RESISTANCE TO ENZALUTAMIDE AND ABIRATERONE DRIVES TUMOR PHENOTYPIC PLASTICITY AND RESISTANCE TO IMMUNE-MEDIATED CYTOTOXICITY

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.727>

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Background Background: Treatment of patients with castration-resistant prostate cancer (CRPC) includes the use of next-generation hormonal therapies such as abiraterone or enzalutamide. Although these agents extend survival, a significant proportion of patients exhibit primary or acquired resistance to treatment. In recent years, immune checkpoint blockade has led to remarkable responses in patients with several tumor types, however, CRPC has remained resistant to immunotherapy. Previous studies have demonstrated that different tumor variants could emerge along the progression of prostate cancer, including tumors undergoing phenotypic plasticity in the context of an epithelial-mesenchymal transition. Our laboratory and others have shown that phenotypic plasticity is a driver of resistance to immunotherapy. Based on this knowledge, we investigated whether changes in tumor phenotype could affect the response of CRPC to immune-based therapies, and ways this can be mitigated.

Methods The androgen sensitive LNCAP prostate cancer cell line was used to derive LNCAP cells resistant to enzalutamide (LNCAP-EnzaR) or abiraterone (LNCAP-AbiR). Resistant cell lines and parental LNCAP cells were comparatively evaluated for features of EMT and neuroendocrine phenotype via RT-PCR, ELISA, western blot, immunofluorescence, and RNAseq. Changes in the susceptibility to NK-cell mediated cytotoxicity were evaluated with NK cells isolated from peripheral blood from healthy donors. LNCAP-EnzaR cells were also grown in vivo in NSG MHC-deficient mice, and tumors were characterized for phenotypic markers and potential therapeutic targets.

Results Acquisition of resistance to both enzalutamide and abiraterone was associated with a significant increase in mesenchymal tumor features, including high levels of vimentin and fibronectin, and the loss of epithelial features and cell-to-cell attachments. LNCAP-EnzaR and LNCAP-AbiR cells showed a significant reduction (up to 90%) in susceptibility to NK-cell mediated cytotoxicity and antibody-dependent cell cytotoxicity (ADCC), compared with parental cells. These results prompted us to investigate approaches to improve immune-mediated lysis, including inhibition of estrogen receptor 1 (ESR1), which was identified as highly upregulated in LNCAP-EnzaR cells via RNAseq analysis. In a xenograft model of LNCAP-EnzaR cells, we corroborated the maintenance of tumor phenotypic plasticity and the expression of actionable targets.

Conclusions Our data indicates that acquisition of resistance to androgen receptor inhibition is associated with marked reduction of susceptibility to immune attack, and the acquisition of tumor phenotypic plasticity. Future studies will investigate approaches that revert tumor plasticity, including blockade of ESR1, TGF-beta or IL-8, for potential improvement of tumor susceptibility to immune attack in CRPC.

Ethics Approval PBMCs were obtained from healthy donors at the NIH Clinical Center Blood Bank (NCT00001846). All animal studies were approved and conducted in accordance with an IACUC-approved animal protocol (LTIB-57) with the approval the NIH/NCI Institutional Animal Care and Use Committee.