Inhibition of Deubiquitinating Enzyme USP7 : A potential therapeutic strategy for prostate cancer

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The androgen receptor (AR), a nuclear receptor superfamily transcription factor, plays a key role in prostate cancer. AR signaling is the principal target for prostate cancer treatment, but current androgen-deprivation therapies (ADT) cannot completely abolish AR signaling owing to the heterogeneity of prostate cancers. Therefore, unraveling the mechanism of AR reactivation in androgen-depleted conditions can identify effective prostate cancer therapeutic targets. Increasing evidence indicates that AR activity is mediated by the interplay of modifying/demodifying enzymatic co-regulators. To better understand the mechanism of AR transcriptional activity regulation, we used antibodies against AR for affinity purification and identified the deubiquitinating enzyme ubiquitin-specific protease 7 (USP7) as a novel AR co-regulator in prostate cancer cells. We showed that USP7 associates with AR in an androgen-dependent manner and mediates AR deubiquitination. Sequential ChIP assay indicated that USP7 forms a complex with AR on androgen-responsive elements (AREs) of target genes upon stimulation with the androgen 5- α -dihydrotestosterone (DHT). Further investigation indicated that USP7 is necessary to facilitate and maintain androgen-activated AR binding to chromatin. Transcriptome profile analysis of USP7-knockdown LNCaP cells also revealed the essential role of USP7 in the expression of a subset of androgen-responsive genes. Hence, inhibition of USP7 represents a compelling therapeutic strategy for the treatment of prostate cancer.