Cytokine Regulation of MDSC Maturation: Impact on Tumor Immunotherapy

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Introduction

- The ability of tumor-specific cytotoxic T cells and natural killer cells to eliminate tumors is hindered by immunosuppressive cells that infiltrate the cancer microenvironment.

- Monocytic myeloid-derived suppressor cells (mMDSC) are the most active of these tumor infiltrating leukocytes and are key contributors to the immunosuppressive milieu.

- MDSC are immature myeloid cells that arise in the bone marrow and are present at increased frequency in mice and humans with cancer.

- Immunostimulatory agents that trigger Toll-like receptors can reduce tumor growth by inducing MDSC to differentiate into tumoricidal macrophages (mθ).

- Our efforts are directed towards better defining the mechanisms underlying this effect.
Intratumoral delivery of CpG ODN reduces tumor growth

Findings:
Early systemic delivery of CpG ODN improves host survival after tumor challenge.

However, TLR agonist efficacy wanes as tumor size increases.
  CTL activity is subverted by the immunosuppressive microenvironment present in large established tumors (Tregs, MDSC, tumor infiltrating m\theta).

Hypothesis: The “danger signal” provided by local delivery of a TLR agonist can overcome tumor-induced immunosuppression.
Intra-tumoral CpG ODN induces mMDSC to differentiate into macrophage

Analysis of CD45⁺, Gr-1⁺, CD11b⁺ cells infiltrating CT26 tumors.
CpG ODN generate M1 macrophages

**Protocol:** Isolate Ly6c+, Gr-1int, CD11b+ mMDSC from tumor bearing mice, Rx *in vitro* for 2 days then transfer into tumor-bearing recipients or CT26 tumor targets.
CpG ODN increase M1 macrophage in the tumor milieu

Effect on immune cells in the tumor milieu

- M1 mθ
- CD8

Effect on tumor cells

- Apoptotic

Untreated

Rx’d with TLR agonists

* p < .05
** p < .01
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