Androgen receptor–regulated lncRNA PRCAT71 promotes AR signaling through the interaction with KHSRP in prostate cancer

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Background: Previous studies have elucidated the role of long noncoding RNAs (lncRNAs) in the progression of various cancers. However, its role in prostate cancer (PCa), one of the most prevalent cancers among males, have yet to be explored. Androgen receptors (AR) have been the key focus of PCa therapeutics, however most PCa patients advance to develop drug resistance within a short amount of time post-treatment. LncRNAs are RNAs that contain more than 200 nucleotides in size and cannot be translated to a secondary or tertiary structure, but can regulate several molecular mechanisms, which can be highly dysregulated to cause cancer progression. Transcriptomic analyses have shown a few lncRNAs have been found to regulate AR signaling by interaction to induce PCa progression, one of which is PCa-associated transcript 71 (PRCAT71), a lncRNA highly expressed in PCa tissues and is correlated with PCa progression, in which its mechanistic role will be clarified.

Objective: To investigate the role of the aberrant expression of PRCAT71 in the AR signaling mechanism to induce prostate cancer progression and the molecular mechanism underlying it.

Results: Firstly, the authors performed *in vitro* assays using PRCAT71 knockdown PCa cells, which showed reduced overall cancer hallmarks and induced cell cycle arrest in the G_0-G_1 phase. Using next-gen RNA-seq and gene set enrichment analysis of PRCAT71 knockdown cells compared to normal PCa cells, PRCAT71 silencing suppressed AR up-regulated genes, proven by immunoblotting. Furthermore, chromatin immunoprecipitation (ChIP)-qPCR analysis show that PRCAT71 knockdown reduced AR recruitment to enhancers of its downstream target enhancers. Next, they predicted the interaction site of PRCAT71 and AR mRNA to be located at the 3'UTR of AR mRNA, proven by using RNA-RNA pulldown and interaction assays, RNA protection assay as well as actinomycin D treatment. The authors would then like to elucidate if an RNA-binding protein plays a role between PRCAT71 and AR mRNA interaction. They predicted K homology-type splicing regulatory protein (KHSRP) as the top candidate and performed RNA immunoprecipitation (RIP)-qPCR and RNA pulldown assay, confirming that PRCAT71 was indeed bound to KHSRP in a dose-dependent manner. Next, *in vitro* and *in vivo* assays were performed on KHSRP knockdown PCa cells, in which cancer progression hallmarks were significantly reduced, while also revealing that KHSRP binding protects AR mRNA from XRN2-mediated degradation, highly expressed in PCa patients and correlates to poor survival. Using ChIP-seq, the authors also identified that AR regulates PRCAT71 by occupying regions upstream of PRCAT71, in which subsequent analysis with AR inhibitor drugs and hormone stripping reveals that AR positively regulates the expression of PRCAT71 in a positive feedback loop manner. Lastly, subsequent *in vivo* and datasets analyses revealed that overall higher PRCAT71 expression correlates to tumor progression in castration-resistant prostate cancer (CRPC) patients as well as lower metastasis-free survival.

Conclusion: PRCAT71 as a lncRNA is highly expressed in PCa tissues, which was revealed to interact with the 3'UTR of AR mRNA. PRCAT71 then recruits with KHSRP, an RNA-binding protein, to stabilize AR mRNA and protect it from degradation. In turn, AR binds to PRCAT71 upstream regions to activate its transcription in a positive feedback loop. By targeting PRCAT71, this pathway of AR signaling can be inhibited, slowing PCa progression and improving CRPC patient survival.