191 TARGETING MYELOID-DERIVED SUPPRESSOR CELLS (MDSCS) IN BLADDER CANCER TO ENHANCE EFFICACY OF ADOPTIVE CELL THERAPY (ACT)

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Background MDSCs are a significant barrier to adoptive cell therapy (ACT) due to their suppressive effects on T-cells. We predict that there is an enrichment of MDSCs within bladder tumors and depletion of MDSCs may augment anti-tumor responses after intravesical ACT with tumor reactive T-cells.

Methods For murine studies, orthotopic MB49-OVA bladder tumors were collected, stained for MDSCs, and analyzed by flow cytometry. Urine samples from bladder cancer patients were also collected and stained for MDSCs. From mice, purified MDSCs and OT-I T-cells were cocultured and from bladder cancer patients, purified urine MDSCs and CD3-stimulated peripheral blood T-cells were cocultured to assess suppression of T-cell proliferation or IFN-gamma secretion. Mice bearing MB49-OVA tumors were treated with intravesical instillation of gemcitabine and/or OT-I T-cells and tumor growth was monitored via ultrasound.

Results In mice bearing MB49-OVA tumors, the levels of polymorphonuclear (PMN)-MDSCs averaged between 11.1–23.5% of live cells and monocytic (M)-MDSCs averaged 7.6% of live cells, demonstrating that nearly 20–30% of live cells within murine bladder tumors are MDSCs. In the urine of bladder cancer patients, PMN-MDSCs predominantly make up the live cell population, averaging 71.7%, demonstrating an enrichment for MDSCs within the microenvironment of human bladder cancer. In murine coculture assays, MDSCs reduced the proliferation of OT-I T-cells and in human cocultures, MDSCs reduced T-cell IFN-gamma production to a fourth of control levels. Therefore, MDSCs from bladder tumors suppress anti-tumor T-cells by inhibiting proliferation and reactivity. In mice bearing large MB49-OVA tumors (>50mm3), pretreatment with gemcitabine improved anti-tumor response in combination with intravesical ACT with OT-I T cells in comparison to treatment with gemcitabine only ($p=0.0387$), OT-I only ($p=0.0148$), and untreated ($p=.0039$). In smaller MB49-OVA tumors (<50mm3), gemcitabine pretreatment provided little added benefit to ACT in comparison to treatment with gemcitabine only ($p>0.05$) and OT-I only ($p>0.05$). All p-values generated by performing Mann-Whitney tests on tumor volumes at final time points.

Conclusions MDSCs make up a significant proportion of the immune population within bladder tumors and exert suppressive effects on T-cells. Our studies support the selective targeting of MDSCs via gemcitabine to improve the anti-tumor effects of ACT. While we show that a single instillation of gemcitabine and ACT improves anti-tumor responses, we predict that this effect will be further enhanced with multiple instillations of T-cells.

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Ethics Approval This study was approved by the Advarra IRB; approval number IRB# 00000971 and the University of South Florida IACUC, approval number R IS00007685.