Uncovering Compensatory Innate Immune Checkpoints to Target Aggressive Variant Prostate Cancer

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Background

Aggressive Variant Prostate Cancer (AVPC) occupies over 20% of metastatic Castration-Resistant Prostate Cancer (mCRPC). This highly lethal subtype is characterized by rapid resistance to androgen receptor pathway inhibitors (ARPIs) and multiple alterations among the PTEN, RB1, and TP53. Alternatives to targeted therapies, such as T cell-based immunotherapy, need to be considered. However, prostate cancer has a "macrophage-rich, T cell-poor" tumor microenvironment and responds poorly to T cell-based immunotherapies. Consequently, attention has shifted to tumor-associated macrophages (TAMs), such as CD47-targeted immunotherapy, which blocks a 'don't-eat-me' phagocytic signal on cancer cells. While this innate immune checkpoint strategy shows promise in tumors with abundant macrophages but scarce T cells, clinical outcomes remain modest. We hypothesized that the resistance to the innate immune checkpoint strategy is likely driven by alternative immunoregulatory pathways within the TME, yet these compensatory circuits remain poorly defined.

Methods

We modeled the dominant AVPC genetic alteration using murine prostate organoids subjected to double CRISPR knockout ($Pten^{KO}/Trp53^{KO}$), in comparison to the less common $Rb1^{KO}/Trp53^{KO}$, which undergoes cell-intrinsic neuroendocrine transdifferentiation. These organoids were injected subcutaneously into syngeneic immunocompetent FVB mice, resulting in AVPC tumor development. They were then treated with a combination of degarelix and apalutamide (as ARPI). RNA was extracted from both the pre-injected organoids and the corresponding AVPC tumors for further single-cell RNAseq (scRNAseq) analysis. An additional $Pten^{KO}/Trp53^{KO}/Cd47^{KO}$ organoid was injected to model mono-CD47 inhibition.

Results

The scRNAseq analysis indicated that prostate organoids upregulate Cd47 upon CRISPR-mediated $Pten^{KO}/Trp53^{KO}$, and this is maintained following injection and AVPC tumor formation. Macrophages were the dominant immune cell type in all AVPC tumors, but ARPI-treated $Pten^{KO}/Trp53^{KO}$ tumors were dominated by M2-like macrophage subpopulations enriched with Sirpa, the receptor for Cd47. The additional $Cd47^{KO}$ in the $Pten^{KO}/Trp53^{KO}$ background substantially reduced tumor penetrance *in vivo* to only 50% of injections. The cell-cell interaction analysis revealed that Apoe/Clu-Trem2 interactions (AVPC cancer cells: M2 macrophages) are characteristic ligand-receptor pairs in $Pten^{KO}/Trp53^{KO}$ tumors.

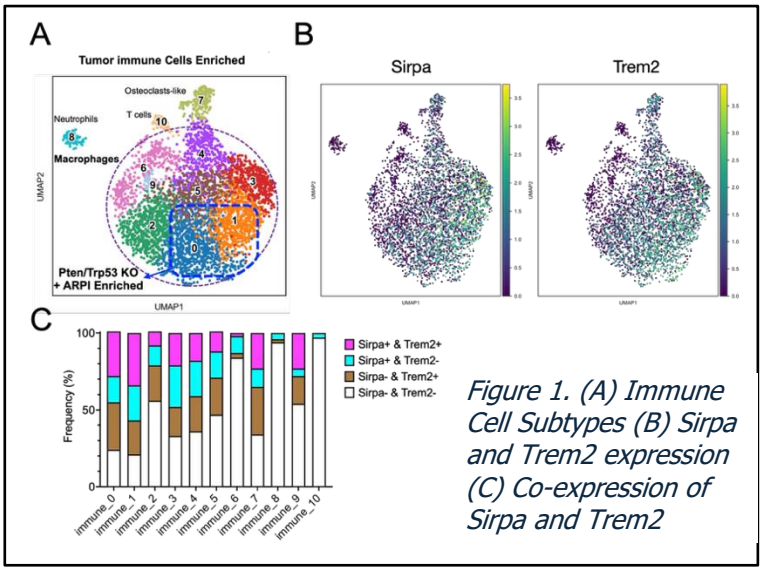

Figure 1. (A) Immune Cell Subtypes (B) Sirpa and Trem2 expression (C) Co-expression of Sirpa and Trem2

Conclusions

ARPI-resistance in the most frequent AVPC subtype ($Pten^{KO}/Trp53^{KO}$) is associated with two signals regarding cancer cell-macrophage communications. The AVPC cancer cells exhibit increased 'don't eat me' signal through Cd47 overexpression, accompanied by an enrichment of $Sirpa^{high}$ macrophages under ARPI-resistant conditions with high Trem2 expression. Therefore, dual targeting of Cd47-Sirpa and Trem2 signaling axes may provide a strategy to overcome the high lethality of AVPC patients.

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Conflicts of Interest Disclosure Statement

The authors have no conflicts of interest to disclose.