EVOLUTION OF MYELOID-MEDIATED MECHANISMS OF IMMUNOTHERAPY RESISTANCE AT SINGLE-CELL RESOLUTION WITH HUMAN PROSTATE CANCER PROGRESSION

1Aram Lyu, 2Zenghua Fan, 3Diamond Luong, 1Aî Setayesh, 1Alex Starzinski, 1Ezieger Van Allen, 1Lawrence Fong, 1University of California San Francisco, San Francisco, CA, USA; 2Parker Institute for Cancer Immunotherapy, San Francisco, CA, USA; 3Dana-Farber Cancer Institute, Boston, MA, USA; 4Broad Institute of Harvard and MIT, Cambridge, MA, USA

Abstract

Patients with metastatic castration-resistant prostate cancer (mCRPC) are refractory to immune checkpoint inhibitors (ICIs). 1 2 Although prostate cancer is highly populated by multiple immunosuppressive myeloid cells especially after androgen deprivation therapy (ADT), 3 efforts to therapeutically target myeloid cells broadly have thus far failed clinically, potentially due to myeloid cell heterogeneity and complexity. 4 -5 Understanding the specific myeloid populations relevant in prostate cancer and the molecular mechanisms mediating immunosuppression is needed to improve the efficacy of immunotherapy in this disease.

Methods

We performed multi-omic single-cell RNA sequencing (scRNA-seq) on biopsies from prostate cancer patients with either ADT-naïve localized prostate cancer, metastatic hormone-sensitive prostate cancer on ADT, or mCRPC progressing on ADT. We also performed scRNA-seq on immune and non-immune cells isolated from a syngeneic mouse model of CRPC. Functional significance of specific myeloid populations was assessed with immune assays in vitro and tumor efficacy in vivo with this syngeneic model.

Results

We identified a specific population of tumor-associated macrophages expressing elevated SPP1 transcripts (SPP1 hi-TAMs) significantly enriched in mCRPC relative to earlier states of prostate cancer. This myeloid population expresses elevated levels of immunosuppressive molecular programs. 6 -8 Notably, CSF1R transcript levels were drastically diminished in SPP1 hi-TAMs relative to other macrophages, implicating this population as a potential mechanism underlying the clinical ineffectiveness of CSF1R blockade. We then utilized a syngeneic mouse model of CRPC to investigate the specific mechanisms by which SPP1 hi-TAMs mediate resistance to ICIs. Using scRNA-seq, we identified an analogous macrophage state and demonstrated their ability to suppress T-cell proliferation and activation in vitro. Administration of an anti-CSF1R antibody failed to ablate Spp1 hi-TAMs in CRPC, pointing to their immunosuppressive signals as potential immunotherapeutic targets. Adoptive transfer of Spp1 hi-TAMs into tumors promoted resistance to ICIs and worsened survival in vivo. Pathway analyses revealed enrichment of gene signatures associated with the adenosine pathway in SPP1 hi-TAM abundance and CD8+ T-cell exhaustion in tumors. Finally, pharmacologic inhibition of A2AR abrogated Spp1 hi-TAM-mediated immunosuppression on activated T cells in vitro.

Conclusions

Our studies demonstrate that as prostate cancer progresses, the abundance of SPP1 hi-TAMs increases. Furthermore, this myeloid population can mediate resistance to ICIs in mCRPC by activating adenosine signaling, supporting the relevance of therapeutically targeting of this pathway in this disease.

REFERENCES


http://dx.doi.org/10.1136/jitc-2023-SITC2023.0548