Tumor Microenvironment; Hijacking The Immune System

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Disclosures

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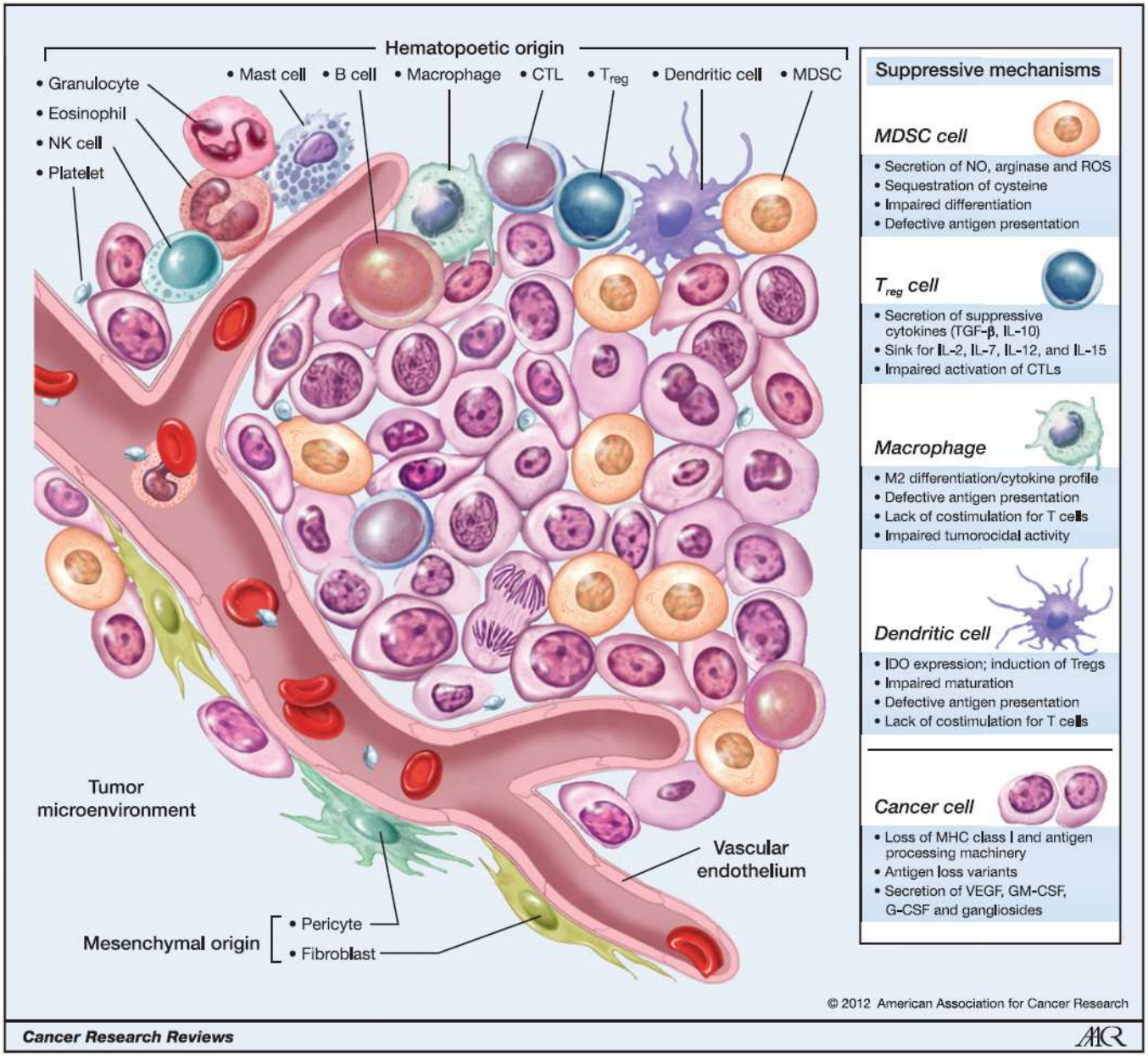
Cellular Composition of the Tumor

- The tumor microenvironment is not only composed of malignant cells it contains:

- neovasculature, fibroblast and myeloid cells

- Immune cells critical for mounting an immune response to tumor.
  - -T lymphocytes, CD4 and CD8 subsets
  - - Dendritic cell subsets
  - - NK/NKT cells
  - -B cells/plasma cells

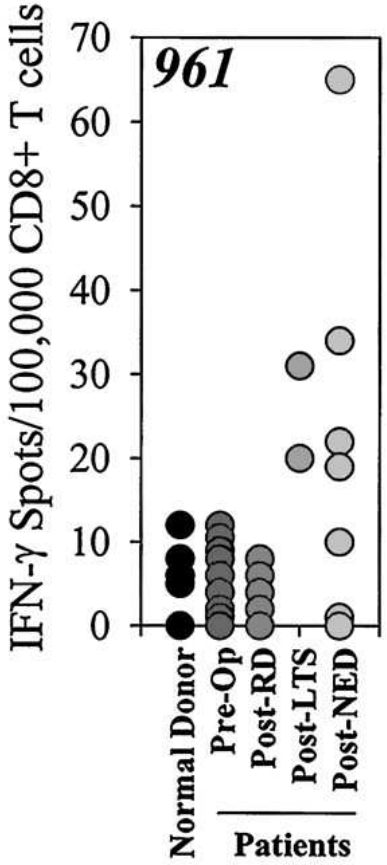
- Many of the tumor infiltrating immune cells are dysregulated, functionally impaired and contribute to tumor progression.
  - -T cells (anergic)
  - -T-regulatory cells
  - -Macrophages
  - -Myeloid derived suppressor cells



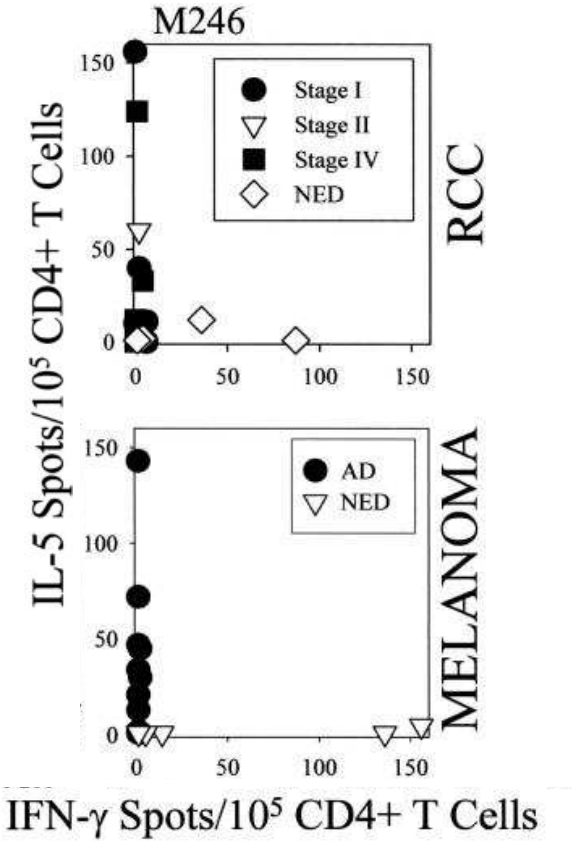
Cellular Constituents of Immune Escape within the Tumor Microenvironment
Kerkar SP, **Restifo** NP.
Cancer Res. 2012 Jul 1;72(13):3125-30. Epub 2012 Jun 21. Review

Diminished Type 1 T cell Response in mRCC is Linked to Active Disease.

- CD8+ EphA2 specific T cells detected in patients who are long term survivors with residual disease and NED.



- In metastatic RCC patients peripheral blood CD4+ and CD8+ T cells showed a skewing toward a TH-2 response against EphA2 and MAGE-6-derived peptides except NED patients



Tatsumi T et al. Cancer Res 2003;63:4481-4489

Features of some solid tumors that may mediate poor immune recognition or reduce immune destruction of tumor.

T cell Priming

-Reduced recruitment of Dendritic subsets for antigen presentation

-Inadequate expression of co-stimulatory molecules on tumor cells or infiltrating DC

Effector Phase

-Inadequate recruitment of activated effector cells

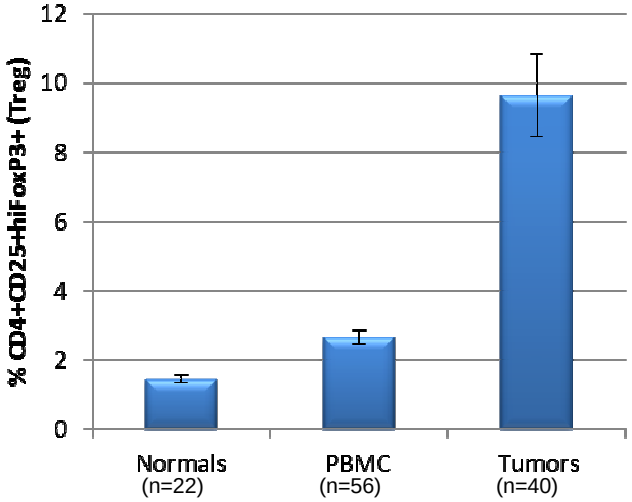
• chemokines

Presence of dominant immune inhibitor mechanisms that suppress T cell effector function

- Suppressive cells (Treg, MDSC, Macrophages, neutrophils)
- Inhibitory cytokines (IL-10, TGFβ)
- Inhibitory receptors (CTLA4, PD1/PDL-1)

Treg Foxp3+ cells

A. **Tregs in Blood and Tumor of RCC patients**



Finke J et al , unpublished and Clin Cancer Res 2008,

B. T-regulatory cell facts

- Foxp3+ Treg cells suppress T effectors via different mechanisms .
- Difficult to selectively reduce Treg cell numbers.
- For adoptive T cell therapy the use of cytoablative strategies to deplete Treq enhances clinical responses. (Dudley EM et al. J Clin Oncology 2008)
- Within different tumor types there is variable correlation between the degree of Treg infiltration and overall survival.
- In colon cancer Treg numbers have not correlated with reduced survival (Loddenkemper C. et al J Trans Med 2006).

Myeloid-derived Suppressor Cells

- **Heterogeneous population of immunosuppressive myeloid cells**
- **Normally present in very small amounts but systemically accumulate under pathologic conditions – tumor-bearing**
- **Accumulation associated with:**

  VEGF, SCF, GM-CSF, G-CSF, S100A9, and M-CSF

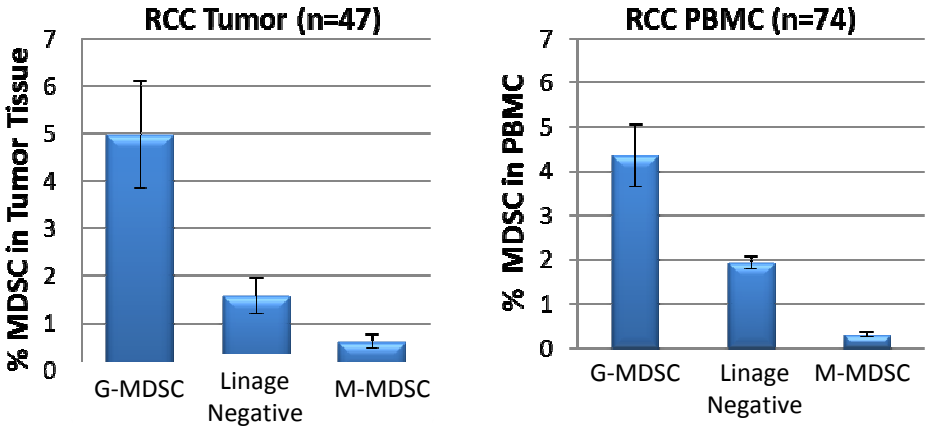
- **Murine MDSC:** Granulocytic (CD11b+Gr1hi+),
  Monocytic (CD11bGr1low)
- **Human MDSC multiple subsets:**
  Granulocytic (CD33lowHLADR-CD15+CD14-)
  Monocytic (CD33lowHLADR-CD15-CD14+)
  Linage Negative (CD33lowHLADR-CD15-CD14-)

Plasticity of MDSC

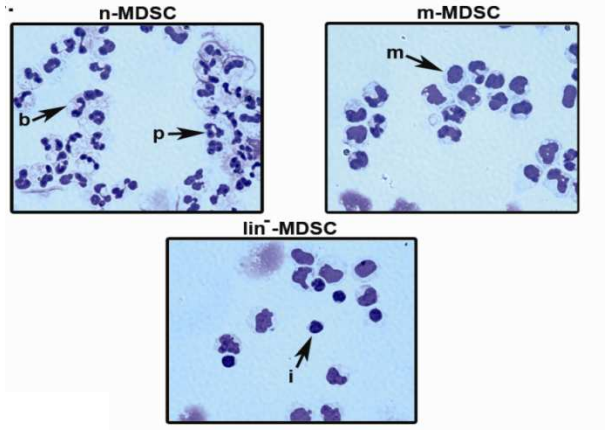
Granulocytic MDSC	differentiate into	CD31 Endothelial cells
Monocytic MDSC	differentiate into	Tumor Associated Macrophage
Monocytic MDSC	differentiate into	Granulocytic MDSC

MDSC in Cancer Patients

A. MDSC subset levels in blood and tumor of RCC pts

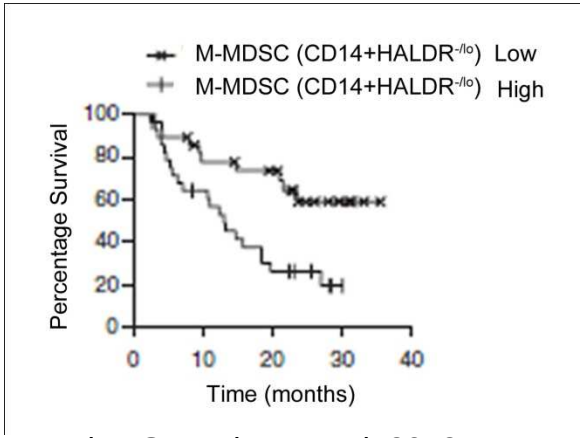


B. MDSC subset morphology .



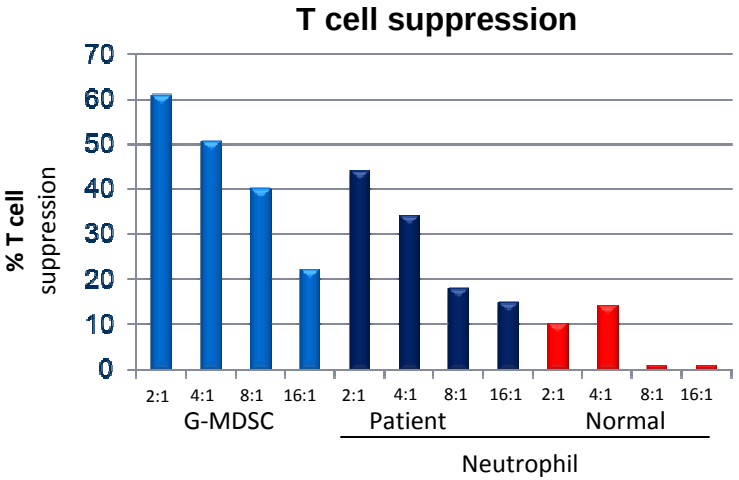
Ko J et al Can Res 2010 and unpublished data

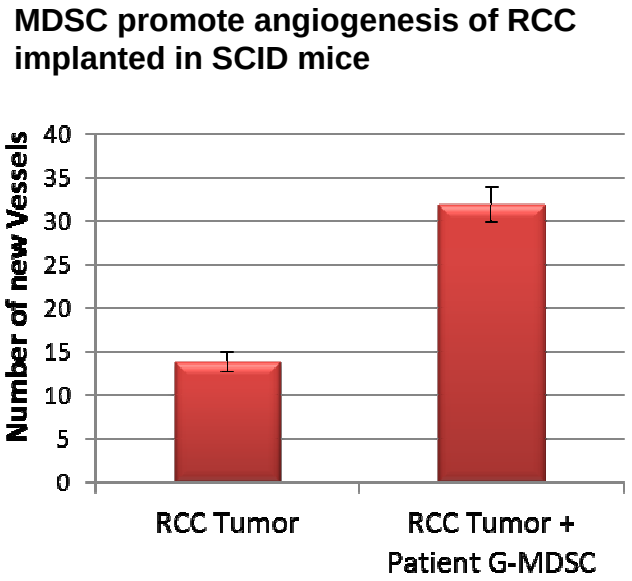
C. Baseline levels of Monocytic and Granulocytic MDSC negatively correlate with overall survival



Walter S, et al Nat Med. 2012 Aug

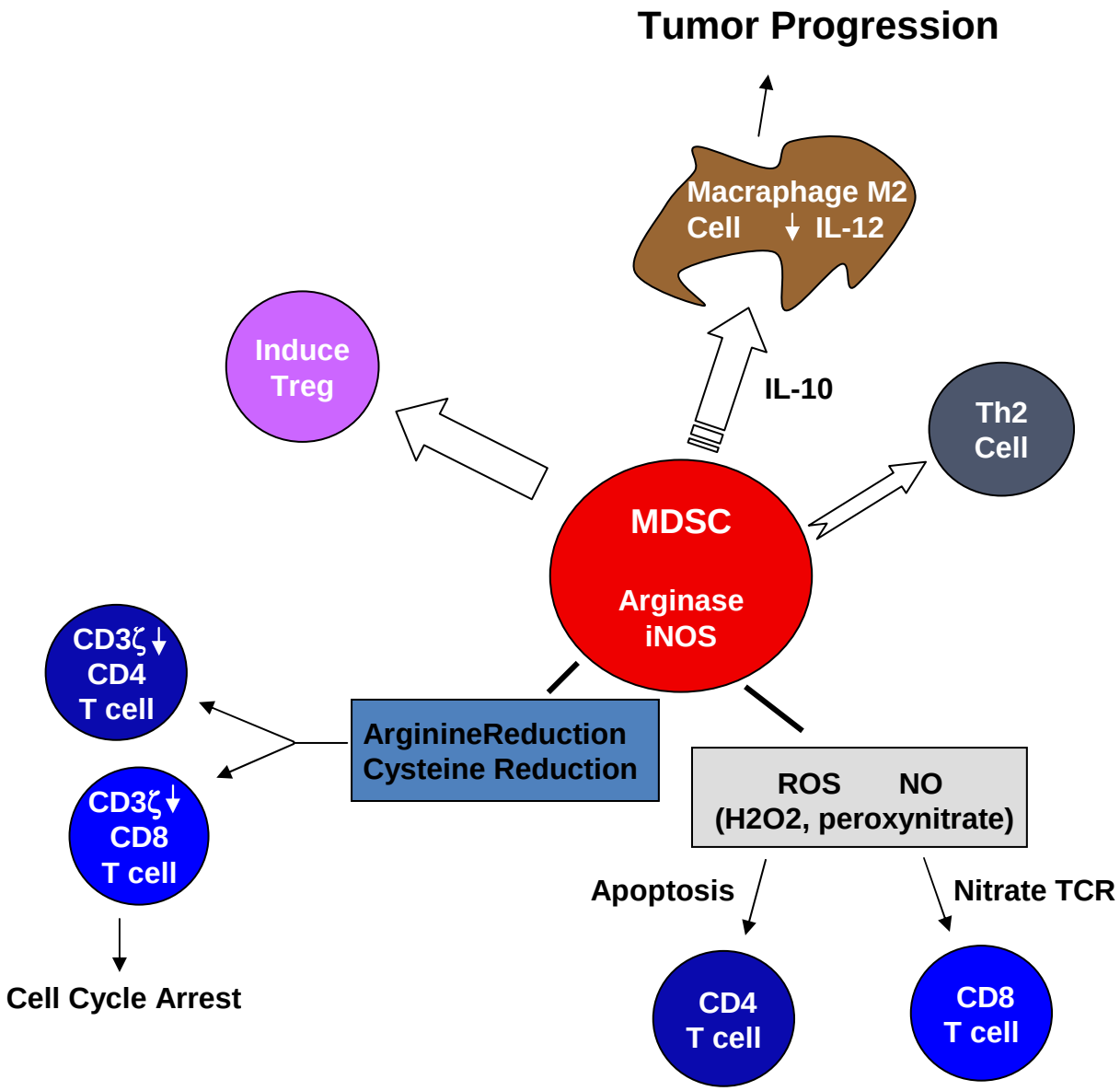
Patient Granulocytic MDSC and Neutrophils: Suppressive and Angiogenic Activities





Ko J et al Manuscript in preparation

MDSC –Mechanisms of Suppression



Granulocytic subset
ROS, Arginase
Monocytic subset
NO, Arginase

Neutrophils

- Elevated blood neutrophils and elevated neutrophil/lymphocytes ratio is associated with poor clinical outcome in several human cancers (RCC, melanoma colorectal, lung , ovarian etc) ((Donskov F. Seminar in Cancer Biology 2013)

- In non-metastatic localized clear cell RCC the presence of intratumoral CD66+ neutrophils was associated with short recurrence-free survival and overall survival (Jensen HK et al J Clin Oncology 2009)

- Neutrophils from cancer patients but not healthy donors can suppress T cell function and produce elevated levels of proangiogenic proteins (Schmielau J. and Finn O., Can Res 2001 , Rodriguez PC et al. Can Res 2009)

- The relationship between granulocytic -MDSC and patients neutrophils is being assessed (functional and gene array studies).

- Tumor microenvironment promotes pro-tumor neutrophils (TAN)

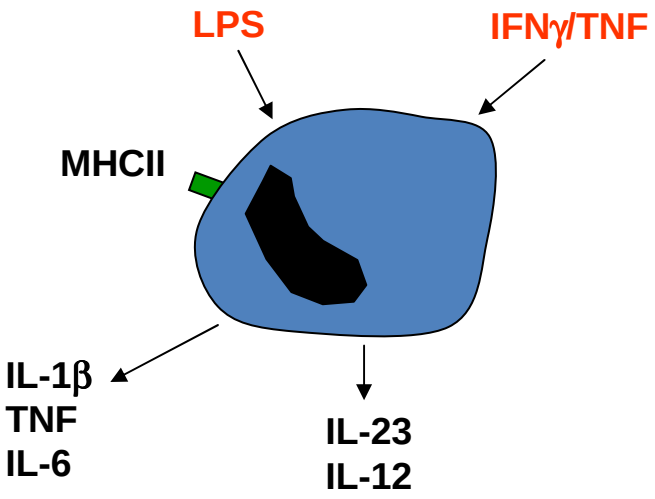
  Claudia A. Dumitru , et al Seminars in Cancer Biology Volume 23, Issue 3 2013 141 - 148

Macrophages

Tissue Macrophages

M1

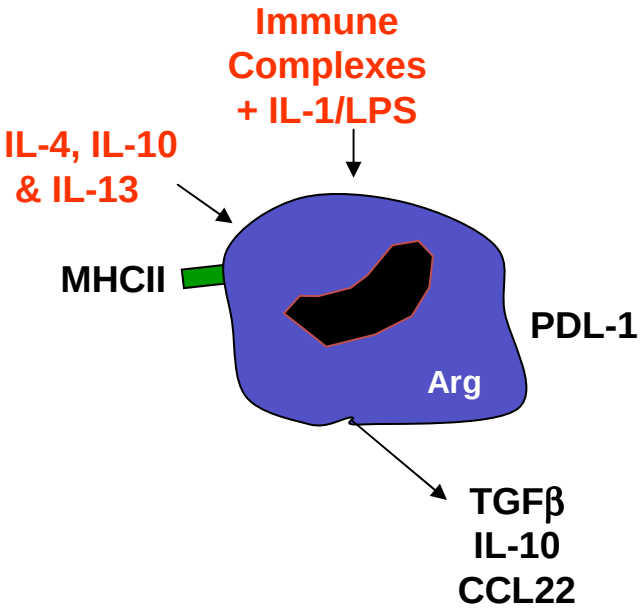
Stimuli



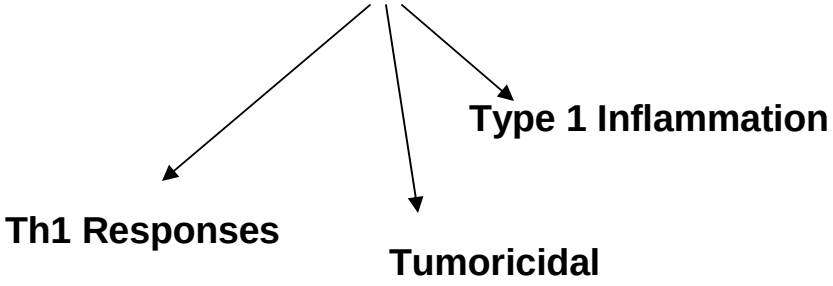
Tumor Associated Macrophages

M2

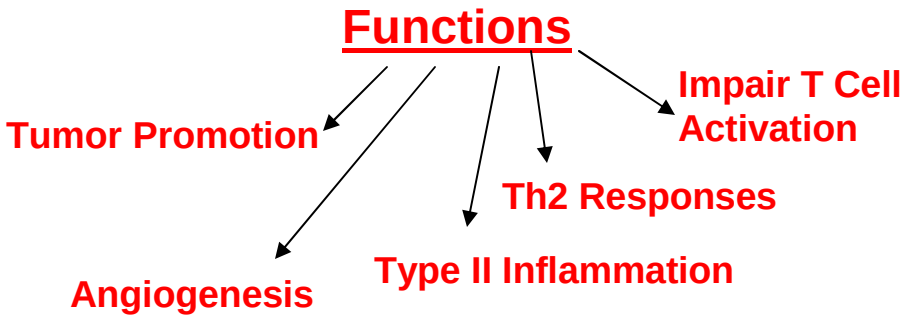
Stimuli



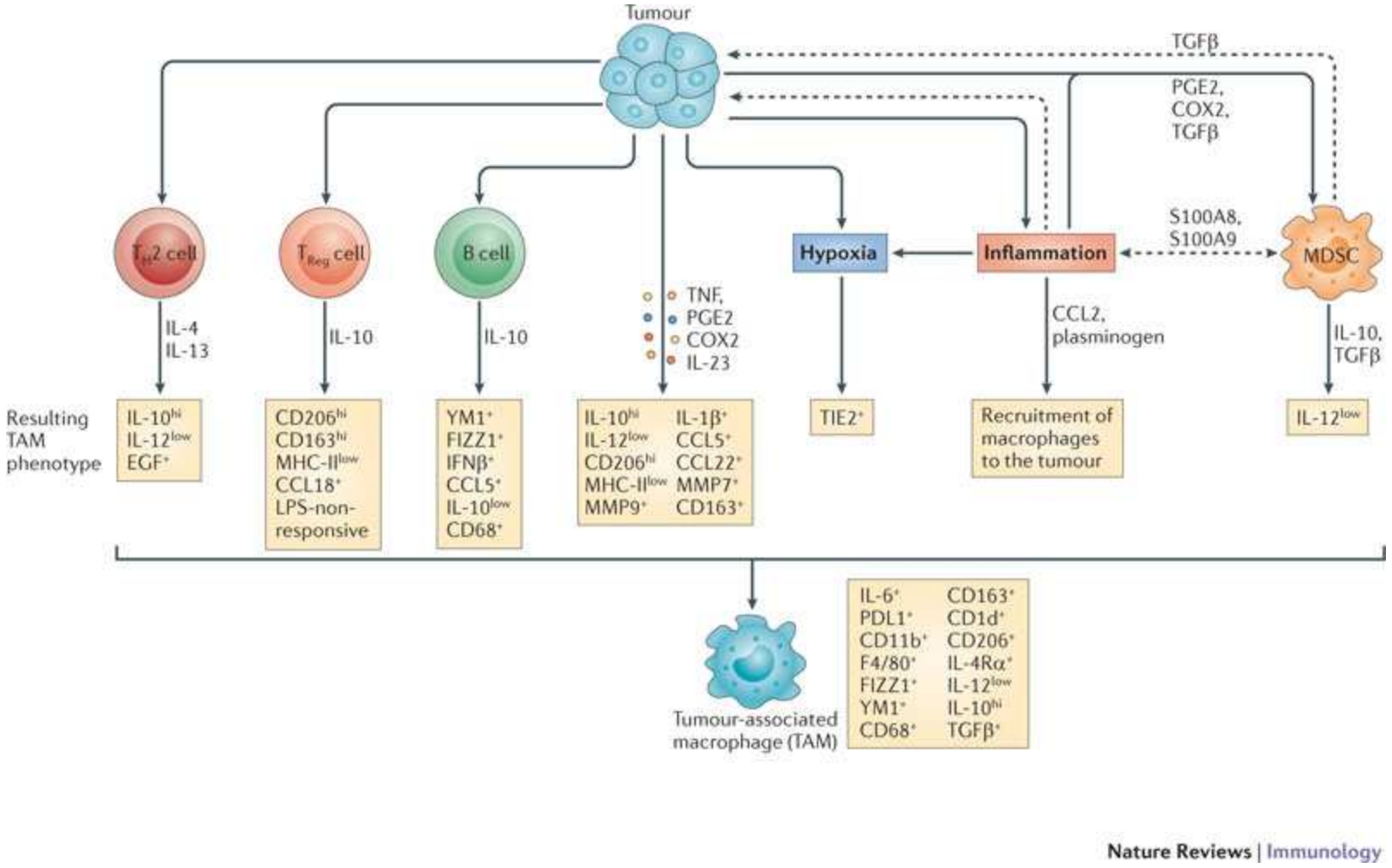
Functions



Functions



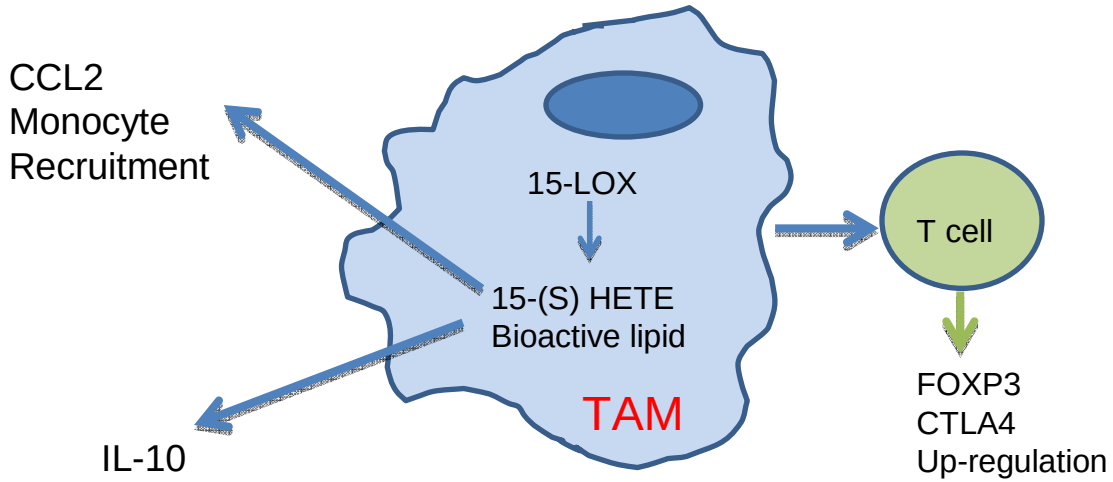
Multiple Subsets of TAM are Induced by the Tumor Microenvironment



Gabrilovich et al Nat Rev Immunol. 2012 Mar 22;12(4):253-68

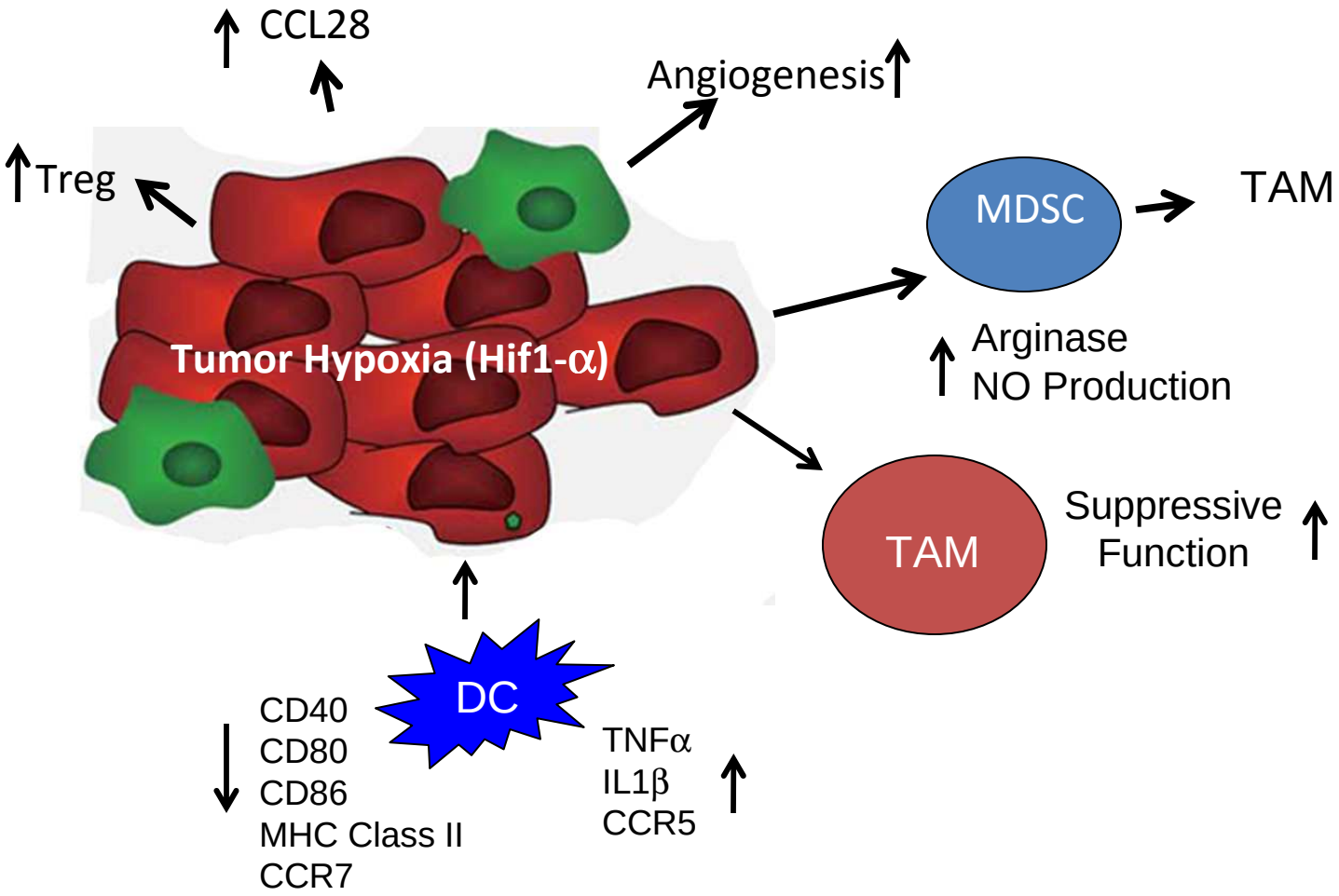
TAMs in RCC

RCC associated TAM can mediate immune suppression and tumor escape via the activation of the 15-Lipoxygenase-2 pathway.



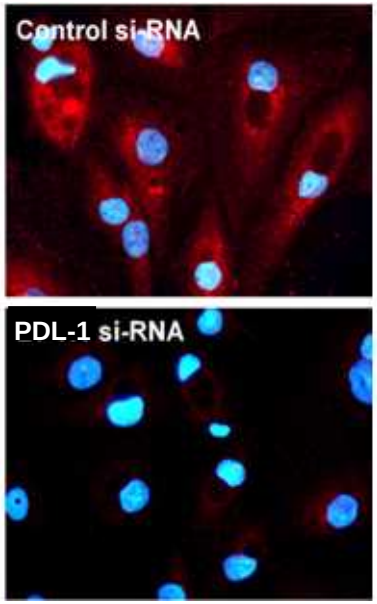
Daukrin I. et al. Can Res ,2011

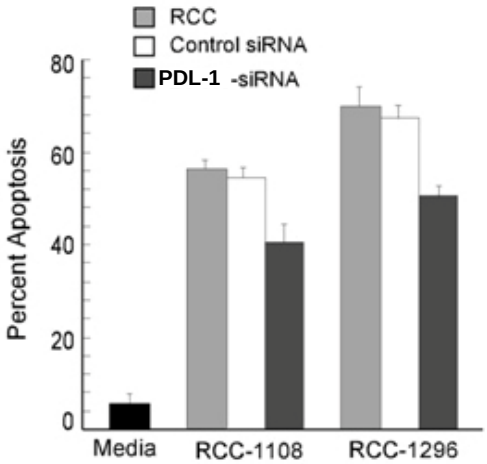
Tumor Hypoxia (Hif1-α)



PDL-1 (B7-H1) Expression by RCC and Its Suppression of T Cell Function

PDL-1





PDL-1 Expression in RCC

-Poor Outcome

Thompson H et. al. Clin Can Res 13:1757-1761, 2007

Can be expressed on

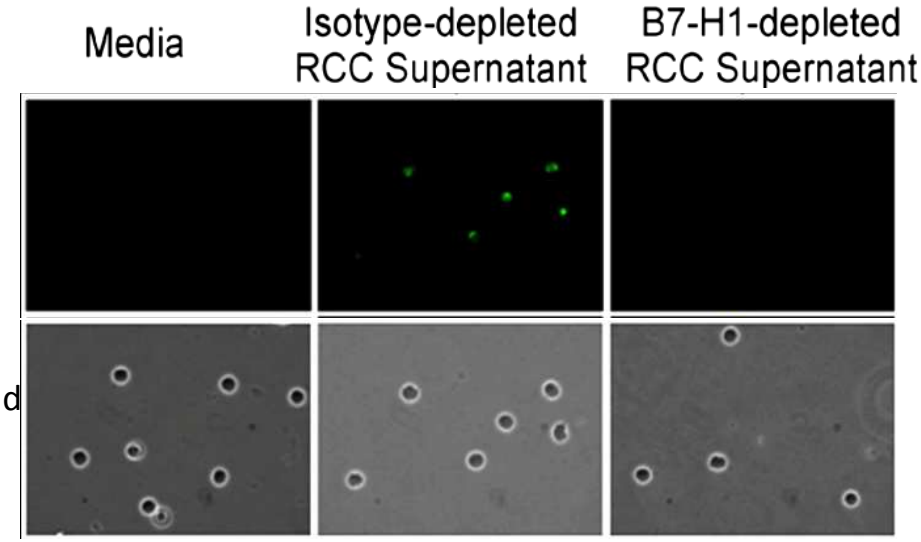
- Tumor
- Macrophages
-Dendritic Cells

Secreted form (sB7-H1)

Immunosuppressive

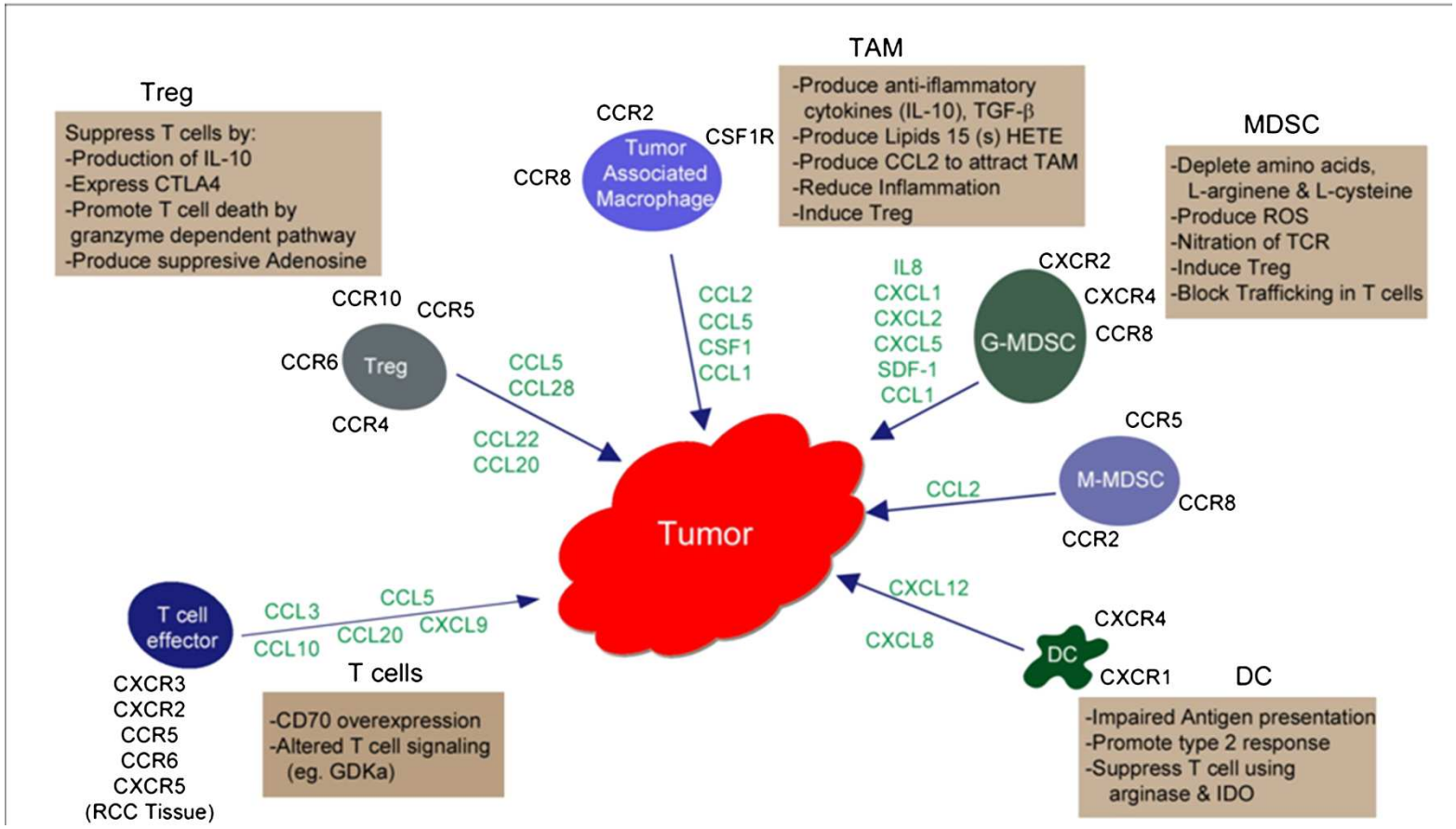
Frigola X et al Clin Can Res 17:1915-1923,2011)

PDL-1 in tumor supernatant binds T cells which is blocked by anti-PDL-1 Ab



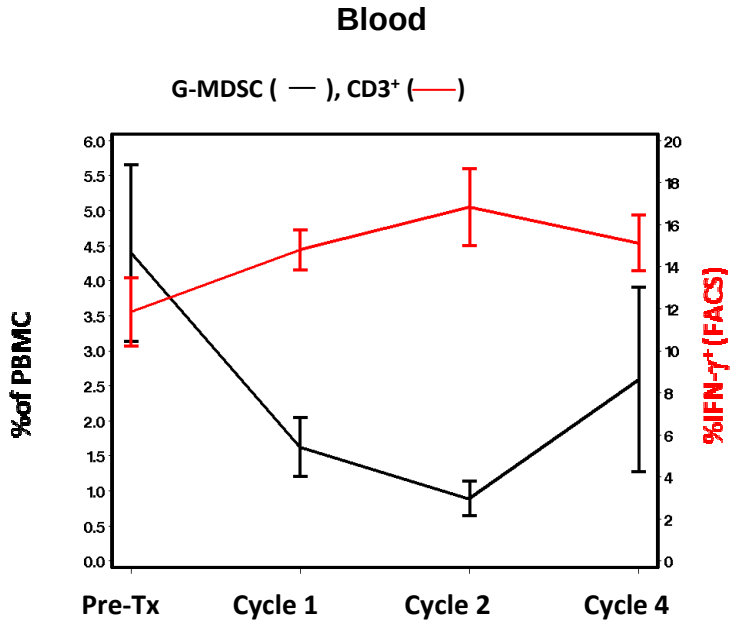
Gaurisankar Sa et al (Unpublished)

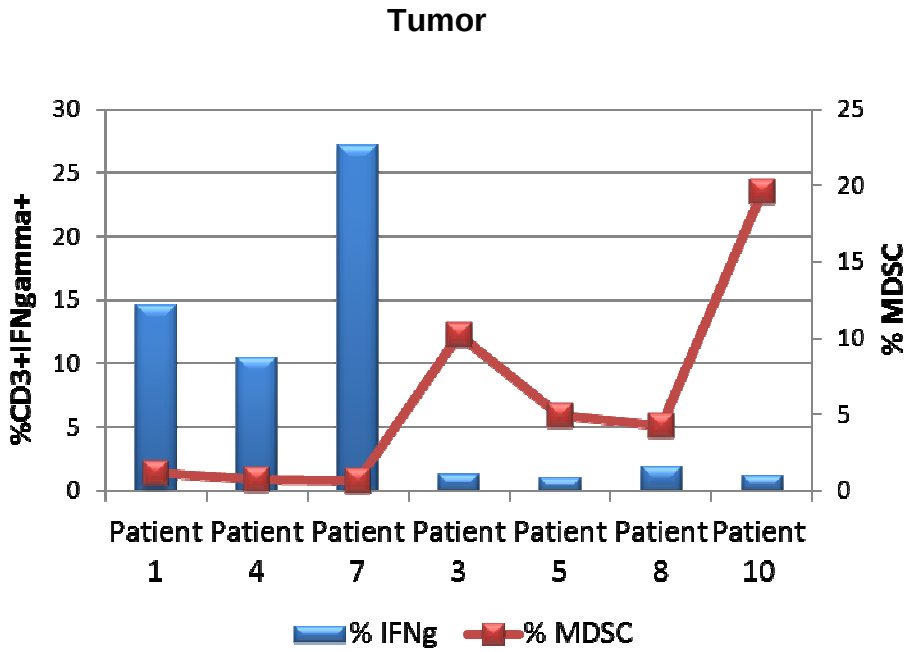
Tumor Microenvironment Promotes the Trafficking of Immune Cells that Display Suppressive Activity in the Tumor



(Cancer J 2013;19: 353Y364)

One Example of Modulating The Tumor Microenvironment : Sunitinib Treatment

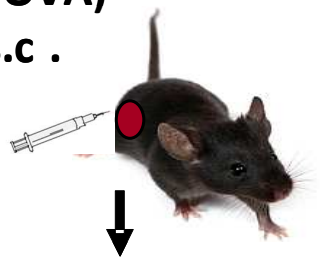




Ko et a Clin Cancer Res. 15:2148-57, 2009 and unpublished data

Superior Anti-Tumor Efficacy of Vaccine + TKI Co-Therapy

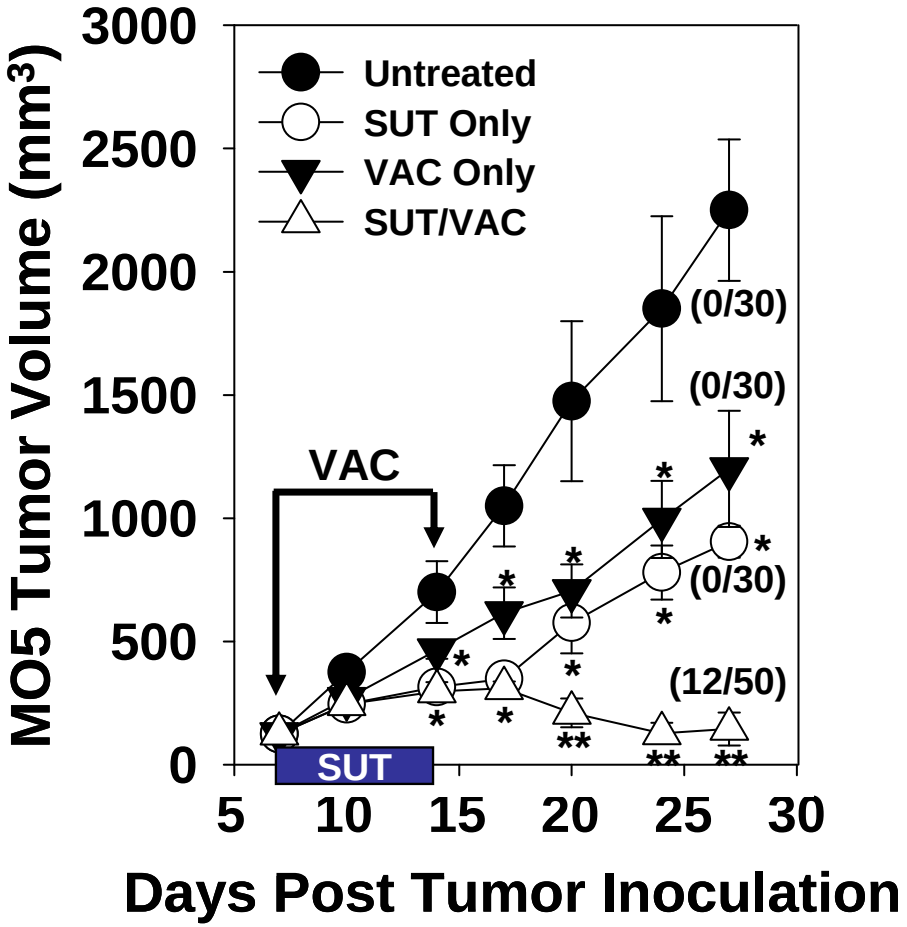
MO5 (B16.OVA)
injected s.c .
(2 x 10 ^{5})



+/- oral Sunitinib
(0.1 mg/day, d10-16)

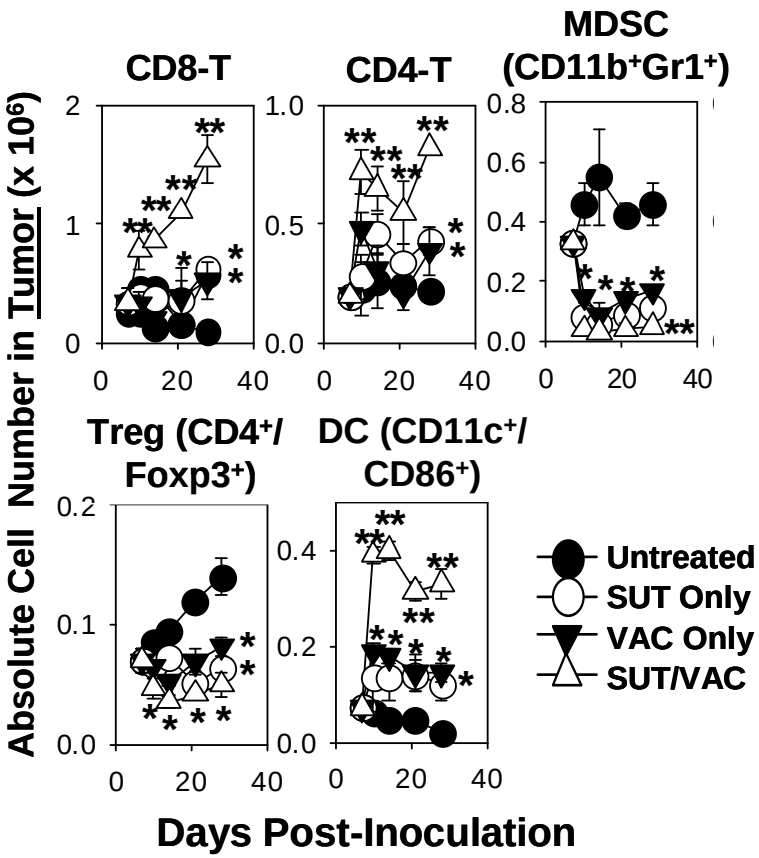
+/- s.c . DC1/OVA $_{257-262}$
vaccines d10, d17

Monitor tumor size
TME analysis (d34)
Immune monitoring (d34)

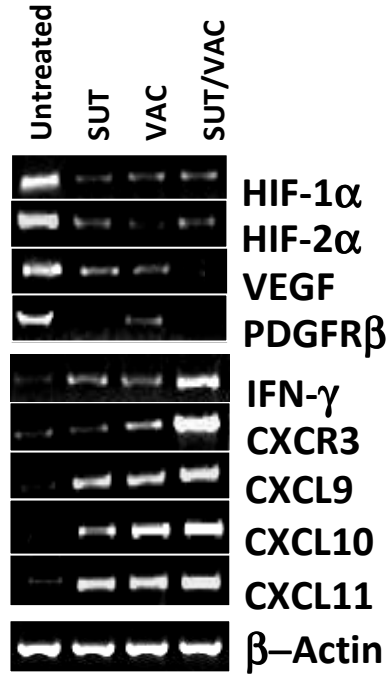


Bose et al. *Int. J. Cancer* 2011; 129: 2158 - 2170.

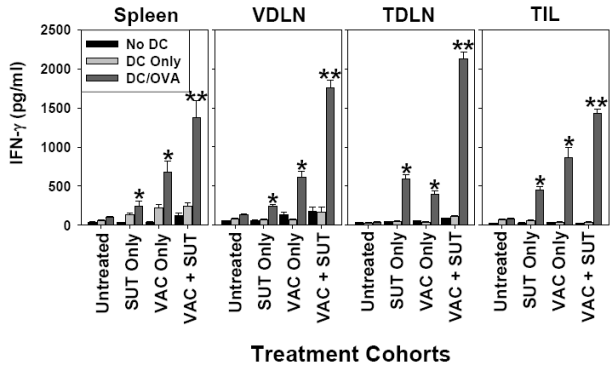
Vaccine/TKI Co-Therapy Promotes the Inhibition of Regulatory Cells and the Activation/Recruitment of Protective CD8⁺ T cells



Combination Therapy Results in a Type-1 Biased Immune Profile in the Tumor



Combination Treatment with Vaccine and Sunitinib Improved T cell Response



Bose et al. *Int. J. Cancer* 2011; 129: *2158* - 2170.

Clinical Trials with Sunitinib Plus Vaccine therapy

Argos Therapeutics

DC loaded with autologous total tumor RNA + sunitinib

Immatics Biotechnology

Multipeptide vaccine + sunitinib

UPMC/Cleveland Clinic

DC pulsed with tumor blood vessel-associated antigens (TBVA) + sunitinib

Conclusions

- There is heterogeneity in patient response to immune-based Immunotherapy.

- A significant component of that heterogeneity comes from differences at the level of the tumor microenvironment.

- Key determining factors in the tumor (RCC) environment include recruitment of T effector cells, local production of chemokines and the presence of local immunosuppressive mechanisms.

- Further Identifying the different mechanisms mediating immune suppression and angiogenesis by tumor stromal cells has already yielded new strategies for improving cancer therapy (CTLA4 and PD1 antibodies) and is likely to yield additional targets.

- The fact that different histological types of tumors all share in common the infiltration of stromal cells should provide unique universal targets for therapy of solid tumors including RCC.

Cleveland Clinic