimulated lipid synthesis genes, which mediate a variety of lipid synthesis pathways.

To translate their results into a clinical model, the team then investigated whether AR-binding sites could be identified adjacent to lipid synthesis genes in normal prostate cell and malignant cells from human samples. Interrogation of a public ChIP-seq database showed that >60% of lipid synthesis genes are associated with AR-binding sites at the same location in both the VCaP and VCS2 cells.

Three AR-activated lipid synthesis genes were selected for further investigation: *ACSL3*, *MBOAT2*, and *ELOVL5/7*. Expression of all three were shown to be androgen stimulated, and treatment with enzalutamide blocked impaired AR binding to the previously identified AR occupancy sites. The team compared xenograft tumours before and after castration resistance to determine whether expression of lipid synthesis genes was restored by castration resistance. The expression of the lipid synthesis genes examined in tumour xenografts was generally restored to a similar degree to the AR-regulated *PSA* and *TMPRSS2*. These results were also reflected in samples from patient biopsies, in which lipid biosynthesis genes were restored to a level similar to or greater than *PSA* and *TMPRSS2*. Furthermore, restored expression of the lipid synthesis genes was correlated with poor patient outcomes and recurrence.

The authors hypothesized that this restoration might be promoted by the expression of AR-Vs. They observed increased AR-V7 expression in VCaP xenograft tumours and increased ratio of AR-V7:AR-FL in the castration-resistant VCS2 cells compared with the VCaP cells. Use of an AR-V7-specific antibody showed binding of the AR-binding sites adjacent to lipid synthesis genes. Further investigation using another prostate cancer cell line, CWR22-RV1, showed that AR-V7 binding was enhanced by DHT and blocked by enzalutamide, but that expression of AR-V7 and AR-FL could be silenced using small interfering RNA methods, which completely blocked androgen-induced expression of the lipid biosynthesis genes.

Finally, Han *et al.* investigated whether lipid biosynthesis suppresses the growth of CRPC. Their data showed that DHT treatment of CWR22-RV1 increased cellular cholesterol; thus, they treated the cells with simvastatin, which did not affect AR activities, although it did suppress cell proliferation, and treatment greatly reduced mTOR activity, which could inhibit G1/S progression. Treatment of xenografts also impaired proliferation and induced apoptosis. Simvastatin treatment of another cell line, C4-2, blocked mTOR activation and decreased basal AR activity and prevented cell cycle progression in partially and completely hormone-depleted medium. "We were initially trying to determine if the AR cistrome is reprogrammed in CRPC using a VCaP-derived model," corresponding author Changmeng Cai told NRU. "However, our data did not indicate any major reprogramming of AR signalling. Instead, we found that the androgen-regulated lipid biosynthesis remains the major function of AR in this CRPC model".

Finally, they investigated whether the lipid synthesis genes contribute to CRPC progression by treating cells with the specific inhibitor triacsin C and a statin to target *ACSL3* and short hairpin RNA against *ELOVL7*. Both treatments reduced cell proliferation and growth of xenograft tumours.

"In this study, we demonstrated that transcriptional regulation of lipid biosynthesis genes is reactivated following castration relapse and increased expression of these genes is associated with reduced disease-free survival times in localized prostate cancer," corresponding author Hansen He commented.

He concluded: "Future studies are warranted to investigate the mechanisms underlying lipid biosynthesis pathways and aggressive obesity-associated prostate cancer."

Annette Fenner

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