

Resistance to CD47-directed Macrophage Immunotherapy Identifies TREM2 as a Rationale for Dual Macrophage Checkpoint Blockade in Lethal Prostate Cancer

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Background

Macrophage-directed immunotherapy has re-emerged as a promising strategy in solid tumors. Although first-generation CD47-directed therapies showed limited clinical activity and were hindered by on-target hematologic toxicity, recent studies with the high-affinity SIRPα fusion protein “evorpacept” suggest that tumor CD47 expression may serve as a predictive biomarker, renewing interest in CD47-directed therapy. Whether CD47-directed therapy will be effective in prostate cancer, a macrophage-rich, T cell-poor malignancy, and what mechanisms may limit response remain unknown. We sought to define macrophage immunoregulatory pathways in aggressive variant prostate cancer (AVPC) that could mediate resistance to CD47-directed therapy.

Methods

We analyzed human bulk transcriptomic cohorts spanning normal prostate through metastatic castration-resistant disease and reanalyzed two independent human single-cell RNA sequencing datasets. In parallel, we developed immunocompetent genetically engineered AVPC organoid models (Pten/Trp53 or Rb1/Trp53 loss) treated with androgen receptor pathway inhibition (ARPI) and profiled tumors by single-cell RNA sequencing. CD47 knockout studies combined with lentiviral clonal barcoding were used to define mechanisms of immune escape following CD47 loss.

Results

Across human cohorts, macrophages progressively replaced T cells as the dominant immune population as disease advanced, while genomically defined AVPC was enriched in metastatic tumors and associated with significantly worse overall survival. The mouse models reproduced this macrophage-dominant tumor microenvironment. Following ARPI, *Pten*/Trp53-loss tumors demonstrated marked increases in immune infiltration and macrophage abundance, whereas neuroendocrine *Rb1*/Trp53-loss tumors did not. CD47 expression increased progressively along the malignant trajectory, and ligand-receptor analysis confirmed active tumor-to-macrophage CD47-SIRPα signaling. Despite this, CD47 loss prevented tumor formation in only half of the mice, and clonal barcoding demonstrated convergent immune escape rather than stochastic resistance, consistent with selection of a shared CD47-independent resistance program. Analysis of macrophage populations in ARPI-treated *Pten*/Trp53-loss tumors found expansion of a TREM2+ subset. As TREM2 expression is associated with a lack of productive immune response, we hypothesize that TREM2+ tumors suppress T cell activation in the context of CD47 loss.

Conclusions

Advanced prostate cancer is characterized by a conserved macrophage-dominant immune microenvironment in which CD47 signaling is progressively induced during tumor evolution. However, genetic disruption of CD47 alone provides only partial protection, revealing adaptive macrophage resistance programs. Our findings identify TREM2 as a leading compensatory pathway operating within the same macrophage population engaged by CD47-SIRPα signaling. Together with emerging clinical evidence supporting CD47 expression as a predictive biomarker for macrophage-directed immunotherapy, these findings provide a mechanistic rationale for dual CD47/TREM2 blockade as a therapeutic strategy for lethal prostate cancer.

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Conflicts of Interest Disclosure Statement

The authors have no conflicts of interest to disclose.

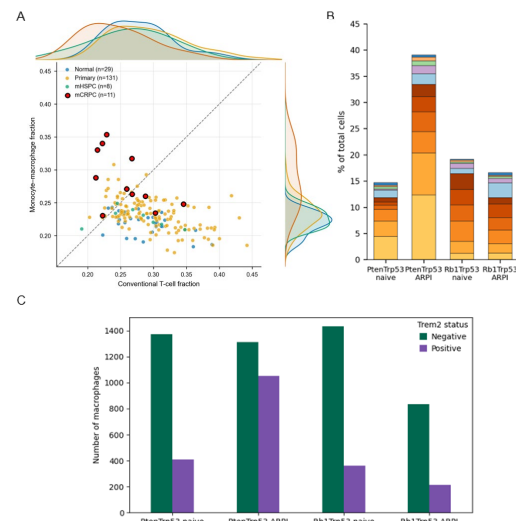


Figure 1: A) Prevalence of immune cell fractions across human prostate cancer cohorts B) Immune cell type fractions in Pten;Trp53 and Rb1;Trp53 null murine tumors C) Quantification of TREM2+ macrophages across tumor subtypes