A PRC2 Independent role of EZH2 in Androgen Receptor Signaling in Prostate Cancer

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Background: Prostate cancer is the most frequently diagnosed cancer and third most frequent cause of cancer deaths in US males. Prostate cancer patients have benefitted from androgen deprivation therapy and small molecular inhibitors targeting androgen receptor (AR). However, 30% of patients have primary resistance to both forms of treatment with a majority of patients eventually developing resistance to these therapies and progressing from androgen dependent prostate cancer (ADPC) to castration resistant prostate cancer (CRPC). Unfortunately, there are no effective therapeutic options available for CRPC patients, so novel and more effective therapeutic strategies for CRPC are urgently needed. Enhancer of Zeste 2 (EZH2) is a well-characterized oncogene that is one of the most highly upregulated genes in aggressive PCa and suggested as a prognostic biomarker. EZH2 is a part of polycomb repressive complex2 (PRC2) with embryonic ectoderm development (EED) and suppressor of zeste 12 (SUZ12) to function as a repressor through the SET domain, especially Histidine 689 to methylate H3K27. Recently, some studies suggest a context-dependent or PRC2 independent function of EZH2, but new functional role of EZH2 in cancer that are yet to be delineated.

Methods: First, we utilized siRNA or shRNA gene editing methods to knock down endogenous EZH2 in both ADPC and CRPC cells to examine the effects of EZH2 in AR and its target genes. Second, we utilized ChIP sequencing, RNA sequencing and CRIPSR technique to further demonstrate the role of EZH2 in AR transcriptional networks. Further, catalytic inhibitors of EZH2 and catalytic dead EZH2 mutant were utilized to demonstrate the PRC2 independent role of EZH2 in AR regulation. Lastly, we performed in-vivo mouse Xenograft experiments to demonstrate the combination of small molecule inhibitors targeting EZH2 and AR that showed synergistic effects in the inhibition of CRPC progression.

Results: In the present study, we demonstrated that EZH2 enhances AR signaling through direct AR promoter occupancy at exon1, independent of its histone methyltransferase activity. EZH2 has a dual role as a transcriptional activator mediated by AR and an epigenetic silencer mediated by H3K27me3. Therefore, simultaneously targeting EZH2 and AR by drug inhibitors, EPZ6438 and enzalutamide (Enz), respectively, leads to synergistic cell growth inhibition in CRPC.

Conclusion: Taken together, our data reveal a dual function of EZH2 in PCa as a transcriptional activator and an epigenetic silencer. We believe that this study provide not only a novel function of EZH2 in the regulating AR signaling pathway but also provide novel therapeutic strategies for advanced prostate cancer which currently has no therapeutic options available.

Conflict of Interest: No potential conflicts of interest were disclosed.

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