Tumor associated immune cell spatial heterogeneity in prostate cancer

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Introduction

Prostate cancer remains the second most common cancer in men. The lethality of metastatic castrate-resistant prostate cancer is powered by the lack of therapeutic approaches, including immunotherapy. Strategies to relieve immunosuppression mediated by myeloid-derived suppressor cells and tumor associated macrophages (TAMs) might be effective in patients with these tumors. Interestingly, levels of TAM infiltration were predictive for malignancy grade, tumor size and disease recurrence and are associated with extracapsular tumour extension in prostate cancer. Therefore, deep exploration of tumor associated macrophages, study of their context-dependent and spatial heterogeneity may uncover many aspects of this question.

Aim of Study

Our aim was to explore macrophage spatial heterogeneity and intensity in prostate cancer tissues and their association with pathological parameters.

Methods

47 formalin fixed paraffin embedded prostate cancer samples were stained with CD163, CD68 and CD204 antibodies by immunohistochemistry and statistically processed to find associations of different populations of macrophages with clinical and pathological data. Web based tools were used to identify prostate cancer associated macrophage profiles using TCGA database.

Fig. 1. Prostate TAM populations, abundance of M2 type macrophages and negative or no association with M1 and M0 macrophages .

cancer	Macrophage EPIC	Macrophage TIMER	Macrophage XCELL	Macrophage M0 CIBERSORT	Macrophage M0 CIBERSORT-ABS	Macrophage M1 CIBERSORT	Macrophage M1 CIBERSORT-ABS	Macrophage M1 QUANTISEQ	Macrophage M1 XCELL	Macrophage M2 CIBERSORT
PRAD (n=498)	0.395	0.215	0.104	-0.119	0.005	0.218	0.476	0.081	0.127	-0.004

cancer	Macrophage M2 CIBERSORT-ABS	Macrophage M2 QUANTISEQ	Macrophage M2 XCELL	Macrophage M2 TIDE	Macrophage Monocyte MCP-COUNTER	Monocyte CIBERSORT	Monocyte CIBERSORT-ABS	Monocyte MCP-COUNTER	Monocyte QUANTISEQ	Monocyte XCELL
PRAD (n=498)	0.481	0.441	-0.057	-0.587	0.163	0.108	0.333	0.163	-0.13	0.118

Results

Immunohistochemical analysis demonstrated higher density of CD68+ monouclear phagocytes and CD163+ scavengers in prostate cancer adjacent stroma in comparison to benign prostate hyperplasia (both $p<0,05$). In previous experiments we have shown that the number of CD204+ tumor associated macrophages was also significantly higher in the malignant structure than in benign prostate hyperplasia ($p<0,05$). CD163+ M2 type macrophages were predominantly seen in tumor core than in tumor margin. Interestingly, CD68+ and CD163+ macrophage number was significantly higher in cases with positive lymph nodes. However, no significant correlation was found between pathological variables and selected proteins. Analysis of TCGA prostate adenocarcinoma (PRAD) database also confirmed abundance and positive association of M2 type macrophages and negative or no association with macropahges with M1 and M0 phenotype.

Fig. 2. Immunohistochemical expression of CD68 in benign (high load - A, low load – B) and malignant (high load - C, low load – D) prostate tissue sample.

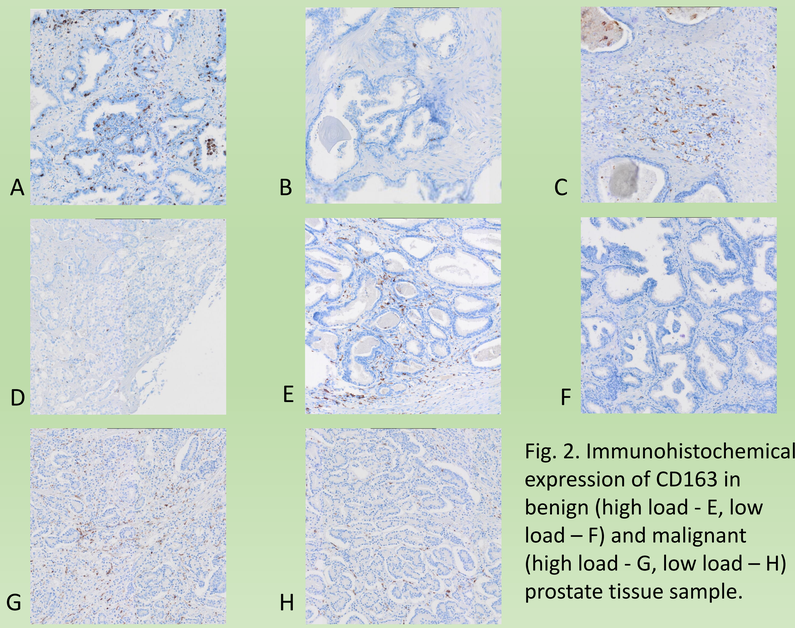
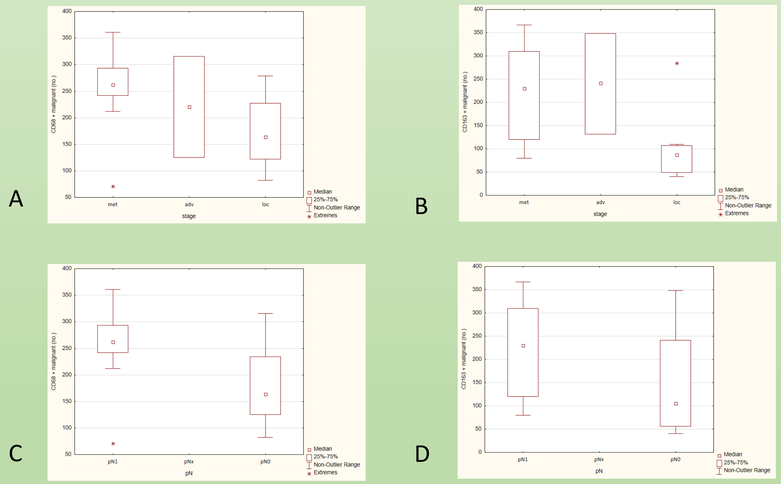


Fig. 2. Immunohistochemical expression of CD163 in benign (high load - E, low load – F) and malignant (high load - G, low load – H) prostate tissue sample.

Conclusion

Our results confirm higher desity of CD68+ macropahge population in prostate cancer and are in agreement with previous findings that M2 type, CD204+ and CD163+ macrophages are more characteristic for malignant structures. Our results were validated on publicly available PRAD dataset. The absence of significant correlation with clinical and pathological parameters of our samples can be explained by the small sample size. Larger cohort and further multiplex immunostainings will uncover more macrophage populations and their prognostic/predictive potential in prostate cancer

Fig. 3. Box plots showing CD68+ (A) and CD163+ (B) expression in tumor stage, and CD68+ (C) and CD163+ (D) in different pN status.



References

1. https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html
2. Gessain G, Blériot C and Ginhoux F (2020) Non-genetic Heterogeneity of Macrophages in Diseases—A Medical Perspective. *Front. Cell Dev. Biol.* 8:613116.
3. Mantovani A, Marchesi F, Malesci A et al. Tumour-associated macrophages as treatment targets in oncology. *Nat Rev Clin Oncol*. 2017;14(7):399-416.
4. Burdová A, Rulíšek P, Bouchal J et al. Infiltration of Prostate Cancer by CD204+ and CD3+ Cells Correlates with ERG Expression and TMPRSS2-ERG Gene Fusion. Klin Onkol 2018; 31(6): 421-428.