48 Long noncoding RNA CRAT1 inhibits castration-resistance of prostate cancer via inhibiting androgen receptor protein translation

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Introduction & Objectives: Castration resistance is the main reason of metastasis and death in advanced prostate cancer patients. Androgen receptor (AR) signaling persistently activates in CRPC and plays pivotal role in the progression of the disease, but the mechanism is not fully understood. Emerging evidence reveals that lncRNAs may play an important regulatory role in cancer by acting as oncogenes or tumor suppressors. However, the roles of lncRNAs in CRPC remain elusive. In this study, a novel lncRNA-Castration Resistant Associated Transcription 1 (CRAT1) has been identified and explored in CRPC cells.

Materials & Methods: Firstly, we establish CRPC cell line model and investigate the CRPC associated lncRNAs by transcriptome microarray. The expression and clinical features of lnc-CRAT1 are analyzed in three independent large-scale cohorts. The functional role and mechanism of lnc-CRAT1 are further investigated by gain and loss of function assays in vitro and in vivo.

Results: Lnc-CRAT1 is significantly down regulated in CRPC cells and cancer tissues, and correlates with tumor stage, Gleason score and prognosis. Moreover, lnc-CRAT1 markedly inhibits proliferation, castration-resistance and tumor growth of CRPC cells both in vitro and in vivo. Mechanistically, lnc-CRAT1 directly recruits hnRNPK to 5'UTR region of AR mRNA and repress AR protein translation, leading to AR signaling inactivation. Either deletion the hnRNPK binding site in lnc-CRAT1 or knockdown hnRNPK abolishes the repression role of lnc-CRAT1 on AR and its signaling.

Conclusions: As a novel regulator, lnc-CRAT1 plays an important tumor suppressor role in CRPC cells proliferation and castration-resistance, contributing to weak tumorigenesis and enhanced castration-sensitivity. The lnc-CRAT1-hnRNPK-AR regulatory axis may represent a therapeutic target for clinical intervention in castration-resistance prostate cancer.