Vitamin D Increases Sensitivity to Radiotherapy in Advanced Metastatic African American Prostate Cancer Cell Lines

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Background/Significance: Prostate cancer (PCa) disproportionately affects African American (AA) men, who experience higher incidence and mortality rates compared to European American (EA) men. Variations in the responsiveness of cancer cells to radiation therapy between these groups may impact treatment outcomes. Studies suggest AA men may have a lower response to radiotherapy than EA men, potentially affecting therapeutic efficacy. Vitamin D, a steroid hormone known for its anti-proliferative effects on PCa cells, could play a role here: data indicate that AA men are more likely to experience vitamin D deficiency, which may contribute to reduced radiotherapy sensitivity. The active form of vitamin D, $1\alpha,25(OH)_2D_3$, shows promise in enhancing radiosensitivity. Our study investigates how vitamin D modulates transcriptome profiles in advanced metastatic PCa cell lines derived from AA men. **We hypothesize that vitamin D will modulate signaling pathways involved in radiotherapy differentially in AA advanced metastatic PCa cell lines than EA advanced metastatic PCa cell lines.**

Methods: Whole-transcriptome analysis was performed using RNA sequencing (RNAseq) on MDA-PCa-2b, an AA PCa cell line, and 22RV1, a European American (EA) PCa cell line. Both were treated with the active vitamin D_3 metabolite, $1\alpha,25(OH)_2D_3$, and untreated controls were included for comparison. Bioinformatic and pathway enrichment analysis were conducted from RNAseq data to identify differential gene expressions between treated and untreated samples, pinpointing significant biological pathways that are impacted.

Results: RNA seq revealed significant gene expression changes in response to treatment, identifying 4,615 differentially expressed genes (DEGs) in MDA-PCa-2b and 479 DEGs in 22RV1 (FDR p value < 0.05). Hierarchical clustering heatmaps demonstrated clear separations between treated and untreated groups, indicating significant treatment effects on gene expression in both cell lines. Principal Component Analysis (PCA) confirmed the distinct transcriptomic changes following treatment. Volcano plots identified key DEGs, with TPD52L1 and MOSMO prominent in MDA-PCa-2b, and TMPRSS2 and CYP24A1 significant in 22Rv1. Venn analysis showed 245 overlapping DEGs, showing common response, while MDA-PCa-2b had 4,370 unique DEGs and 22Rv1 had 234, indicating cell line-specific responses. Pathway enrichment analysis identified IGF1R, PARP1, XRCC6, ATM, and XRCC5 as central mediators in radiosensitivity, with repression of IGF1R and ATM showing potential contributions to increased radiosensitivity in MDA-PCa-2b cells. This network analysis was not significant in the 22RV1 cell line.

Conclusions and Implications: In conclusion, we highlight differential radiosensitivity response of AA PCa cell lines to $1\alpha,25(OH)_2D_3$ treatment, with a distinctive gene network. Our study highlights potential treatment with $1\alpha,25(OH)_2D_3$ and therapeutics targets, such as IGF1R and ATM, to improve radiosensitivity in high-risk populations, thereby addressing and alleviating PCa disparities in AA men.

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