DPP4 and HER2-Mediated Mechanisms of Resistance to Androgen Deprivation Therapies in Advanced Castration-Resistant Prostate Cancer (CRPC)

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Background: In an effort to identify additional drivers of AR and pro-survival signaling in advanced castration-resistant prostate cancer (CRPC), we have developed an androgen deprivation therapy (ADT)-resistant PCa model system that consists of a VCaP xenograft resistant to long-term combined therapy with abiraterone (Abi) plus enzalutamide (Enza) (AER VCaP xenograft). Our initial work has focused on leveraging RNA sequencing and protein level data generated from the AER VCaP xenograft in combination with sequencing data generated in our laboratory from ADT-resistant clinical PCa samples to identify and further interrogate mechanisms of ADT resistance. Combining the data we have identified several potential mechanisms of resistance to ADT including decreases in the growth factor-degrading dipeptidase DPP4 and increases in HER2 signaling.

Methods: VCaP xenografts were generated from cultured VCaP cells transplanted into mice. Tumors were serially biopsied prior to castration (Pre-Cx), at tumor relapse (CRPC), and following tumor relapse on combined Abi/Enza therapy (AER). Biopsies were submitted for RNA sequencing, followed by RT-PCR, immunohistochemical, and reverse-phase protein array (RPPA) validation of gene/protein expression changes. For sitagliptin studies, mice carrying xenografts were castrated and immediately provided daily sitagliptin or vehicle in drinking water. For kinase inhibitor studies, mice with castration-resistant xenografts were treated with daily intraperitoneal injection of afatinib or lapatinib.

Results: The AER VCaP xenograft model is resistant to long-term combined therapy with Abi plus Enza as indicated by continued tumor growth and continued expression of AR target genes. RNA sequencing of tumor serial biopsies and comparison to Pre-Post ADT clinical datasets have identified downregulation of the dipeptidase, DPP4, in resistant tumors. Downregulation of the AR-regulated DPP4 occurs despite reconstitution of AR signaling in the resistant tumors. DPP4 is known to degrade numerous growth factors and cytokines. Inhibition of DPP4 activity by sitagliptin leads to faster relapse of xenograft tumors post-castration. AER VCaP xenografts also exhibit increased HER3/HER2 signaling and increased expression of a constitutively-active splice variant of HER2 lacking exon 16, d16HER2. Treatment of castration-resistant xenograft models with the irreversible HER2 inhibitor afatinib is more effective at inhibiting tumor growth then the reversible inhibitor lapatinib.

Conclusions: These results suggest that CRPC utilizes multiple methods to enhance growth factor/cytokine signaling through receptor kinases as a mechanism of ADT resistance. DPP4 downregulation likely results in increased growth factor/cytokine availability and DPP4 inhibition results in faster tumor relapse. Significantly, DPP4 inhibitors are widely used to treat Type II diabetes and the interaction of DPP4 inhibitors with ADT treatment are not yet known. Tumors with upregulated HER2 signaling (possibly d16HER2-driven) respond better to irreversible inhibitors such as afatinib. HER2 might still be a viable target in the CRPC setting with the use of more effective HER2 inhibition or better patient selection.

Conflicts of Interest: The authors declare no conflicts of interest.

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