A Somatically Acquired Enhancer of the Androgen Receptor Is a Noncoding Driver in Advanced Prostate Cancer

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Androgen targeted therapies remain the most effective therapy for prostate cancer making the androgen receptor (AR) a critical therapeutic target. We know from the success of potent second generation antiandrogens that acquired resistance is mediated through restoration of androgen signaling by multiple mechanisms including genomic amplification of the AR locus, which occurs in approximately 60% of castrate resistant prostate cancer (CRPC). In addition to the AR gene itself, we discovered that the amplicon frequently involves a noncoding region located several hundred kilobases centromeric to the transcriptional start site of AR. ChIP-seq performed in patient samples revealed the presence of an active enhancer in metastatic CRPC but not in localized prostate cancer. Chromosomal conformation capture in LNCaP cells demonstrate interaction of the enhancer with the AR promoter. We used a genome editing approach to systematically interrogate the region and confirmed that the enhancer regulates AR expression and AR-dependent proliferation. Moreover, addition of a second copy of AR enhancer in LNCaP cells resulted in increased proliferation at low concentrations of androgen and decreased sensitivity to enzalutamide, consistent with a castration-resistant phenotype. We hypothesize that epigenetic activation of the enhancer and subsequent genomic amplification occurs in response to the selective pressure exerted by androgen targeted therapies. These results suggest potential new opportunities for targeting AR in advanced prostate cancer.

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