Single cell and spatial transcriptomics reveal tumor associated macrophages mediate prostate cancer progression and metastasis.

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Abstract

Tumor-associated macrophages (TAMs) are a transcriptionally heterogeneous population, and their abundance and function in prostate cancer is poorly defined. We integrated parallel datasets from single-cell RNA-sequencing, spatial transcriptomics and multiplex immunofluorescence to reveal the dynamics of TAMs in primary and metastatic prostate cancer. Four TAM subpopulations were identified. Notably, one of these TAM subsets was defined by the co-expression of SPP1+ and TREM2+ and was significantly enriched in metastatic tumors. The SPP1+/TREM2+ TAMs were enriched in the metastatic tumor microenvironment in both human patient samples and murine models of prostate cancer. The abundance of these SPP1+/TREM2+ macrophages was associated with patient progression free survival. Spatially, TAMs within prostate cancer bone metastases were highly enriched within the tumor region, consistent with their pro-tumorigenic role. Hypothesizing that this TAM population was strongly immunosuppressive, we interrogated the effect of eradicating this population within the RM1 mouse model of prostate cancer. Using an antibody to transiently eliminate SPP1-expressing TAMs, we demonstrated that this approach improved the efficacy of anti-PD-1 treatment, and increased CD8 T cell infiltration within tumor. These findings suggest that targeting SPP1+ TAMs may offer a promising therapeutic strategy, and one that would enhance the effects of immune checkpoint inhibition (ICI) in advanced prostate cancer. This study expands our understanding of the diverse roles of macrophage populations in prostate cancer metastases and highlights new therapeutic targets.

Conflicts of Interest Disclosure Statement

D.B.S. is a co-founder and holds equity in Clear Creek Bio. The remaining authors declare that they do not have any competing interests.

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