Society for Immunotherapy of Cancer (SITC)

Basic Mechanisms of Tumor Immune Suppression

Wei-Zen Wei, PhD
Wayne State University

Advances in Cancer Immunotherapy™ - Michigan
July 31, 2015

Presentation originally prepared and presented by
Brent Hanks, MD, PhD
Duke University Medical Center

sitc
Society for Immunotherapy of Cancer

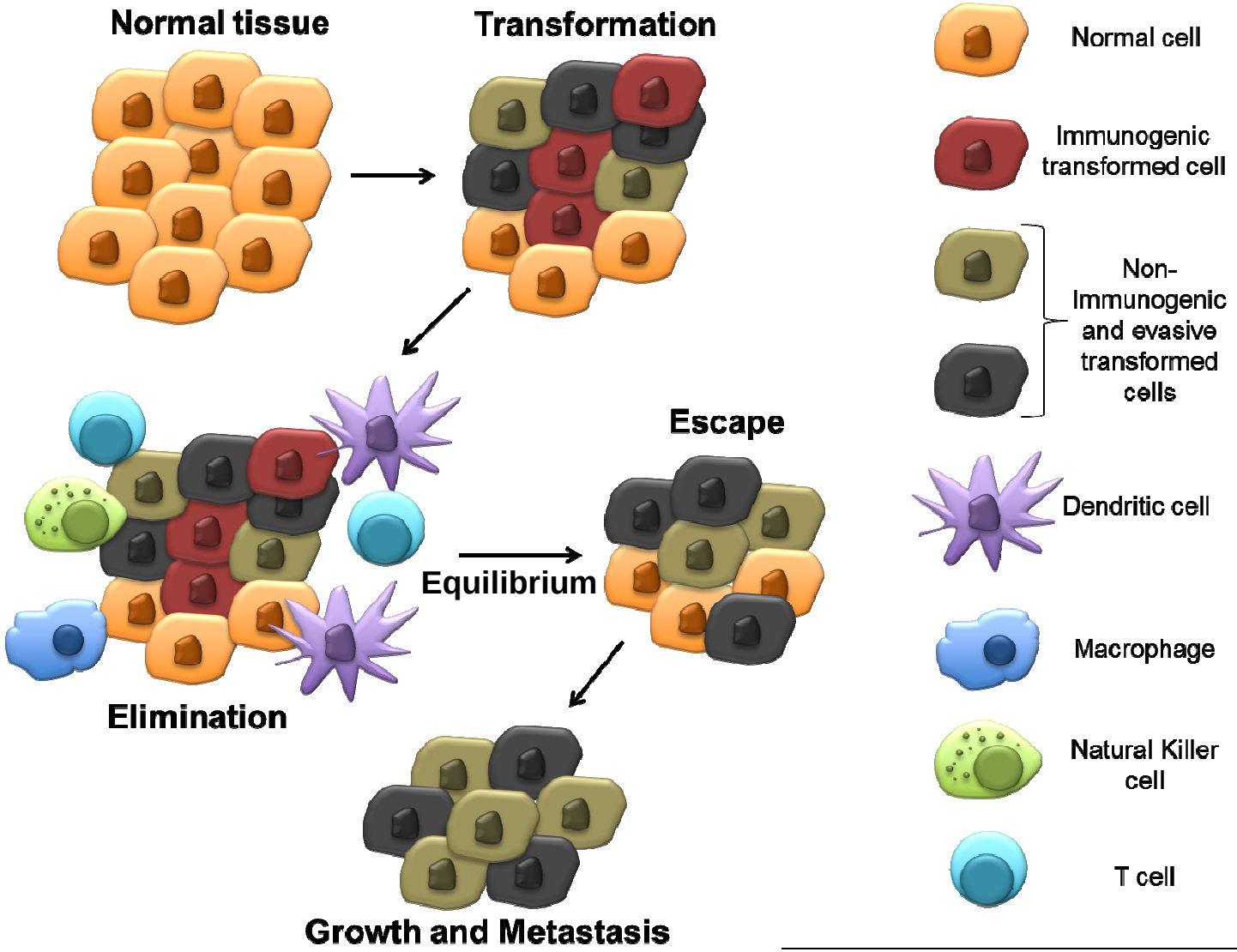
Disclosures

No relevant financial relationships to disclose.

Outline: Basic Mechanisms of Tumor Immune Suppression

1. **Cancer Immunoediting Hypothesis**
2. **Cell Surface Molecular Mechanisms**
   - **CTLA-4** : cytotoxic T-Lymphocyte associated antigen 4
   - **PD-L1** : programmed cell death 1
   - **LAG3**: lymphocyte activation gene 3
3. **Soluble Molecular Mechanisms**
   - **TGF-β** : transfoming growth factor -beta
   - **IL-10** –interleukin 10
4. **Cell-dependent Mechanisms**
   - **Tregs** – regulatory T cells
   - **TAMs** – tumor associated macrophages
   - **MDSCs** – myeloid derived suppressor cells
   - **Tolerized DCs** – dendritic cells

Cancer Immunoediting: The Interplay between the host Immune System and the Developing Tumor



Holtzhausen, A. et al. *Frontiers in Immunology*. 2014. 5: 438.

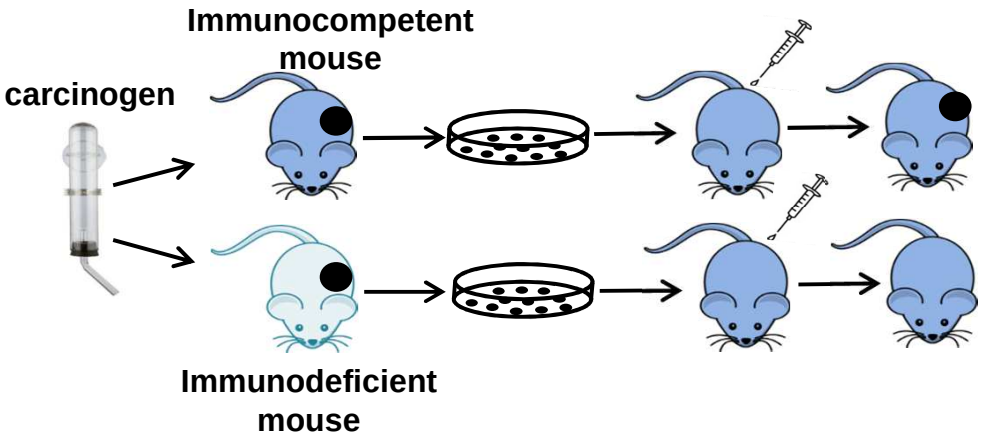
Cancer Immunoediting – the 3 E's

- **Elimination Phase:** The immune system protects the host against tumor formation by destroying immunogenic cancer cells.

- **Equilibrium Phase:** The immune system prevents tumor cell outgrowth while "sculpting" the immunogenicity of the tumor. Many genetic alterations may occur during the Equilibrium phase.

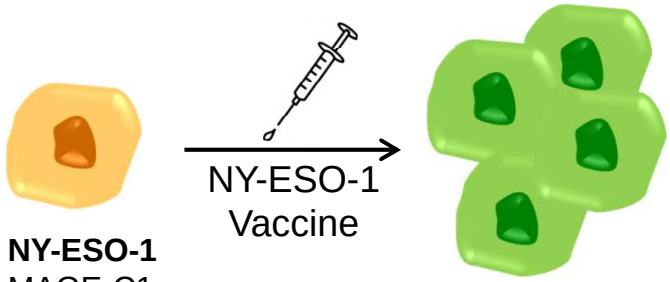
  1. **Defective antigen presentation**
     - Down-regulation in antigen presentation machinery (e.g. MHC class I)
     - Down-regulation of antigen expression

Pre-clinical Example



Schreiber, R. et al. *Science.* 2011. 331: 1565.

Clinical Example

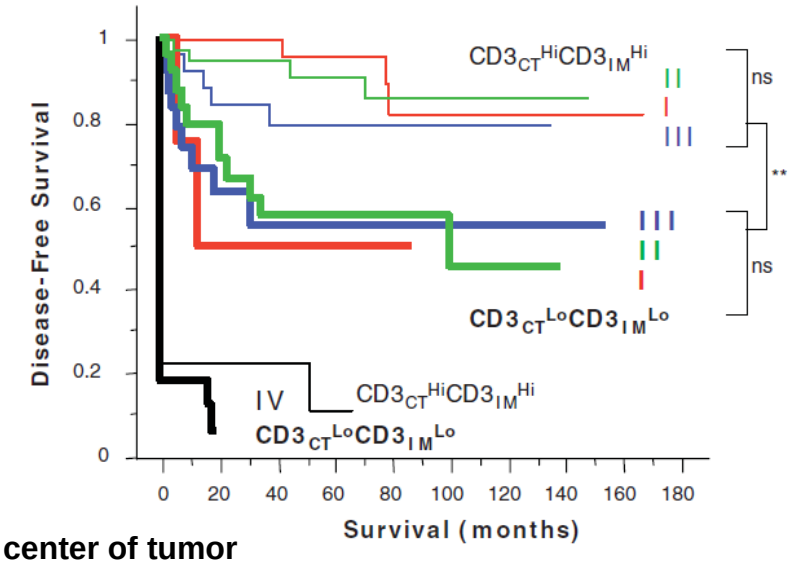


Mittal, D. et al. *Curr Opin Immunol*. 2014. 27: 16.
Von Boehmer, L. et al. *Cancer Immunol*. 2013. 13: 12.

Cancer Immunoediting – the 3 E's

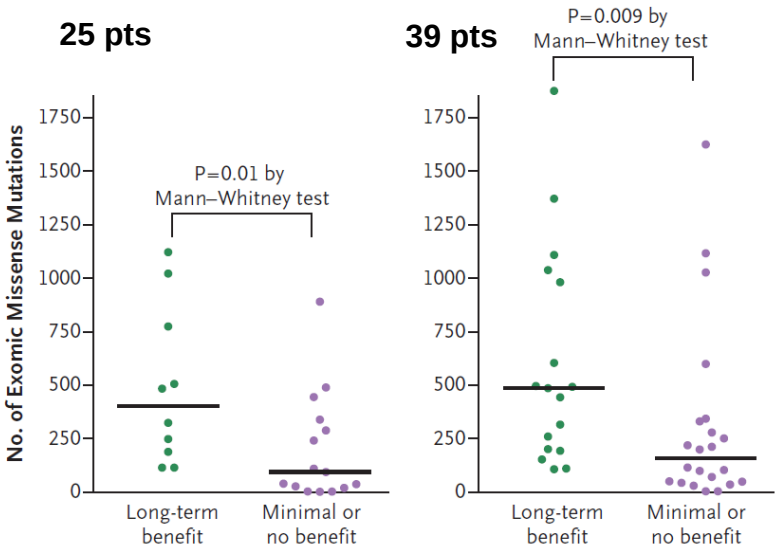
- Defective antigen processing and presentation, by itself, does not account for functional tumor-infiltrating lymphocytes (TILs) and poor prognosis for many solid tumors: evidence of clinical activity in several immunotherapy clinical trials
- Some cancers with high mutational loads, that can be targeted by immune cells, fail to respond to anti-CTLA-4 antibody immunotherapy

Colon Cancer – CD3+ TIL# correlate with longer DFS



CT: center of tumor
IM: invasive margin

Melanoma – Mutational Load correlates with CTLA-4 treatment outcome, but is not sufficient to predict response



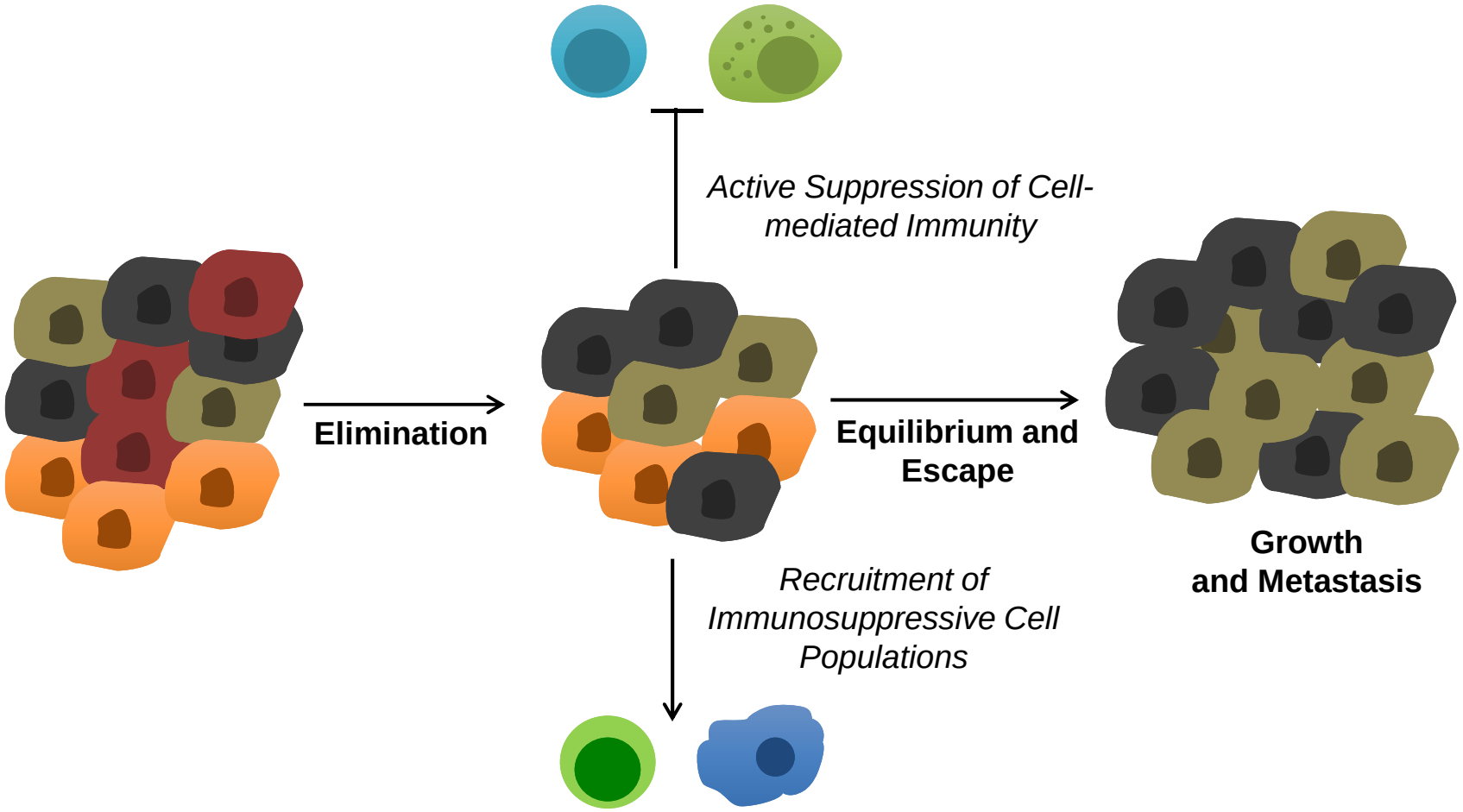
Galon, J. et al. *Science*. 2006. 313: 1960.

Snyder, A. et al. *NEJM.* 2014. 271: 2189.

Cancer Immunoediting – the 3 E's

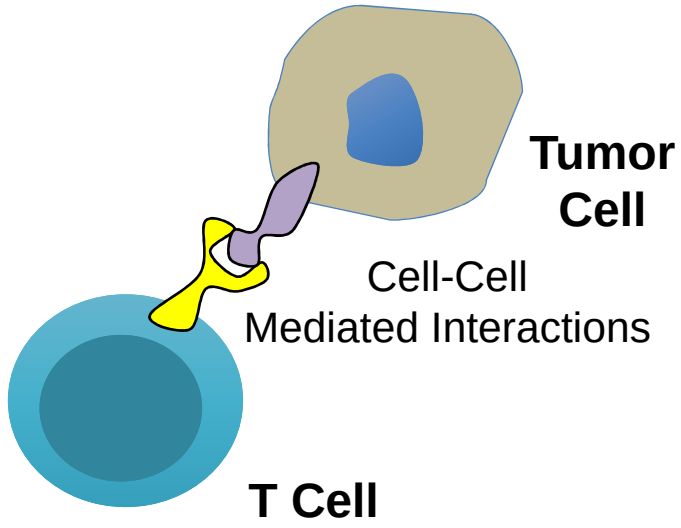
2. Upregulation of immune suppressive mechanisms

- Better explains tumor expression of immunogenic antigens and existence of tumor antigen-specific T cell populations
- Consists of both molecular mechanisms and cell-dependent mechanisms



Outline: Basic Mechanisms of Tumor Immune Suppression

1. **Cancer Immunoediting**
2. **Cell Surface Molecular Mechanisms**
   - CTLA-4
   - PD-L1
   - LAG3
3. **Soluble Molecular Mechanisms**
   - TGF-β
   - IL-10
4. **Cell-dependent Mechanisms**
   - Tregs
   - TAMs
   - MDSCs
   - Tolerized DCs



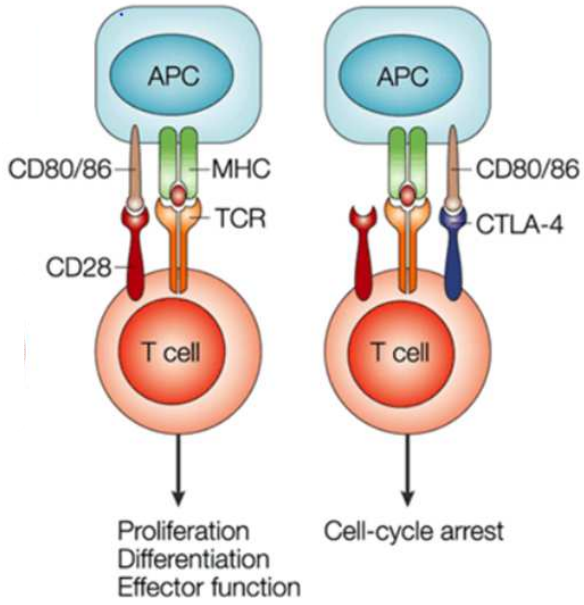
CTLA-4: cytotoxic T-Lymphocyte associated antigen 4

T cell activation occurs after interaction between T cell receptor (TCR) and antigen in the context of MHC (signal 1) plus CD28 costimulation (signal 2).

- **Tumor cells (especially early stage) express MHC I**
- **Most tumor cells do not express co-stimulatory molecules**
- **APC express MHC I and MHC II as well as co-stimulatory molecules, such as B7 (CD80/86).**
- **APC, but not tumor cells stimulate T cells**

CTLA-4: cytotoxic T-Lymphocyte associated antigen 4

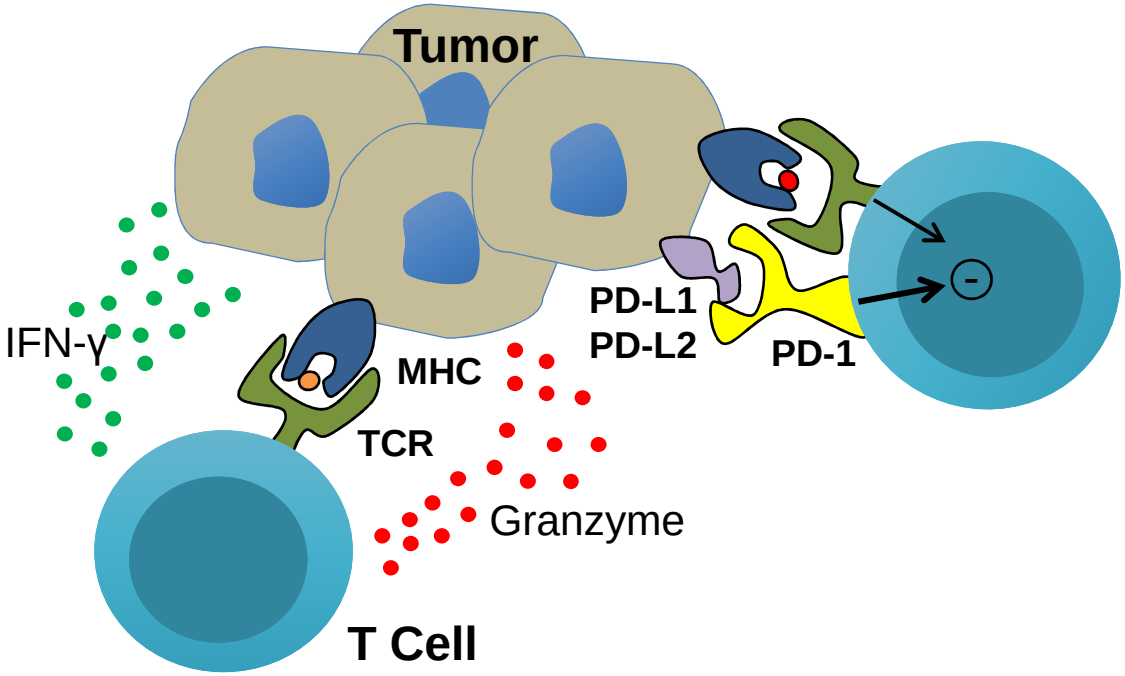
- expressed on activated T cells
- similar to CD28, but binds ligands stronger and transmit inhibitory signals.

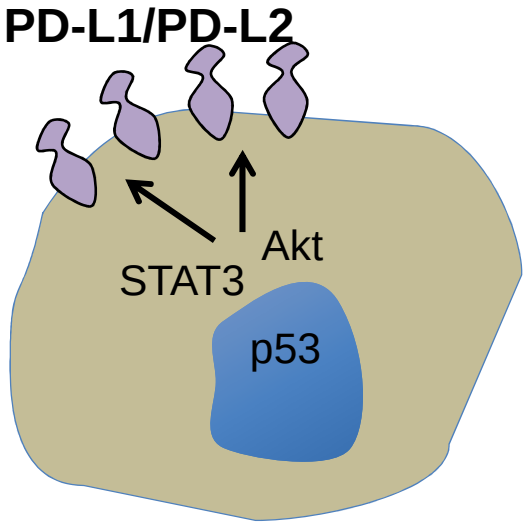


Sharma and Allison, Science, 2015

PD-1 : PD-L Inhibitory Pathway

- PD-1 expression is upregulated in activated and exhausted T cell populations
- PD-L1 and PD-L2 bind PD-1 receptor on T cells to trigger inhibitory signals
- Many tumor tissues express PD-L1 allowing for the suppression of T cell activation
- Tumor PD-L1 expression is regulated via two general mechanisms:
  1. Adaptive immune resistance: upregulated by IFN-γ in peripheral tissues
  2. oncogenic signaling pathways



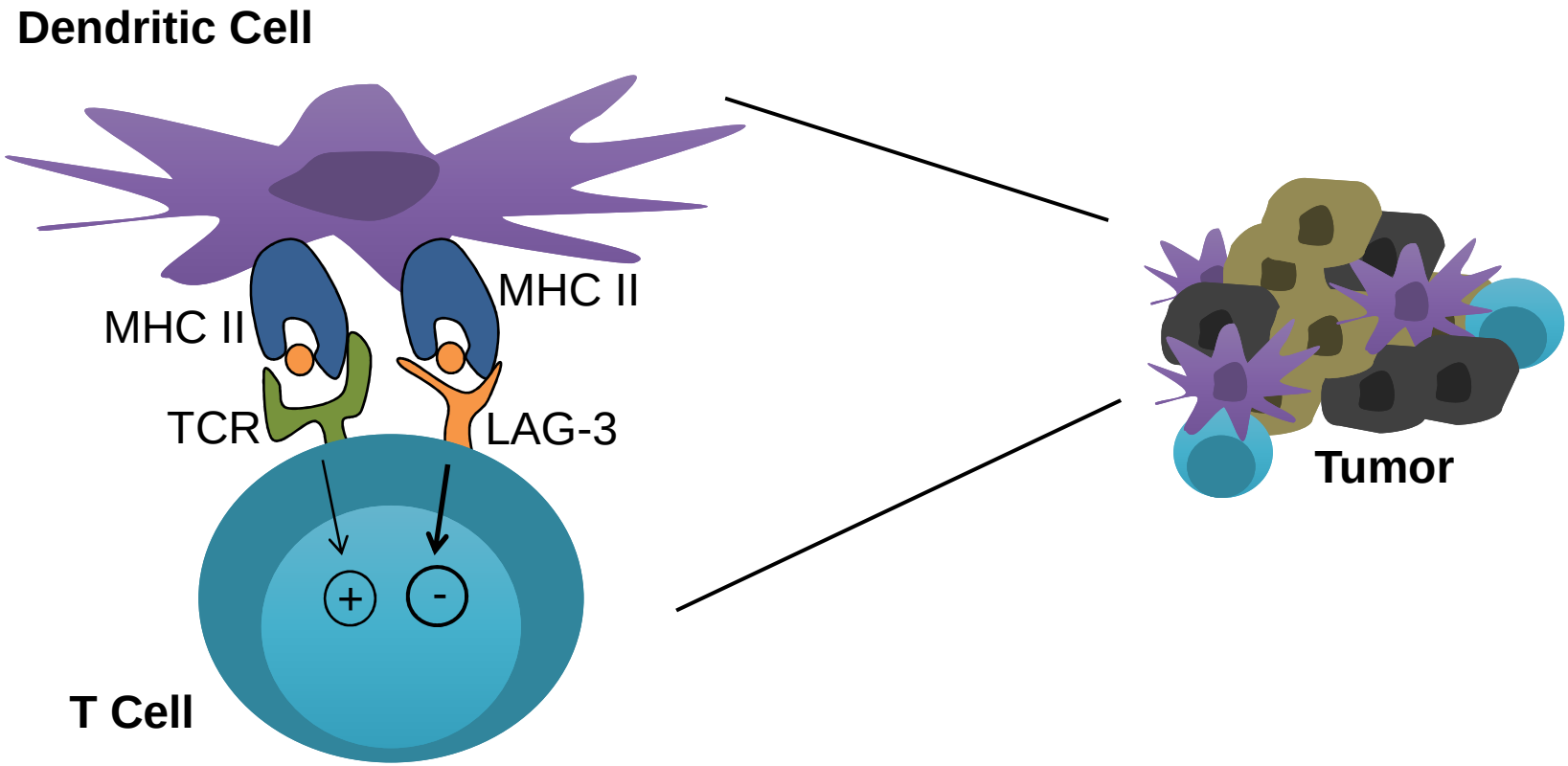


Francisco, L. et al. *Immunol Rev.* 2010. 236: 219.

Pardoll, D.M. *Nat Rev Cancer*. 2012. 12: 252.

LAG3: lymphocyte activation gene 3

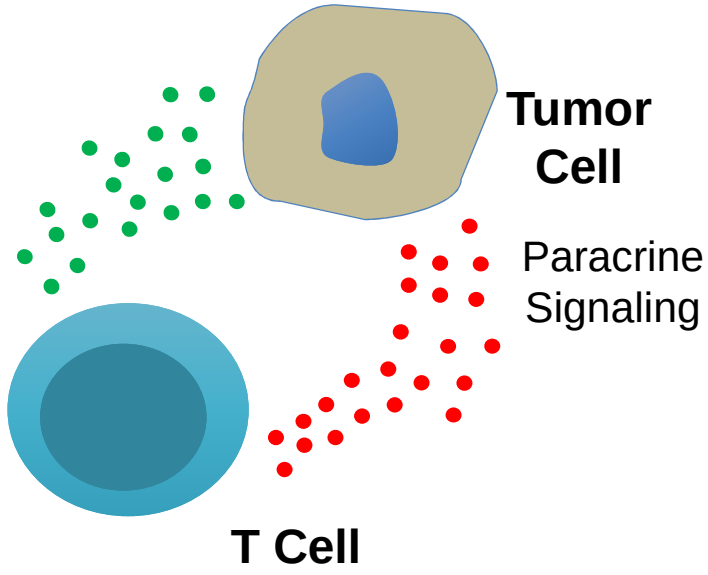
- Upregulated on activated and exhausted T cells
- Binds, with high affinity, to MHC II molecules on the surface of dendritic cells and macrophages
- Engagement of LAG3 co-stimulatory receptor suppresses effector T cell activation
- Expressed by regulatory T cells (Treg); promote Treg-mediated immune suppression



Nguyen, L. and Ohashi, P. *Nat Rev Immunol.* 2015. 15: 45.
Driessens, G. et al. *Immunol Rev.* 2009. 229: 126.

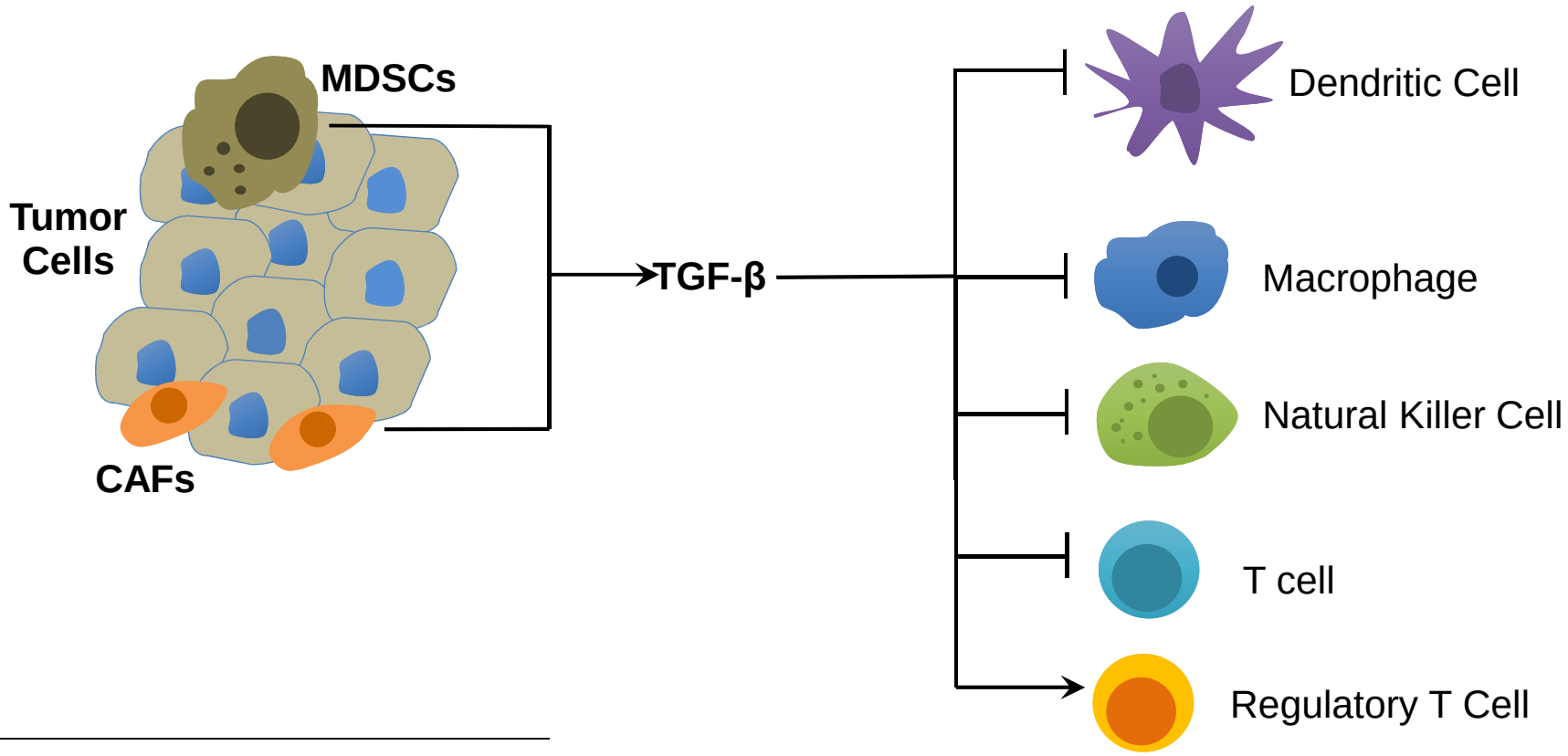
Outline: Basic Mechanisms of Tumor Immune Suppression

1. **Cancer Immunoediting**
2. **Cell Surface Molecular Mechanisms**
   - PD-L1
   - CTLA-4
   - LAG3
3. **Soluble Molecular Mechanisms**
   - TGF-β
   - IL-10
4. **Cell-dependent Mechanisms**
   - Tregs
   - TAMs
   - MDSCs
   - Tolerized DCs



TGF-β: Transforming Growth Factor-β

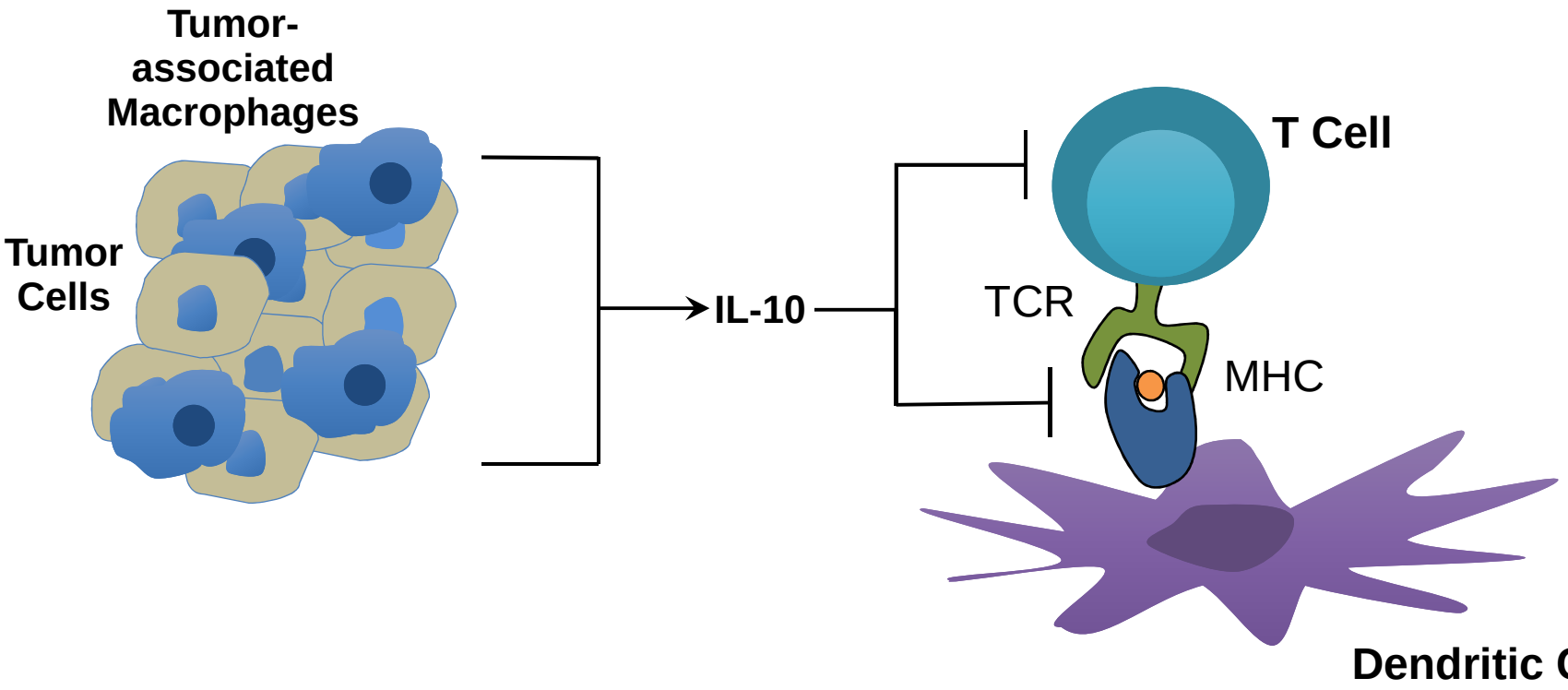
- TGF-β is a soluble cytokine expressed by several tumor types
- TGF-b is expressed by cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) in the tumor microenvironment
- TGF-β potently suppresses the proliferation and activation of $CD8^+$ T cells, $CD4^+$ T cells, and Natural Killer (NK) cells while promoting the differentiation of regulatory T cells



Flavell, R. et al. *Nature Rev Immunol*. 2010. 10: 554.
Hanks, B.A. et al. *J Clin Inves*. 2013. 123: 3925.

IL-10

- IL-10 is expressed by a variety of cell types within the tumor microenvironment including macrophages, $CD4^+$ T cells, and regulatory T cells
- IL-10 suppresses the activation, proliferation, and effector function of naïve T cells.
- IL-10 suppresses the function of antigen-presenting cells such as dendritic cells; promotes regulatory T cell function
- IL-10 enhances the expression of TGF-β and its receptor

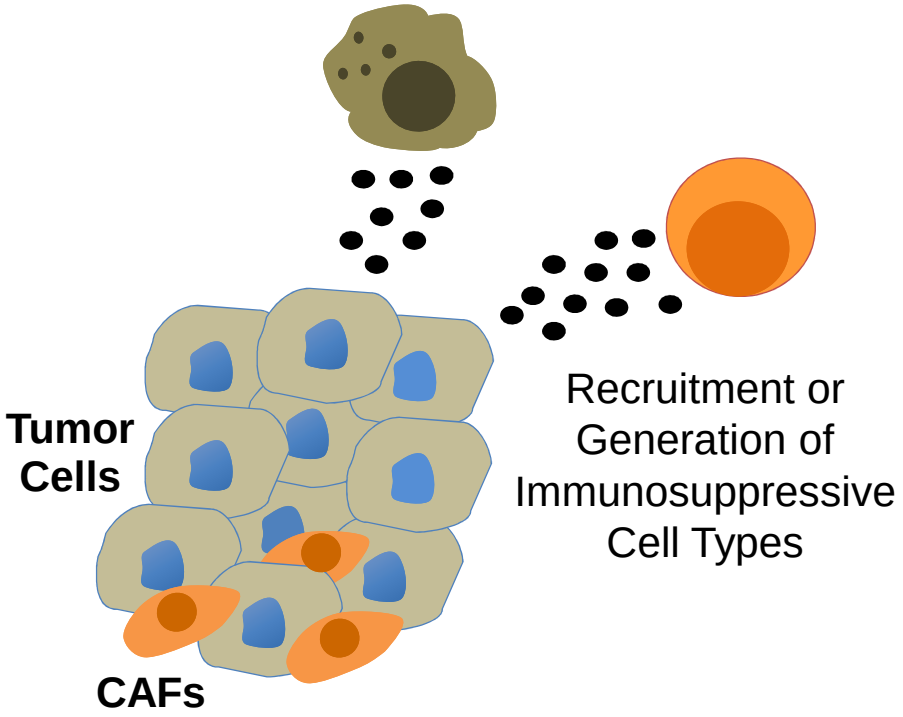


Ruffell, B. et al. *Cancer Cell.* 2014. 26: 623.
Mittal, S. and Roche, P. *Curr Opin Immunol.* 2015. 34: 22.

Mocellin, S. et al. *J Leukocyte Biol.* 2005. 78: 1043.

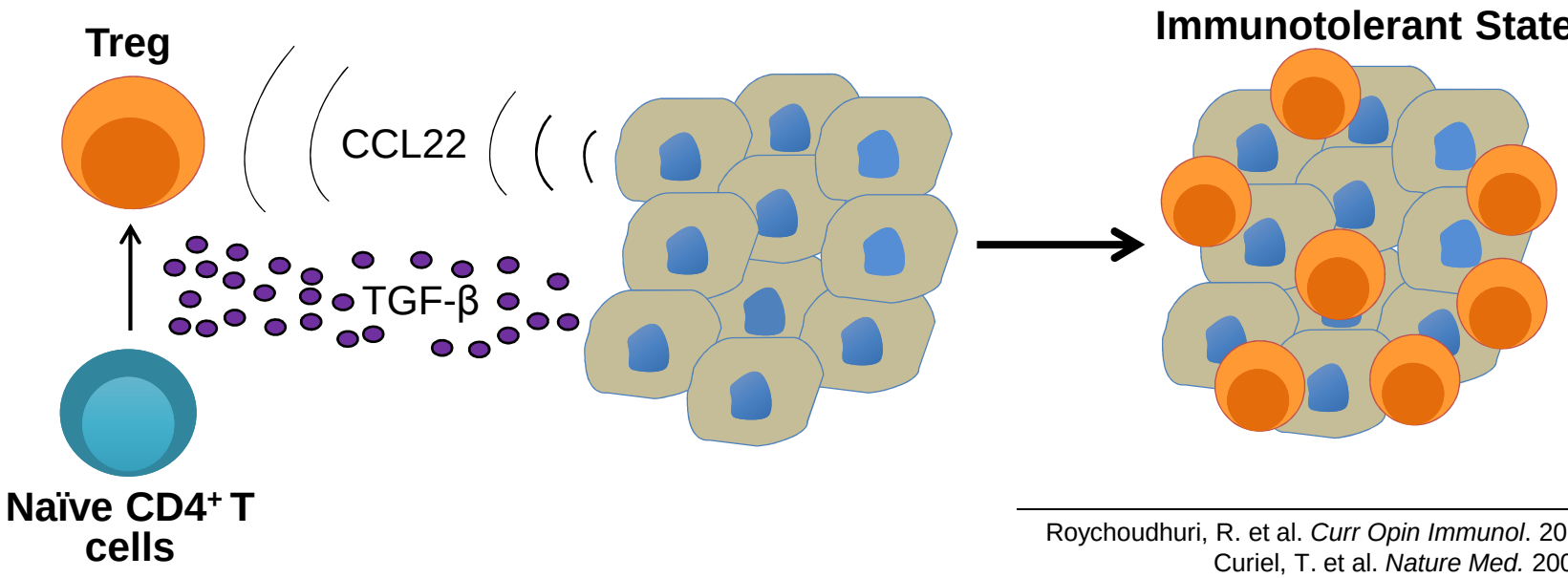
Outline: Basic Mechanisms of Tumor Immune Suppression

1. **Cancer Immunoediting**
2. **Cell Surface Molecular Mechanisms**
   - PD-L1
   - CTLA-4
   - LAG3
3. **Soluble Molecular Mechanisms**
   - TGF-β
   - IL-10
4. **Cell-dependent Mechanisms**
   - Tregs
   - TAMs
   - MDSCs
   - Tolerized DCs



Treg: Regulatory T Cells

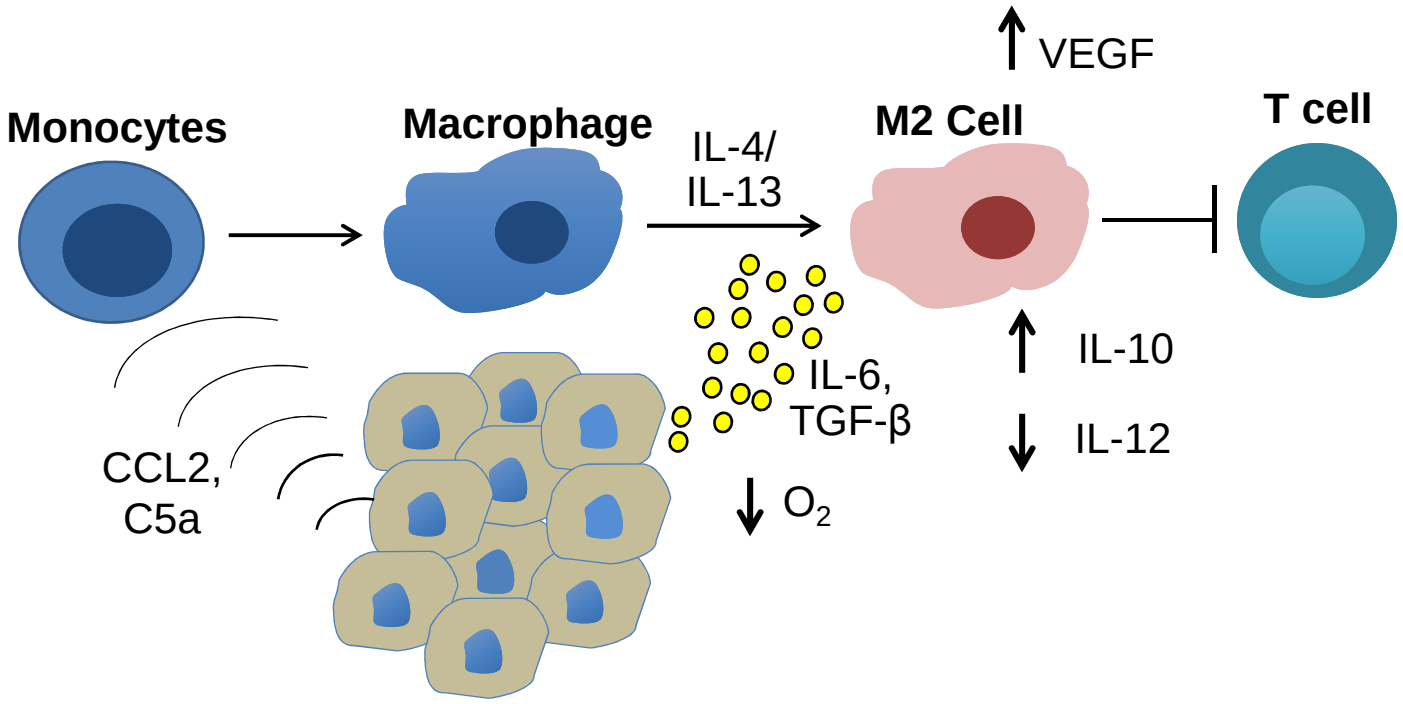
- $CD4^+$ $FoxP3^+$ Treg is a subpopulation of CD4 T cells.
- Treg play a critical role in maintaining peripheral tolerance
  - FoxP3 is a transcription factor that drives the genetic program of Tregs
  - A defect in the FoxP3 gene leads to the development of a lethal autoimmune disease in humans- immunodysregulation polyendocrinopathy enteropathy X-linked syndrome: IPEX
- Tregs mediate effector T cell suppression via cell-cell contact-dependent mechanisms (e.g. CTLA-4) and the production of soluble cytokines (TGF-β, IL-10)
- Low $T_{effector}$/Treg ratios are associated with a poor prognosis in multiple cancer types
- TGF-β promotes the conversion and activation of Tregs within the tumor microenvironment
- Tumors also recruit Tregs to the tumor bed via expression of soluble chemokines



Roychoudhuri, R. et al. *Curr Opin Immunol*. 2015. 33: 101
Curiel, T. et al. *Nature Med.* 2004. 10: 942.

TAMs: Tumor-Associated Macrophages

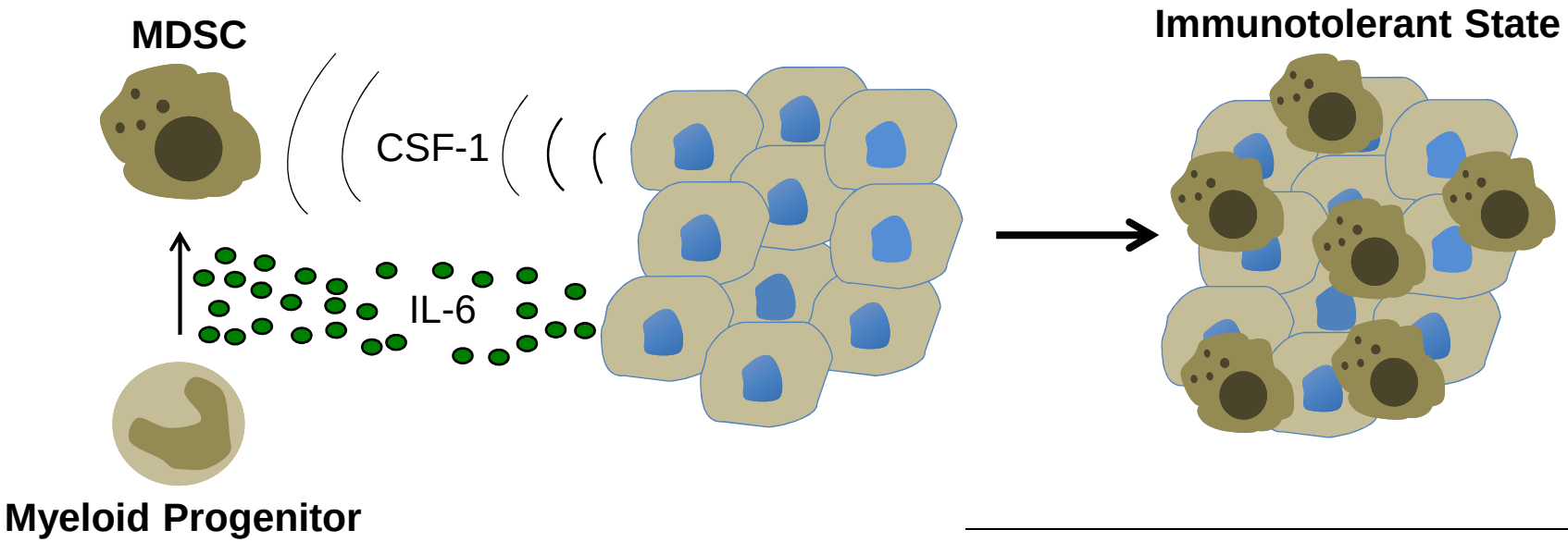
- Circulating monocyte recruitment maintains a population of resident TAMs within the tumor microenvironment (CCL2)
- Various signals within the tumor (cytokines, metabolic products) polarize macrophages to undergo a phenotypic switch (M2) to express several factors that suppress local immunity, promote angiogenesis, and promote tumor cell survival



Mantvani, A. and Allavena, P. *J Exp Med*. 2015. 212: 435.
Noy, R. and Pollard, J. *Immunity*. 2014. 41: 49.

MDSCs: Myeloid-Derived Suppressor Cells

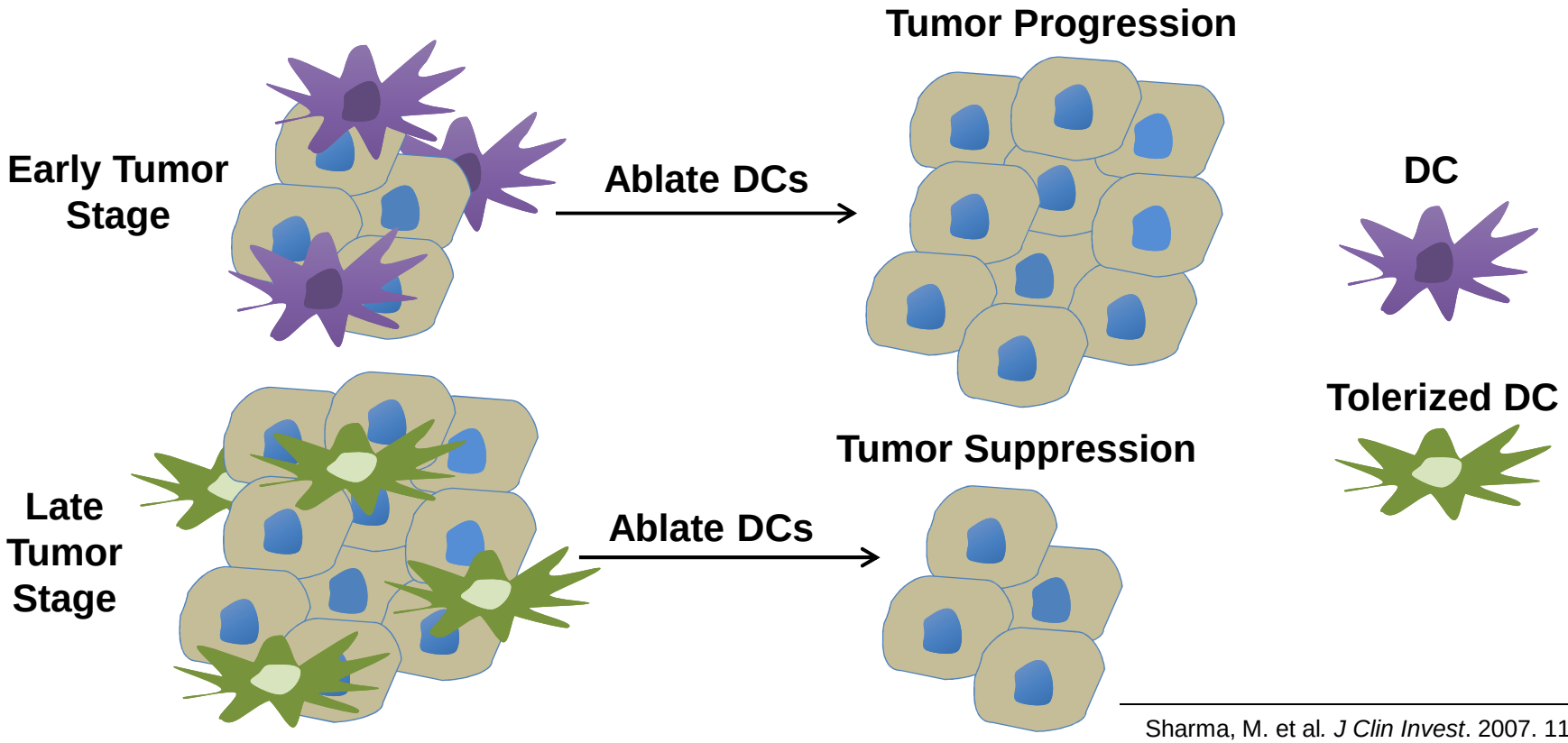
- MDSCs represent a heterogeneous population of immature myeloid cells that develop due to defective differentiation
- MDSC expand cancer and inflammation; tumor-mediated signaling via STAT3 (e.g. IL-6) promotes MDSC expansion
- MDSCs are capable of suppressing T cell response via several mechanisms
  - In the setting of cancer, MDSCs upregulate the expression Arginase and iNOS (inducible nitric oxide synthase) to degrade arginine and generate NO and reactive oxygen species (ROS)
  - Express high levels of TGF-β



Cheng, P. et al. *J Exp Med*. 2008. 205: 2235.
Serafini, P. et al. *Sem Cancer Biol.* 2006. 16: 53.
Gabrilovich, D. and Nagaraj. S. *Nat Rev Immunol*. 2009. 9: 162.

Tolerized Dendritic Cells

- Dendritic cells (DCs) play a key role in tumor immunosurveillance by priming tumor antigen-specific T cell responses and modulating their function
- DCs are capable of promoting Treg generation and activation accumulate within both tumor tissues and nearby draining lymph node tissues
- Tolerized DCs potently suppress nearby effector T cell responses



Sharma, M. et al. *J Clin Invest*. 2007. 117: 2570.
Scarlett, U. et al. *J Exp Med*. 2012. 209: 495.
Hurwitz, A. and Watkins, S. *Cancer Immunol Immunother.* 2012. 61: 289.

Lessons and Take Home Messages

- The cancer immun-editing hypothesis provides a framework for iterating cancer-mediated immune suppression
- Developing cancers actively suppress the host immune system through a variety of mechanisms which promote or enable tumor progression
- Understanding these mechanisms can lead to novel immunotherapeutic approaches which will likely involve combinatorial regimens
- Ranking the dominance of immune evasion mechanisms in individual cancer type or individual patient will facilitate personalized immunotherapy regimens – genetic linkage to treatment response