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

David Y. Takeda,1,2 Sandor Spisak,1,3 Ji-Heui Seo,1,3 Connor Bell,1 Edward O’Connor,1 Keegan Korthauer,4,5 Dezso Ribli,6 Istvan Csabai,6 Norbert Solymosi,7 Zoltan Szallasi,8,9,10 David R. Stillman,1 Paloma Cejas,3 Xintao Qiu,3 Henry W. Long,1,3 Viktoria Tisza,1,8 Pier Vitale Nuzzo,1,11 Mersedeh Rohanizadegan,1,12 Mark M. Pomerantz,1 William C. Hahn,1,2 and Matthew L. Freedman1,2,3

1Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
2The Eli and Edythe L. Broad Institute, Cambridge, MA 02142, USA
3Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, MA 02215, USA
4Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA
5Department of Biostatistics & Computational Biology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
6Department of Physics of Complex Systems, ELTE Eotvos Lorand University, Pazmany P. s. 1A, Budapest 1117, Hungary
7Centre for Bioinformatics, University of Veterinary Medicine, Istvan str. 2, Budapest 1078, Hungary
8Computational Health Informatics Program (CHIP) Boston Children’s Hospital Harvard Medical School, Boston, MA 02215, USA
9Danish Cancer Society Research Center, Strandboulevarden 49, 2100 Copenhagen, Denmark
102nd Department of Pathology, MTA-SE NAP, Brain Metastasis Research Group, Hungarian Academy of Sciences, Semmelweis University, Budapest 1091, Hungary
11Department of Internal Medicine, School of Medicine, University of Genoa, Genoa, Lgo R. Benzi 10, 16132, Italy
12Division of Genetics and Genomics, Boston Children’s Hospital, Boston, MA 02115, USA

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.

Conflicts of Interest: None

Funding Acknowledgements:
Prostate Cancer Foundation Challenge Award, NIH (R01GM107427, R01CA193910, K08CA218530, R01HG005220, U01CA176058), National Research, Development and Innovation Fund of Hungary Project, Novo Nordisk Foundation Interdisciplinary Synergy Programme, European Social Fund, Breast Cancer Research Foundation, Rebecca and Nathan Milikowsky, and H.L. Snyder Medical Research Foundation.