Prostate tumor-derived TNFα/TGFβ down regulate AR expression in the prostate cancer stroma through TAK1, NF-κB, and p38 signaling

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Background: The ability of stromal AR to secrete differentiation factors that act on the surrounding epithelial cells is a critical determinant of normal prostate gland formation. However, loss of stromal AR is associated with increasing Gleason grade and development of aggressive prostate cancer, resulting in less-differentiated tumors. The mechanisms that lead to stromal AR loss are unknown. In this study, we tested the hypothesis that tumor-secreted factors, such as TGFβ and TNFα, are responsible for AR repression through NF-κB activation.

Methods: Using benign human immortalized prostate stroma cells (BHPrs1) as a model, the mechanistic downregulation of AR was examined. Using cytokine array profiling, we identified TNFα and TGFβ1 as two major factors secreted by two different PCa cell lines, C4-2 and 22RV1. RT-qPCR, immunoblotting, pharmacological inhibitors and shRNA knock-down were utilized to identify the TNFα/TGFβ-mediated signaling pathways contributing AR downregulation.

Results: Treatment of BHPrs1 cells with TNFα or TGFβ leads to loss AR expression within 18-24 hours. This was accompanied by a parallel loss of AR mRNA. TNFα-treated cells showed a time and concentration-dependent activation of NF-κB, TAK1, p38-MAPK, and Jnk, which peaked at 18-24hr. Inhibitors of TAK, p38, and NFκB, but not Jnk, blocked the ability of TNFα to downregulate AR expression. These data indicate that the activation of p38-MAPK and NF-κB via TAK1 are involved in suppressing AR expression in response to TNFα. Future experiments will determine if TGFβ uses the same pathways and whether NF-κB and ATF1 binding sites on the AR promoter are involved.

Conclusion: These results show that there are two pathways downstream of TAK1, p38 and NF-κB, that are responsible for suppressing AR expression in the prostate cancer stroma. Future experiments will explore the significance of these findings in the context of disease.