

Investigating long non-coding RNAs as drivers of therapy resistance in prostate cancer

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Therapy resistance in prostate cancer (PCa) is primarily associated with alterations to the androgen receptor signalling pathway but can also be driven by other factors. One mechanism by which PCa progresses and acquires resistance is through altered expression of non-protein coding RNA transcripts called long non-coding RNAs (lncRNAs). lncRNAs regulate gene expression at the transcriptional and post-transcriptional levels via their ability to interact with and modulate activity of cellular proteins, RNA or DNA. A subset of lncRNAs are transcribed from cis-regulatory regions (CREs) such as enhancers or promoters and play important roles in cellular pathways through regulating host CREs.

In this project, we aimed to identify candidate lncRNAs and the mechanisms by which they drive therapy resistance in prostate cancer. To this end, we have analysed published prostate cancer datasets, comprising of cell lines and patient samples, to identify ~600 lncRNAs whose expression is altered in treatment resistance. These results were integrated with ChIP-seq datasets for H3K27Ac, a mark of active CREs, to identify ~200 CRE associated lncRNAs. Candidate lncRNAs identified by these methods were computationally validated in independent PCa patient datasets for association with disease progression. Currently, in-vitro validation work is being undertaken for two candidate CRE-associated lncRNAs – CEROX1 and COLCA1. We demonstrate that both lncRNAs are repressed by androgen stimulation and show that knockdown of these lncRNAs inhibits proliferation in PCa cell lines. Ongoing work aims to understand their mechanisms of action using transcriptomic and proteomic methods. This work will ultimately identify lncRNA associated pathways with potential for therapeutic targeting, laying the groundwork for more treatment options at advanced stages of PCa.

No conflicts of interest are reported.

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