The immune landscape of prostate cancer

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Abstract

Purpose: Immunotherapy has been less successful in treating prostate cancer than other solid tumors. We sought to better understand the immune landscape in prostate cancer.

Experimental Design: We analyzed gene expression data from 7826 prospectively collected prostatectomy samples collected between 2013-2016, and 1567 retrospective samples with long-term clinical outcomes, all profiled on a commercial clinical platform.

Results: Unsupervised hierarchical clustering of the hallmark pathways of all 9393 samples demonstrated an immune-related cluster of tumors. Increased estimated immune content scores based on immune-specific genes from the literature were associated with worse biochemical recurrence free survival (bRFS, p=0.0002, HR=1.26 [1.12−1.42]), distant metastasis-free survival (DMFS, p=0.0006, HR=1.34 [1.13−1.58]), prostate cancer-specific survival (PCSS, p=0.0003, HR=1.53 [1.21−1.92]), and overall survival (p=0.006, HR=1.27 [1.07−1.50]). Additionally, de-convolution using Cibersort revealed that mast cells, NK cells, and dendritic cells conferred improved DMFS, and macrophages and T-cells conferred worse DMFS, all consistent with the literature. Interestingly, while PD-L1 was not prognostic, consistent with its low expression in prostate cancer, PD-L2 was expressed at significantly higher levels (p<0.0001) and was associated with worse bRFS (p=0.013, HR=1.17 [1.03−1.33]), DMFS (p=0.014, HR=1.25 [1.05−1.49]), and PCSS (p=0.0033, HR=1.45 [1.13−1.86]). PD-L2 may also predict response to post-operative radiation therapy (PORT) on a multivariate interaction analysis (p=0.029) with PD-L2 conferring worse DMFS only in patients who did not receive PORT.

Conclusions: These results illustrate the complex relationship between the tumor-immune interaction, prognosis, and response to radiotherapy, and suggest PD-L2 as a therapeutic target in prostate cancer which merits further investigation, potentially in combination with radiotherapy.

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