Myeloid Cell Regulation in Patients with Advanced Prostate Cancer treated with Bipolar Androgen Therapy

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Background: Prostate cancer patients acquire resistance to standard-of-care strategies resulting in 350,000 yearly deaths. As acquired resistance is mediated by increased androgen receptor (AR) expression, "Bipolar Androgen" therapy (BAT) is being developed to cycle serum testosterone from supraphysiological to near-castrate levels, maximizing toxicity to high and low AR-expressing cells respectively. BAT is a clinically effective, safe and unique approach to treat castration-resistant prostate cancer (CRPC) patients that improves quality of life, produces biochemical and objective responses, and re-sensitizes tumors to AR inhibitors. We previously demonstrated that patients who benefited most from BAT have an enriched inflammatory transcriptional signature in tumors. Thus, despite its conception as a "targeted" therapy, consideration for BAT's effects on the immune system appears critical for success.
Methods: To capitalize on this unappreciated potential we examined immune cells from peripheral blood mononuclear cells (PBMCs) and tumor biopsies before and after BAT, using spectral flow cytometry, single cell RNA sequencing and spatial transcriptomics.
Results: The effect of BAT on immune cells is associated with therapeutic response. The fraction of CD4 and CD8 T cells in PBMCs was significantly decreased in non-responding (NR) patients following BAT, with a concomitant increase in Basophils, suggesting a skewed immune response in these patients. Moreover, the fraction of non-classical monocytes (NCM) was increased in all patients following BAT, with a phagocytic transcriptional (*C1QB*, *C1QA*, *MSR1*) program induced exclusively in NR patients. Intriguingly, classical monocytes (CM) display enhanced expression of Type I IFN response genes (*IFIT3*, *IFIT2*, *ISG15*, *IFI44L*, *EGR1*) only in NR patients. As CM likely infiltrate tumors, we examined how monocyte tumor engraftment was impacted by BAT. Using spatial transcriptomics we found that macrophages in NR patients have increased Type I IFN gene expression closer to the tumor core, suggesting a connection with our observations in CM. Concomitantly, CD8 T cells in the tumor of responding patients displayed enhanced IFN gamma transcriptional signatures consistent with improved tumor control. Interestingly, we observed that stromal cells at tumor cores of NR patients had a transcriptional profile consistent with exposure to type I IFNs.
Conclusions and outlook: We found that BAT reprograms circulating monocytes, conferring a Type I IFN signature that is mirrored by macrophages in tumors from patients with poor therapeutic responses. Moreover, we observed evidence of Type I IFN exposure in stromal cells. Conversely, therapeutic response was associated with enhanced cytotoxic T cell activation. Collectively, our findings suggest that Type I IFN, which has been associated with resistance to other cancer therapies, could play an important role in limiting immune control of prostate cancer following BAT. Critically, BAT reprograms tumor immunity and our results provide an attractive target to improve therapeutic efficacy in the design of future clinical trials.

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