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Soluble PD-1/PD-L1 in prostate cancer: immune cell associations and clinical implications

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Abstract

Background:
Soluble PD-1 (sPD-1) and PD-L1 (sPD-L1) are emerging biomarkers in prostate cancer (PCa), yet their cellular origins and interactions within the tumor microenvironment (TME), particularly with NK cells, immunosuppressive Tregs, and MDSCs, remain poorly understood. This study also explores biomarker combinations for better clinically significant PCa stratification.
Methods:
A total of 88 PCa patients (pT2 and pT3) were enrolled. Plasma levels of sPD-1 and sPD-L1 were measured using ELISA. A control group of 41 healthy individuals was also included. Immune cell populations were characterized by flow cytometry. All parameters were evaluated preoperatively and three months post-radical prostatectomy (RP). Clinically significant PCa was defined as cases with International Society of Urological Pathology (ISUP) ≥ 3. Written informed consent was obtained from all participants.
Results:
sPD-1 exhibited a weak positive correlation with NK cells ($r=0.27$, $p=0.03$) in whole cohort, suggesting NK cells as a source of sPD-1. Higher initial sPD-L1 levels were significantly associated with shorter progression-free survival (PFS) ($p<0.05$), additionally in the biochemical recurrence (BCR) group, sPD-L1 showed a positive correlation with Tregs ($r=0.73$, $p<0.05$), highlighting their coordinated role in cancer progression. Postoperative changes in sPD-L1 divided patients into two distinct groups: one showed a decrease ($p<0.001$), indicating tumor-derived origins, while the other exhibited an increase, suggesting an alternative source ($p<0.05$). In patients with a postoperative decrease in sPD-L1, no correlation was found with pretreatment Tregs and MDSC subsets. However, strong associations between total G-MDSCs and M-MDSCs ($r=-0.51$, $p=0.002$) and between G-MDSC% and M-MDSC% ($r=0.49$, $p=0.001$) were observed, indicating a dynamic interplay between these myeloid subsets, which could contribute to immunosuppressive mechanisms regulating sPD-L1 levels. Moreover, a negative correlation between sPD-L1 and M-MDSC% was found in the BCR group ($r=-0.72$, $p<0.05$). The combination of preopreative levels of sPD-L1 with the G-MDSC fraction (best result: AUC=0.93, specificity 100%) demonstrated superior results for clinically significant prostate cancer stratification compared to the M-MDSC fraction. Combinations with Tregs showed poor predictive value.
Conclusions:
Our findings indicate that sPD-1 is primarily derived from NK cells, while sPD-L1 levels are modulated by Tregs and interactions between MDSC subsets. These insights contribute to a deeper understanding of immune evasion in PCa and may facilitate the development of biomarker-driven approaches for disease monitoring and targeted therapies.