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 progressing to advanced disease and 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. Data from a recent clinical trial (NCT03554317) shows that prostate tumor cells produce inflammatory cytokines following BAT, and patients who benefited most from this therapy 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 and bridge the gap between patients who benefitted or not from this novel strategy, we set out to define the changes in immune cells from patient peripheral blood mononuclear cells (PBMCs) and in tumor biopsies before and after treatment with BAT. We used a combination of high-resolution high-throughput techniques including spectral flow cytometry, single cell RNA sequencing and spatial transcriptomics, then applied state of the art computational methods to extract meaningful insights from these samples.
Results: Our observations indicate that BAT skews the development of classical and non-classical monocytes in peripheral blood, which could impact the resulting infiltration and differentiation of these cells into macrophages in the tumors. The precedent in the literature that testosterone dampens the pro-inflammatory phenotype of macrophages, plus the critical role of the inflammatory response in controlling tumor growth following BAT, lead us to the hypothesis that changes in the myeloid compartment induced by BAT may restrict antitumor immunity leading to reduced therapeutic efficacy.
Conclusions and outlook: We are investigating transcriptional signatures in myeloid cells that are associated with therapeutic response and modeling monocyte tumor engraftment as these cells contribute to the immunosuppressive tumor microenvironment. This effort across the disciplines of computational biology, oncology, and myeloid cell biology, will build a detailed understanding of how BAT reprograms tumor immunity and determine if myeloid cell remodelling underpins resistance to BAT, thus providing a target to improve therapeutic efficacy in the design of future clinical trials.

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