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Control of Androgen Signaling and Metastasis by CARF in Prostate Cancer

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Background: Prostate cancer (PCa) is a leading cause of cancer-associated death among men worldwide. Although localized prostate cancer can be cured by surgery and radiation therapy, metastatic PCa remains a challenge. Androgen therapy (ADT) and androgen signaling inhibitors are the first line of therapy against PCa. However, resistance against these treatments develops, leading to the emergence of castration resistance prostate cancer (CRPC). Studies are required to identify the pathways that contribute to the emergence of CRPC and identify pharmaceutical targets. CARF is a putative transcription regulator reported to play a pivotal role in different cancers, including breast cancer and hepatocarcinoma. We observed that CARF is highly expressed in prostate tumors, but the biological function of CARF in PCa is unknown yet. **Methods:** We performed RNA seq, RT-PCR, and western blot (WB) analyses to show how knockdown of CARF affects the global gene expression in PC3 cells. Gene sort enrichment analysis (GSEA) and Ingenuity Pathway Analysis (IPA) of differentially expressed genes were done to identify the cellular pathways affected upon silencing of CARF. Scratch assay and trans-well migration assay were conducted to show how CARF overexpression influences the motility of the cells. The effect of CARF on PC3 cells growth and proliferation was evaluated by colony-forming and MTT assays. In addition, we analyzed patient datasets to show the relevance of CARF expression, androgen signaling, and epithelial-mesenchymal transformation (EMT) pathways in PCa.

Results: The silencing of CARF inhibited the growth and proliferation of PC3 cells, suggesting the necessity of CARF for PC3 growth and survival. In agreement, overexpression of CARF enhanced the PC3 cells proliferation. We found that silencing of CARF reduced PC3 cells motility in trans-well assay. Mechanistically, RNA seq analysis after CARF knockdown uncovered that gene of AR signaling and EMT pathways were significantly altered in PC3 cells. RT-PCR and WB data confirmed that silencing of CARF enhanced E-cadherin expression and reduced the expression of N-cadherin in PC3 cells, suggesting that CARF regulates EMT in PCa. Silencing of CARF altered the AR-regulated metastatic genes expression in PC3 cells. Our data revealed that the expression of PMEPA1, a negative regulator of metastasis, was increased, but the expression of SGK1, an inducer of EMT, was decreased in CARF cells. Furthermore, CARF could regulate the prostaglandins metabolism by suppressing the expression of HGPD1 and triggering inflammation and angiogenesis in prostate cancer. **Conclusion:** We conclude that by controlling the AR and EMT signaling pathways, CARF may play a crucial role in the development of metastatic CRPC. Future studies by integrating the RNA seq and Chip-Seq will uncover how CARF regulates the AR and EMT signaling pathways contributing to the development and progression of CRPC and paving a way to find a target for intervention.

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