

B11

Title: Androgen deprivation therapy (ADT) induces transcriptional changes in prostate cancer cells to exhibit stem-like features

Author(s): Shiv Shankar Verma

Affiliation: Research Associate

Background

Clinical data suggest that 30% of prostate cancer patients administered with anti-androgen drug enzalutamide acquire resistance. However, the molecular mechanisms underlying this resistance remain unknown. To improve drug efficacy, current research is aimed to understand the molecular mechanism(s) of drug resistance in prostate cancer.

Methods: We employed NGS using paired enzalutamide-sensitive and resistant human prostate cancer LNCaP and C4-2B cells. The NGS data determine the global transcript pattern of differentially expressed genes. The results were validated using qRT-PCR, western blot, IHC, and mapping the signature signaling and identified pathways associated with the acquisition of drug resistance.

Results: RNA-Seq analysis of LNCaP and C4-2B cells exhibit 35504 expressed genes, 9409 genes were differentially expressed (DEGs) identified in LNCaP enzalutamide resistant cells (NCBI-GEO accession GSE150807), 3027 expressed genes, and 7757 DEGs were identified (NCBI-GEO accession GSE151083) in C4-2B enzalutamide resistant cells. The analysis revealed that genes associated with cancer stem cells such as ALDH1, BMI1, BMP2, CD44, NANOG, POU5F1 (OCT4), POU6F1, SOX2, SOX8, and SOX9 were differentially upregulated in enzalutamide resistant cells. Amongst the pathways enriched in the enzalutamide-resistant cells were those associated with β -catenin, hedgehog, RUNX2, and molecules associated with elastic fibers. Further examination of a patient cohort undergoing ADT and its comparison with no-ADT demonstrated high expression of ALDH1, POU5F1, and SOX2 in ADT specimens, suggesting that they may be clinically relevant therapeutic targets.

Conclusion: Our approach identified that stem cell marker genes may be responsible for enzalutamide drug-resistant, and future putative therapeutic targets, demonstrating their translational significance.