Tumor draining lymph nodes in prostate cancer harbor immune suppressor cells that may impair tumor-reactive T cells

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Background:
Prostate Cancer (PCa) persistence in Tumor Draining Lymph Nodes (TDLNs) in the pelvis after radical prostatectomy (RP) may eventually lead to distant metastases. This remains one of the hypothesized oncologic benefits salvage Pelvic Lymph Node Dissections (sPLNDs), a procedure increasingly being investigated for nodal recurrent PCa. The role regional TDLNs play in local immunity to prostate cancer (PCa) remains unknown.

Methods:
Here we prospectively enrolled 10 hormone therapy naive men undergoing salvage Pelvic Lymph Node Dissection (sPLND). Median PSA at sPLND was 3.1ng/mL (range 1.0-5.6ng/mL), median nodes removed 23 (range 7-32 nodes), and median nodes positive 3 (range 1-15 nodes). Lymph nodes analyzed consisted of the largest positive nodes involved for each patient. We analyzed their peripheral blood (PB) and TDLNs for tumor reactive CD8 T cells and myeloid derived suppressor cells (MDSC) using flow cytometry. MDSCs were stratified into CD14+monocytic and CD14-granulocytic. PD-L1/2 expression was also analyzed on MDSCs.

Results:
Relative to PB, Tumor-reactive CD8 T-cells accumulated in TDLNs ($p<0.01$) yet had decreased proliferation with low Ki67($p<0.05$). Both CD14+monocytic and CD14-granulocytic MDSCs were found in TDLNs, but there was evidence for an increase in the proportion of CD8 T cells in TDLNs compared to PB ($p<0.01$). These granulocytic MDSCs exhibited an increase in immunosuppressive activity (supported by high pSTAT3 levels) and also expressed high levels of B7-H1 (PD-L1) and B7-DC (PD-L2). Thus, granulocytic MDSCs likely suppress tumor-reactive CD8 T-cells in TDLNs and exhibit a high expression of immune checkpoint molecules in PCa nodal metastases.

Conclusions:
Taken together, our data demonstrates that tumor-reactive CD8 T-cells accumulate in TDLNs but had reduced proliferation relative to the blood. Simultaneously, TDLNs had a higher proportion of granulocytic MDSCs, which exhibited a higher degree of immunosuppressive activity within the TDLNs and also express high levels of B7-H1 (PD-L1) and B7-DC (PD-L2). The expression of these immune checkpoint signals by granulocytic MDSC corresponds with our prior finding of increased expression of complementary receptors (ie. PD-1) on tumor-reactive CD8 T-cells. Thus, our data forms a hypothesis that PCa cells in TDLNs may harness immunosuppressive granulocytic-MDSCs to bypass anti-tumor immunity, and we are currently working on large scale more mechanistic studies to see of this theory holds true.

Conflicts of Interest: None to declare

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