OVERCOMING RESISTANCE TO NK-MEDIATED LYSIS IN ENZALUTAMIDE-RESISTANT PROSTATE CANCER CELLS

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Background

Enzalutamide, a next-generation hormonal agent, is approved for the treatment of metastatic castration-resistant prostate cancer (CRPC). Although treatment with enzalutamide results in initial clinical benefit in men with CRPC, resistance to therapy and disease progression are ultimately observed in the majority of patients. Several mechanisms of resistance have been described in this context, including reactivation of androgen receptor (AR) signaling via gene amplification, splice variants or mutations, activation of the glucocorticoid receptor (GR), and tumor cell plasticity. Our laboratory and others have shown that tumor cell plasticity, a phenomenon characterized by the acquisition of mesenchymal markers and the loss of epithelial features by carcinoma cells, can drive tumor resistance to immune effector cell lysis; however, the link between enzalutamide resistance, tumor cell plasticity, and resistance to immune-mediated lysis has not been yet investigated. In this study, we interrogated enzalutamide-resistant prostate cancer models for their susceptibility to NK-mediated cell lysis, and evaluated approaches to enhance immune-mediated lysis of prostate cancer cells that are resistant to enzalutamide.

Methods

Models of enzalutamide-resistant prostate cancer were developed by long-term exposure of LNCAP and MDA-PCa 2b human prostate cancer cells to enzalutamide in culture. Resistant and parental cells were comparatively evaluated for phenotypic features via RT-PCR, ELISA, western blot, immunofluorescence, and RNAseq analysis. Sensitivity to NK-cell mediated cytotoxicity was evaluated with NK cells isolated from peripheral blood from healthy donors. Xenografts established in NSG MHC1/II-deficient mice were characterized for phenotypic markers and potential therapeutic targets.

Results

Our findings demonstrated that LNCAP and MDA-PCa 2b cells resistant to enzalutamide had acquired a phenotype consistent with the occurrence of an epithelial-mesenchymal switch. In addition, enzalutamide-resistant cells had significantly decreased sensitivity to NK cell-mediated lysis. RNAseq and PCR analyses demonstrated a significant upregulation of estrogen receptor alpha (ESR1) in enzalutamide-resistant cells. Treatment with fulvestrant, a selective estrogen receptor degrader (SERD) was able to increase sensitivity to NK killing while decreasing mesenchymal tumor features and increasing expression of epithelial E-cadherin. In vivo data confirmed the ability of fulvestrant to increase epithelial tumor features in LNCAP enzalutamide-resistant xenografts.

Conclusions

Our data indicates that blockade of estrogen receptor signaling in enzalutamide-resistant prostate cancer cells can revert mesenchymal tumor features resulting in increased sensitivity to immune attack. Future studies will evaluate combination of fulvestrant or other estrogen antagonists with NK-based immunotherapy in models of enzalutamide-resistant prostate cancer.