COOPERATIVE ACTIONS OF A NOVEL ERβ LIGAND, OSU-ERB-12, AND ENZALUTAMIDE IN ADVANCED PROSTATE CANCER

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Prostate cancer (PCa) is the most widely diagnosed cancer contributing to approximately 10% of all cancers diagnosed in the United States every year. Initially, PCa is dependent on the androgen hormone to drive tumor progression through activity of the androgen receptor (AR). At this stage surgery for example can be curative but if tumor re-emerges, androgen deprivation therapy (ADT) is applied but this inevitably leads to tumor resistance and a more aggressive and fatal disease (ADT-RPCa). Early on in development of therapeutics for PCa, estrogens were used with success, but the treatment was discontinued due to the adverse side-effects. It is now known that there are two different estrogen receptors that stimulate distinct cellular pathways; estrogen receptor alpha (ERα) leads to promotion of cell proliferation while estrogen receptor beta (ERβ) leads to cell differentiation and pro-apoptotic cell states. The OSU Drug Development Institute has developed a novel compound, OSU-ERb-12, that can selectively target ERβ, allowing for the possibility to study the effects of ERβ in ADT-RPCa cell lines on tumor cell suppression. We undertook a high-throughput viability screen to identify drugs that co-operate with OSU-ERb-12, and revealed a strong interaction with the ADT drug, Enzalutamide (ENZA). We hypothesize that that OSU-ERb-12 can augment ENZA to form a potent therapy for advanced PCa. To investigate this interaction further, RNA-Seq, cell cycle and apoptosis assays were performed in the PCa cell line 22RV1 with OSU-ERb-12 alone or in combination with ENZA. The RNA-Seq analysis revealed that the combination of OSU-ERb-12 with ENZA led to a significant global down regulation of genes including key AR target genes such as KLK3, TMPRSS2, NKX3-1 as well as MYC; indeed GSEA analyses identified significant enrichment of MYC genes in the repressed gene signature. To investigate if the MYC repression was seen at protein level, we dosed 22RV1 cells with OSU-ERb-12 alone or in combination with ENZA for 24hrs and collected nuclear lysates for Western immunoblot analysis, which revealed that only the combination of OSU-ERb-12 with ENZA led to reduction in c-Myc protein versus either drug alone. In conclusion, the genomic analyses have revealed that effects of OSU-ERb-12 with ENZA involve repression of an AR transcriptome including c-Myc repression. Others have previously established that AR repression of c-Myc occurs in normal prostate epithelial cells to drive differentiation. The current finding suggests that OSU-ERb-12 can restore normal AR-mediated differentiation in advanced PCa. Ongoing studies are applying a CRISPR-editing approach to label the ERβ and then undertake AR and ERβ ChIP-Seq to test their interactivity.