Risk SNP-mediated bifunctional regulatory element drives prostate cancer through lncRNA PCAT19

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Background: Long noncoding RNA (lncRNA) is one of the most pervasive class of noncoding RNA. In multiple cancer types including prostate cancer (PCa), studies have reported the functional role and biomarker potential of selective lncRNAs. Despite this, most lncRNAs remain poorly understood and there exists a need to prioritize for functionally important lncRNA candidates. We recently identified 45 high-confidence functional lncRNA candidates in PCa through genome-wide associations with single nucleotide polymorphisms (SNPs). In this study, we investigated the association between lncRNA PCAT19 and rs11672691, a risk SNP previously associated with PCa aggressiveness, and their functional mechanisms and clinical significance in PCa.

Methods: Expression quantitative trait loci (eQTL) analysis and luciferase assays were used explore the association between rs11672691 genotype and PCAT19 isoform expression. Motif analysis and chromatin immunoprecipitation (ChIP) assays were subsequently performed to identify transcription factors (TFs) affecting this association. RNAi-mediated knockdown followed by functional assays and transcriptomic profiling, and RNA pull-down followed by mass spectrometry, were used to investigate the biological functions and mechanisms of PCAT19.

Results: The genotypes of rs11672691 modulate the binding of TF NKX3-1 at a bifunctional regulatory element that regulates the expression of two gene isoforms of PCAT19, PCAT19-long and PCAT19-short. Notably, PCAT19-long is oncogenic and promotes PCa cell proliferation and aggressiveness *in vitro* and *in vivo*. Subsequent transcriptomic profiling and RNA pull-down assays conclude that PCAT19-long forms a complex with HNRNPAB to upregulate a subset of cell cycle target genes. Lastly, patients with high expression of PCAT19-long is associated with decreased biochemical recurrence-free survival.

Conclusions: We have characterized the regulatory and functional mechanisms of a novel

oncogenic lncRNA isoform (PCAT19-long) in prostate cancer. Our results also highlighted the importance of integrative analyses involving risk SNPs and lncRNAs in understanding PCa.

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