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PROSTATE CANCER

Risk SNPs modulate lncRNAs

> *PCAT1* expression was considerably upregulated in primary prostate tissue

Single nucleotide polymorphisms (SNPs) that are associated with susceptibility to prostate cancer modulate long noncoding RNA (lncRNA) expression, according to new data published in *Nature Genetics*. This mechanism could be important in understanding how SNPs promote cancer tumorigenicity and targeting lncRNAs could mitigate cancer risk.

Genome-wide association studies (GWAS) have identified many SNPs in different populations that are associated with prostate cancer risk. In their study, Guo and colleagues generated an associated variant set (AVS) of risk-associated loci in prostate cancer using data from the GWAS catalogue. This AVS was significantly enriched in DNase I-hypersensitive sites (DHS) and also in the cistromes of the androgen receptor (AR) and AR cofactors.

In vitro, risk loci were significantly enriched in regions with active epigenetic modifications in LNCaP cells. Furthermore, DHS that overlapped with risk-associated SNPs in these cells were close to sites encoding lncRNAs and had the potential to modulate them.

Integrative analysis of regions containing risk-associated SNPs in benign and cancerous prostate tissue samples from The Cancer Genome Atlas revealed 45 candidate lncRNAs associated with prostate cancer risk loci, including SNPs in the promoter regions of five expressed lncRNA genes (*PCAT1*, *RP11-400F19.18*, *RP11-242D8.1*, *RP11-552F3.10* and *RP11-328M4*).

A scoring system was used prioritize which lncRNAs to take forwards for validation and characterization and identified *PCAT1* as the top-scoring lncRNA gene. The gene desert region in which *PCAT1* is located harbours ten loci associated with prostate cancer risk. *PCAT1* expression was considerably upregulated in primary prostate tissue and suppression of its expression reduced prostate cancer cell proliferation *in vitro*. *In vivo*, *PCAT1* knockdown reduced xenograft tumour growth and improved survival of tumour-bearing mice.

Further analysis predicted associations between the *PCAT1* promoter and the DHS-containing risk-associated SNP rs7463708. The T risk allele of this SNP is associated with increased biochemical relapse rates. Cross-correlation analysis identified a strong correlation between this DHS signal and the *PCAT1* promoter, suggesting an interaction. Validation of this interaction revealed the strongest interaction occurred on stimulation with dihydrotestosterone (DHT) and that *PCAT1* expression and the DHS signal were highest in LNCaP cells, suggesting that the rs7463708-containing DHS might regulate *PCAT1* expression. Analysis of enhancer activity of the rs7463708 locus revealed that the T risk allele has stronger enhancer activity than the nonrisk G allele. Disruption of this locus reduced interaction between *PCAT1* and rs7463708 and resulted in reduced *PCAT1* expression.

Motif analysis suggested that rs7463708 overlaps with the binding motif of ONECUT2, an AR-interacting transcription factor, with the motif showing significantly higher preference for the T risk allele. DHT treatment increased ONECUT2 and AR binding to this locus, with AR binding being enriched at the T risk allele and silencing of ONECUT2 decreasing AR binding.

In vitro, *PCAT1* expression in LNCaP cells was significantly increased at 16 h after DHT treatment, but increased expression was blocked by enzalutamide treatment and ONECUT2 silencing, indicating that *PCAT1* is an androgen late-response gene. *PCAT1* bound to AR and LSD1 in an androgen-dependent manner and knockdown reduced the expression of AR and LSD1 target genes, including *GNMT* and *DHCR2*.

These data provide evidence that modulation of lncRNAs by risk-associted SNPs contributes to men's genetic susceptibility to prostate cancer. LncRNAs are an attractive target for novel therapeutics to mitigate cancer risk.

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