Androgen receptor inhibition increases MHC Class I expression and improves immune response in prostate cancer

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Background: Immune checkpoint blockade (ICB) is a treatment option that has had limited success in prostate cancer patients. The major histocompatibility complex Class I (MHCI) plays a pivotal role in the adaptive immune response by presenting neo-antigens on the surface of cancer cells to CD8+ T cells. Prostate cancer cells have markedly lower expression of MHCI genes compared to immunoresponsive cancers. Loss of MHCI is also associated with more aggressive disease and immune evasion in prostate cancer. However, the mechanisms that control MHCI downregulation in prostate cancer are still unknown. We hypothesize that increasing MHCI expression in prostate cancer cells will increase antigen presentation and improve immunotherapy efficacy.

Methods: We employed a genome-wide, CRISPR interference (CRISPRi) flow cytometry-based screening approach to identify regulators of MHCI in prostate cancer cells. Significant gene hits involved in *AR* signaling were validated as suppressors of MHCI using *in vitro* and *in vivo* models. We validated these observations in four phase II clinical trials and identified a mechanism by which *AR* transcriptionally represses MHCI gene expression.

Results: Gene knockdown of *AR, GRHL2*, and *FOXA1*, as well as treatment with *AR* inhibitors, significantly increased MHCI expression over time in *AR*-positive but not *AR*-negative cell lines. Mechanistically, elimination of androgen response elements upstream of MHCI processing and presentation gene transcriptional start sites also increased MHCI expression, indicating a role for transcriptional repression in *AR*'s regulation of MHCI. Increased MHCI expression due to *AR* inhibition also increased antigen presentation and T cell response in co-culture *in vitro* models. These results were replicated *in vivo* using an *AR*-deficient TrampC1 model which showed increased MHCI expression, increased CD8 T cell tumor infiltration and TCR engagement, and decreased tumor growth compared to wild-type tumors. Within the clinical trials we analyzed, we demonstrated that *AR* and MHCI expression are inversely correlated in multiple disease stages of prostate cancer. Importantly, low *AR* and high MHC expression showed improved response to ICB treatment in a subset of mCRPC patients.

Conclusions: Overall, our data show that *AR* suppresses MHCI expression in prostate cancer, and that androgen-targeted therapies can increase expression of these antigen presenting proteins to improve immune cell recognition. By understanding how *AR* regulates MHCI expression, we can better identify the optimal time and subset of patients that would benefit from combination treatments utilizing *AR* signaling inhibition and immunotherapy, to improve anti-cancer responses.

Conflicts of Interest: Lisa Chesner has no conflicts of interest to disclose.

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