Club-like cells and PIGR expression are associated with inflammatory high-risk, localized prostate cancer

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Background
Immunotherapy such has check-point inhibitors have transformed the treatment of many solid malignancies. Despite the advance in mechanistic understanding of treatment resistance, high-risk, localized prostate cancer are largely unresponsive towards immunotherapy. Interestingly, various publications have observed proportion of localized prostate cancer to be immunogenic that are unlikely to harbor microsatellite instability high or mismatch repair deficiency.
To better understand the mechanism of immunogenicity, we compared prostate specimens with high or low tumor infiltrating lymphocytes (TILs) using spatial transcriptomics in order identify the mechanism immune recruitment.

Methods
Patient cohort
Radical prostatectomy specimens from untreated, high-risk, localized prostate cancer patients obtained from the UCLA biobank were screened for intra-tumoral T-cell infiltration (TILs) by multiplex immunohistochemistry for immune and tumor cells. A total of four samples were selected and profiled using the 10X Visium platform for FFPE specimens. Validation were performed using OPAL multiplex immune-fluorescence (mxIF) staining for CD4, CD8A, CD68, PIGR (marker of club cells), and PSA on 18 specimens from a separate cohort of untreated, intermediate to high-risk localized prostate cancer.

Statistics
Spatial analysis were performed on Visium data after clustering and spatial deconvolution to identify cell types. Co-occupancy analysis were used to identify T-cell colocalization partners. Cell segementation were performed on mxIF images using HALO system. Spatial regression were performed on all stained images. All analysis were performed in R version 4.2.0.

Results
Spatial transcriptomic from four patients have identified myeloid cells and club cells to preferentially colocalize with T-cells. In areas of co-enrichment, interferon-gamma pathway and MHC-I were upregulated. MxIF confirmed the co-enrichment of T-cells with PIGR+ cells with CD4+ as the dominant population of T-cells. We observed PIGR to be expressed predominantly by benign or atrophic epithelium. Cancer can also express PIGR. Tumor PIGR are spatially associated with TILs. In-addition, pathological features, cribriform morphology and PTEN loss was associated with increased TILs.

Conclusions

We defined a subset of immunogenic localized prostate cancer that expresses PIGR either in benign epithelium or in tumor. The expression of PIGR is associated with TILs. The finding suggests the possible immune recruitment and activation by a non-conical pathway.

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Conflict of Interest
None