

# Society for Immunotherapy of Cancer (SITC)

## Basic Mechanisms of Tumor Immune Suppression

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Advances in Cancer Immunotherapy™ - Illinois  
May 29, 2015



Society for Immunotherapy of Cancer

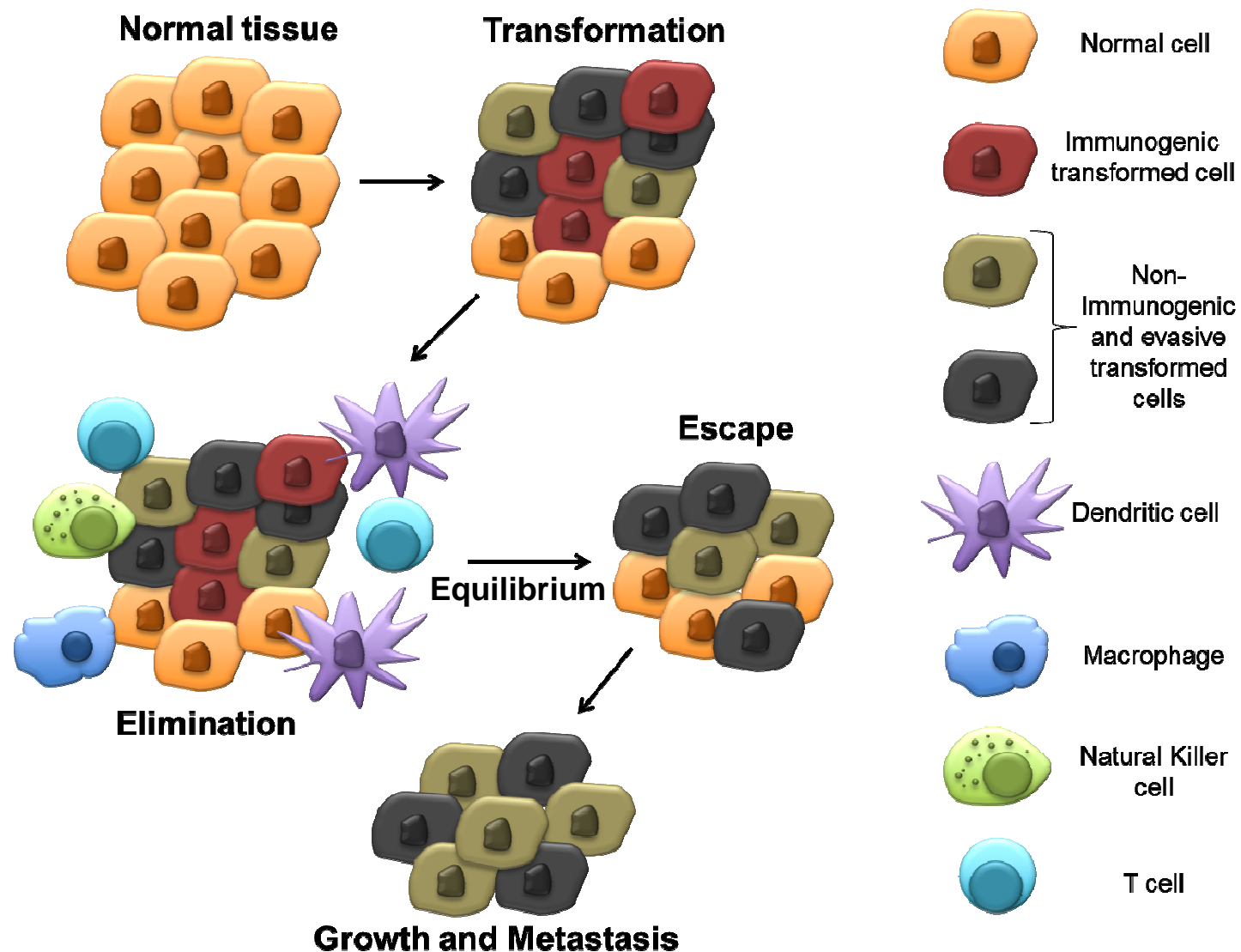
# Disclosures

- Shareholder in Bellicum Pharmaceuticals, Inc.
- Research Funding from Merck & Co.
- Research Funding from Med-Pacto, Inc.

# Outline: Basic Mechanisms of Tumor Immune Suppression

- 1. Cancer Immunoediting Hypothesis**
- 2. Cell Surface Molecular Mechanisms**
  - PD-L1
  - LAG3
- 3. Soluble Molecular Mechanisms**
  - TGF- $\beta$
  - IL-10
  - IDO
- 4. Cell-dependent Mechanisms**
  - Tregs
  - TAMs
  - MDSCs
  - Tolerized DCs

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



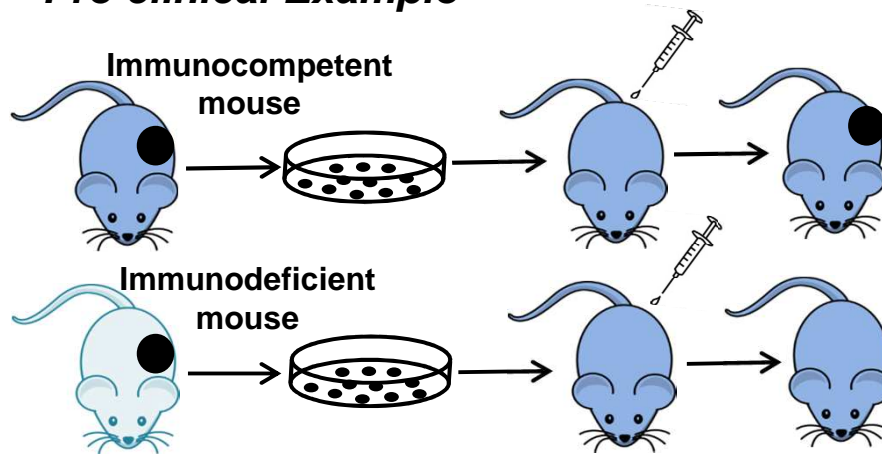
# Cancer Immunoediting – the 3 E's

- **Elimination Phase:** The immune system protects the host against tumor formation by selectively destroying the more immunogenic cancer cells.
- **Equilibrium Phase:** The immune system prevents tumor cell outgrowth while “sculpting” the immunogenicity of the tumor. Many genetic alterations occur during the Equilibrium phase referred to as immunoediting.

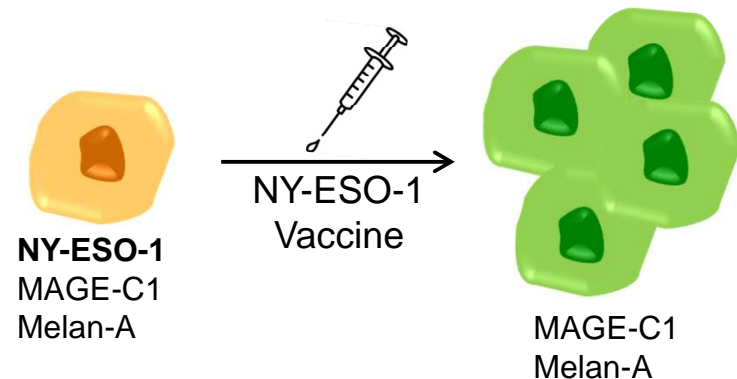
## 1. Defective antigen presentation

- Downregulation in antigen presentation machinery (e.g. MHC class I)
- Downregulation of antigen expression

### Pre-clinical Example



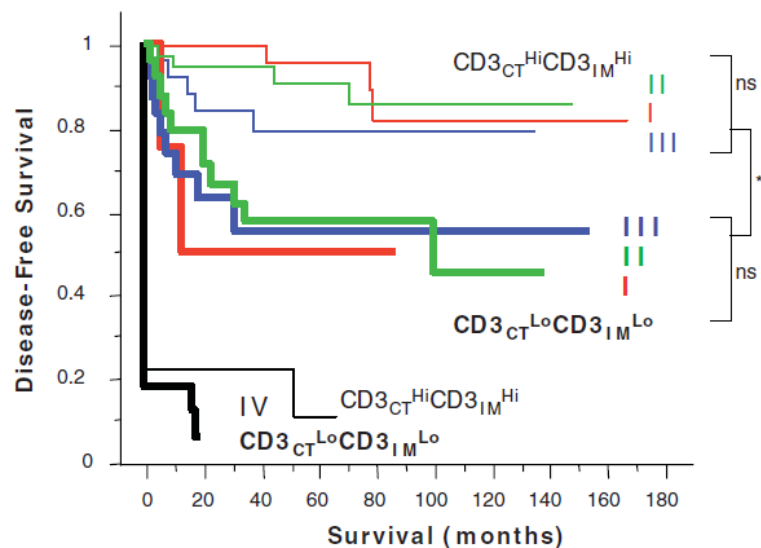
### Clinical Example



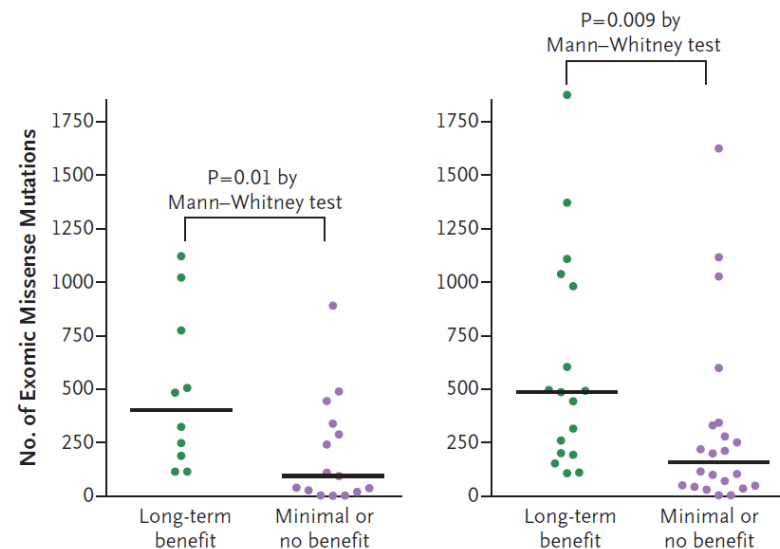
# Cancer Immunoediting – the 3 E's

- Defective antigen processing and presentation alone does not explain the relationship observed between tumor-infiltrating lymphocytes (TILs) and prognosis for many solid tumors; evidence of clinical activity in several immunotherapy clinical trials
- This mechanism also fails to explain the existence of high mutational loads in cancers that fail to respond to anti-CTLA-4 antibody immunotherapy

## Colon Cancer - TILs



## Melanoma – Mutational Load



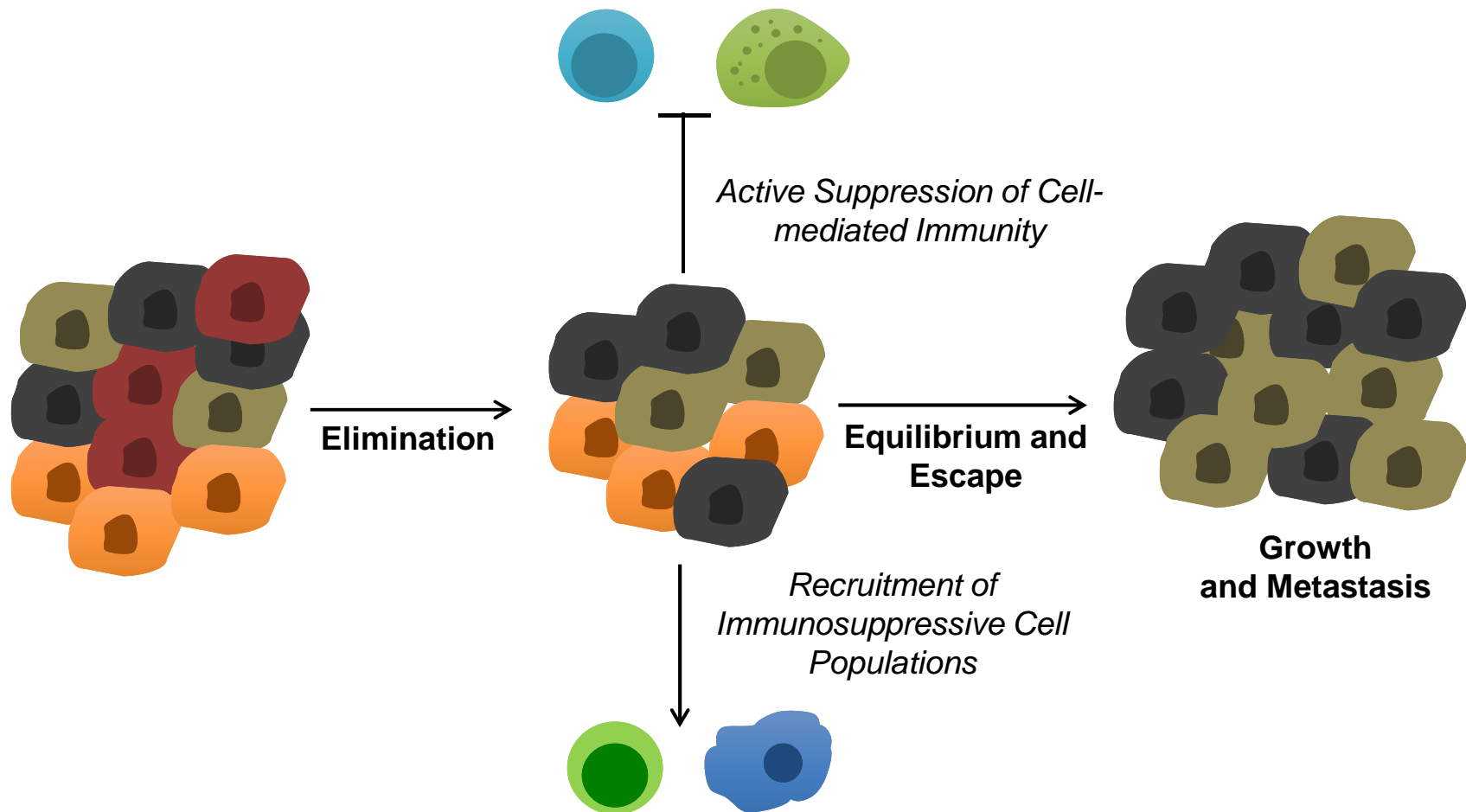
Galon, J. et al. *Science*. 2006. 313: 1960.

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

# Cancer Immunoediting – the 3 E's

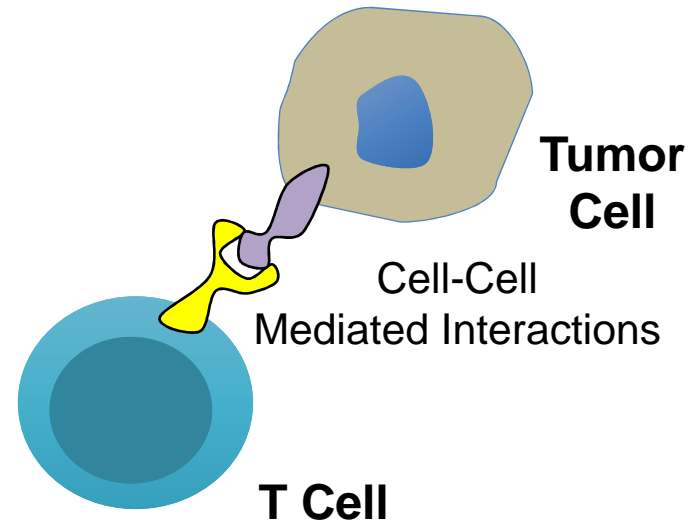
## 2. Upregulation of active immune suppressive mechanisms

- 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

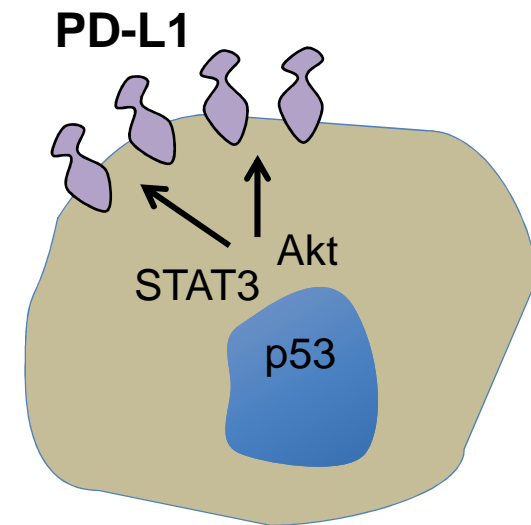
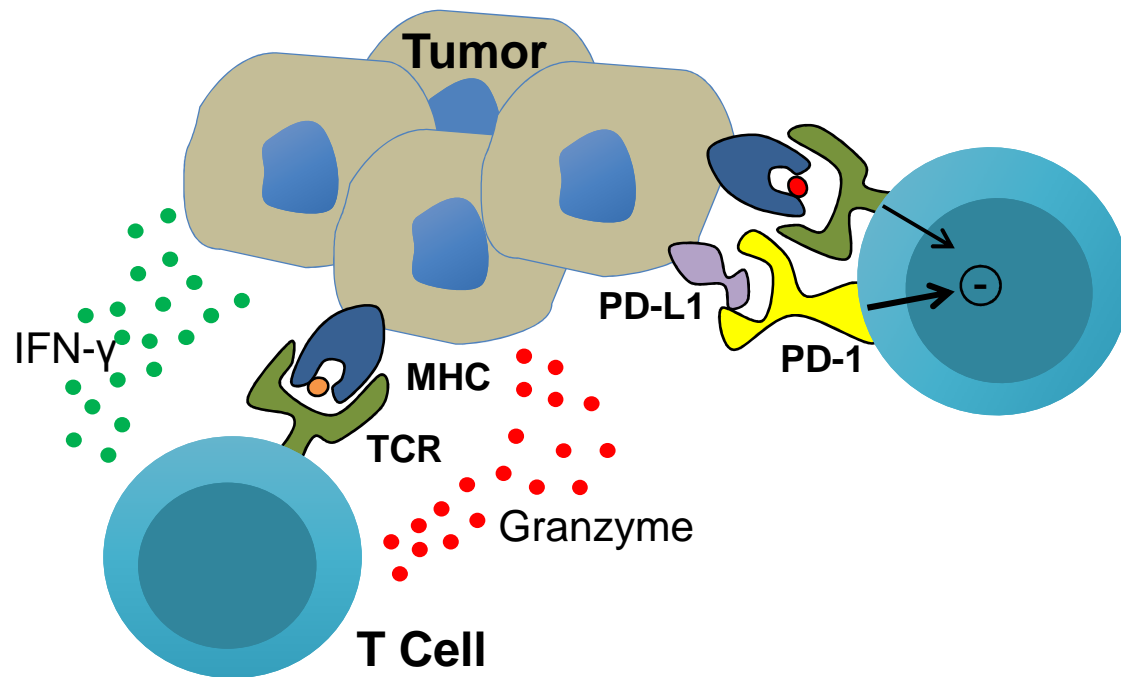
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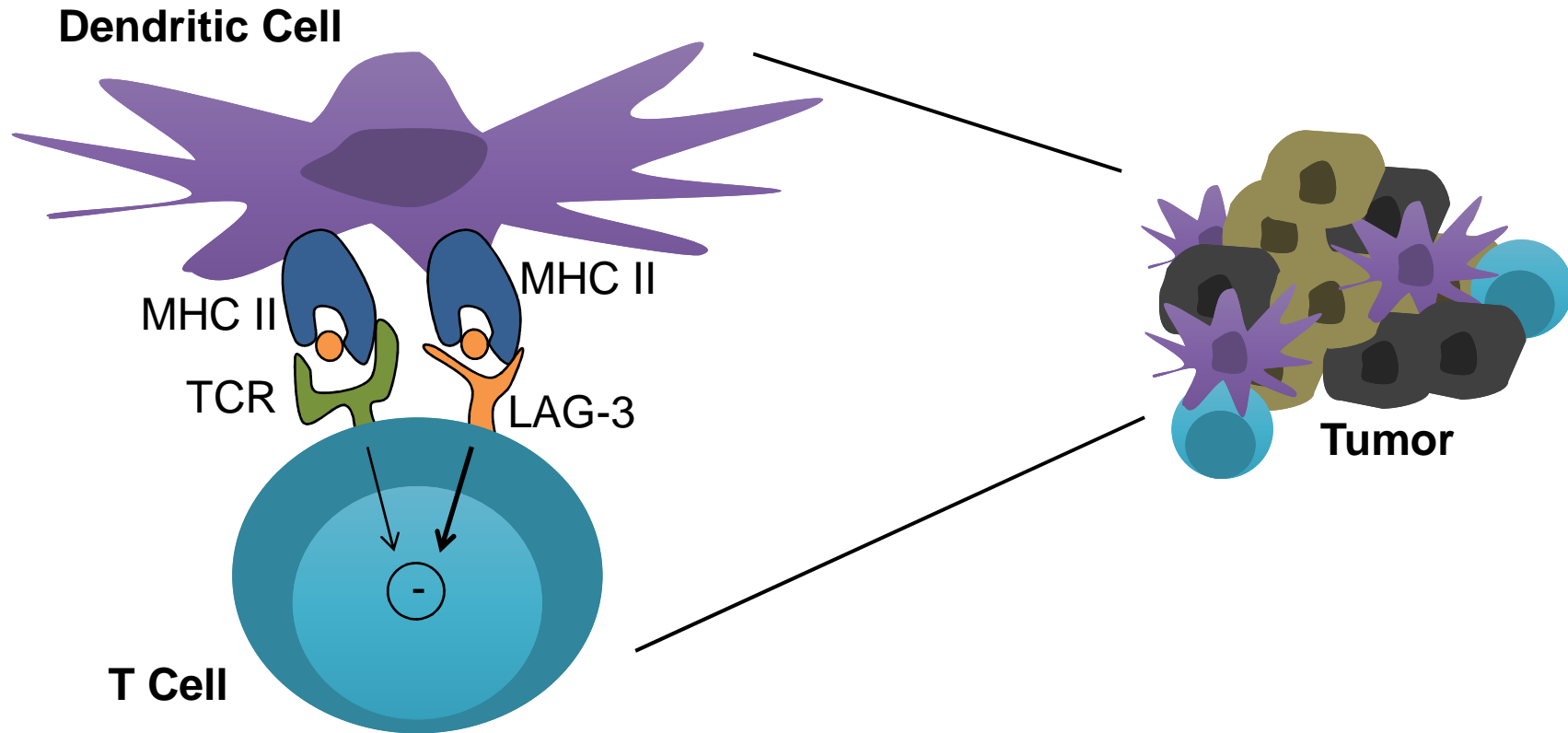
# PD-1 : PD-L Inhibitory Pathway

- PD-1 signaling promotes T cell tolerization by inhibiting downstream activation signals
- PD-1 expression is upregulated by activated and exhausted T cell populations
- T cell surface PD-1 receptor binds to and is activated by PD-L1 and PD-L2
- 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- $\gamma$  in peripheral tissues
  2. Innate immune resistance: oncogenic signaling pathways



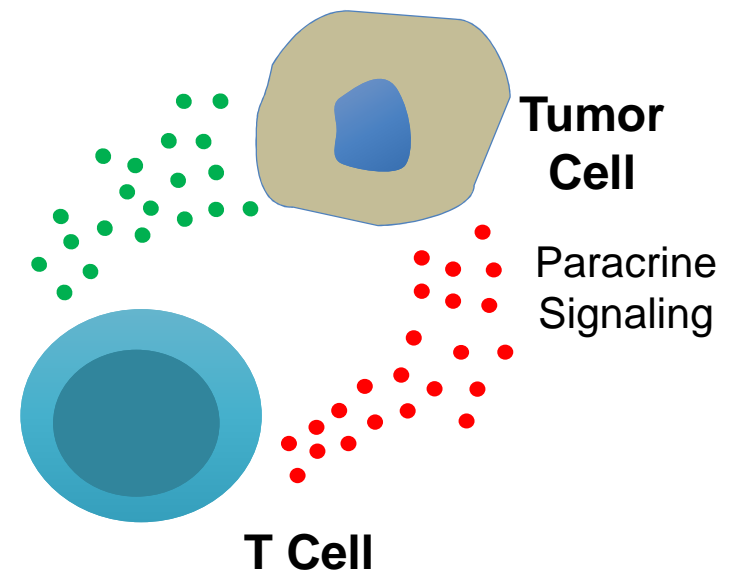
# LAG3: lymphocyte activation gene 3

- Upregulated by activated and exhausted T cells
- Negative co-stimulatory receptor that suppresses T cell activation
- Expressed by regulatory T cells; promote regulatory T cell-mediated immune suppression
- Binds to MHC II molecules with high affinity on the surface of tumor-infiltrating DCs and macrophages



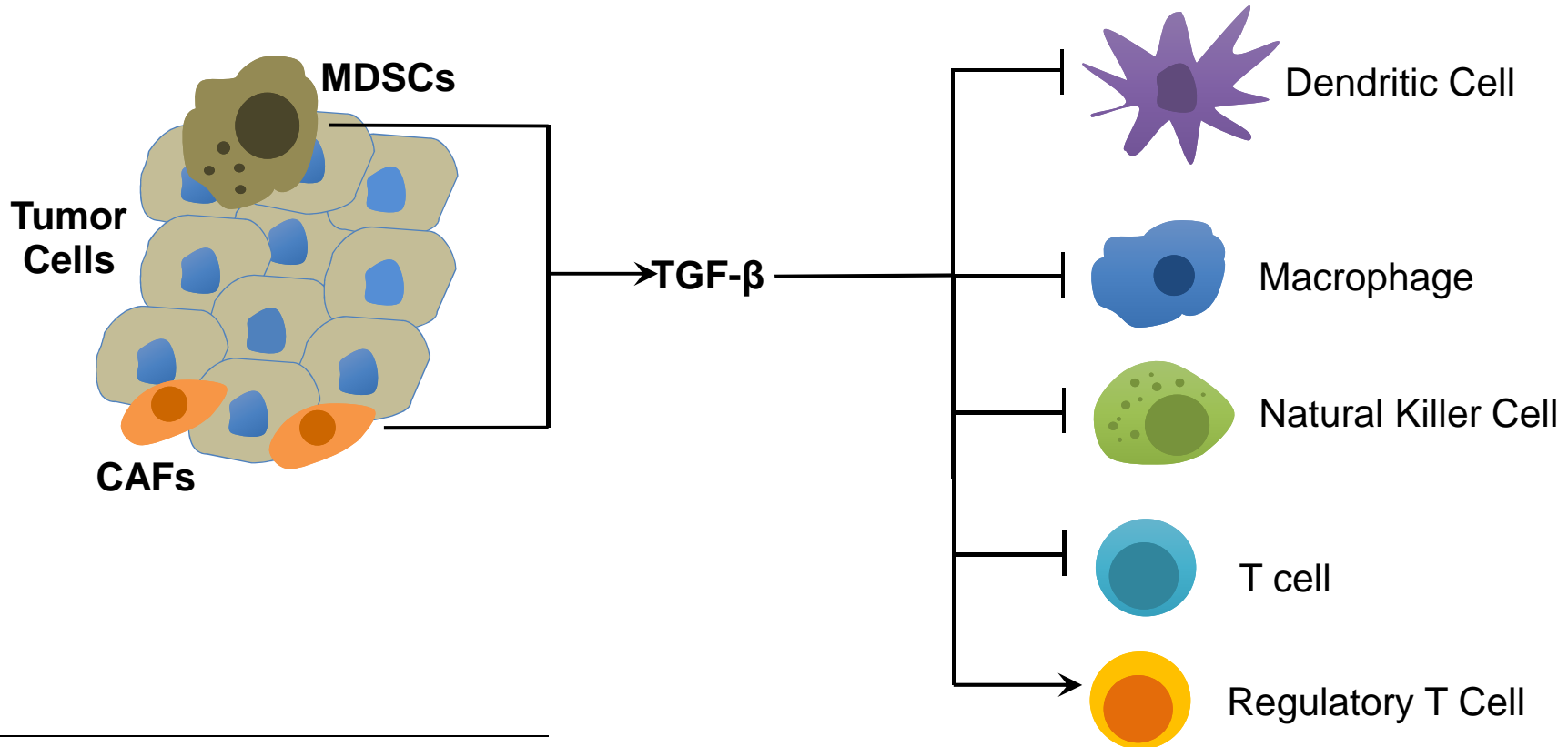
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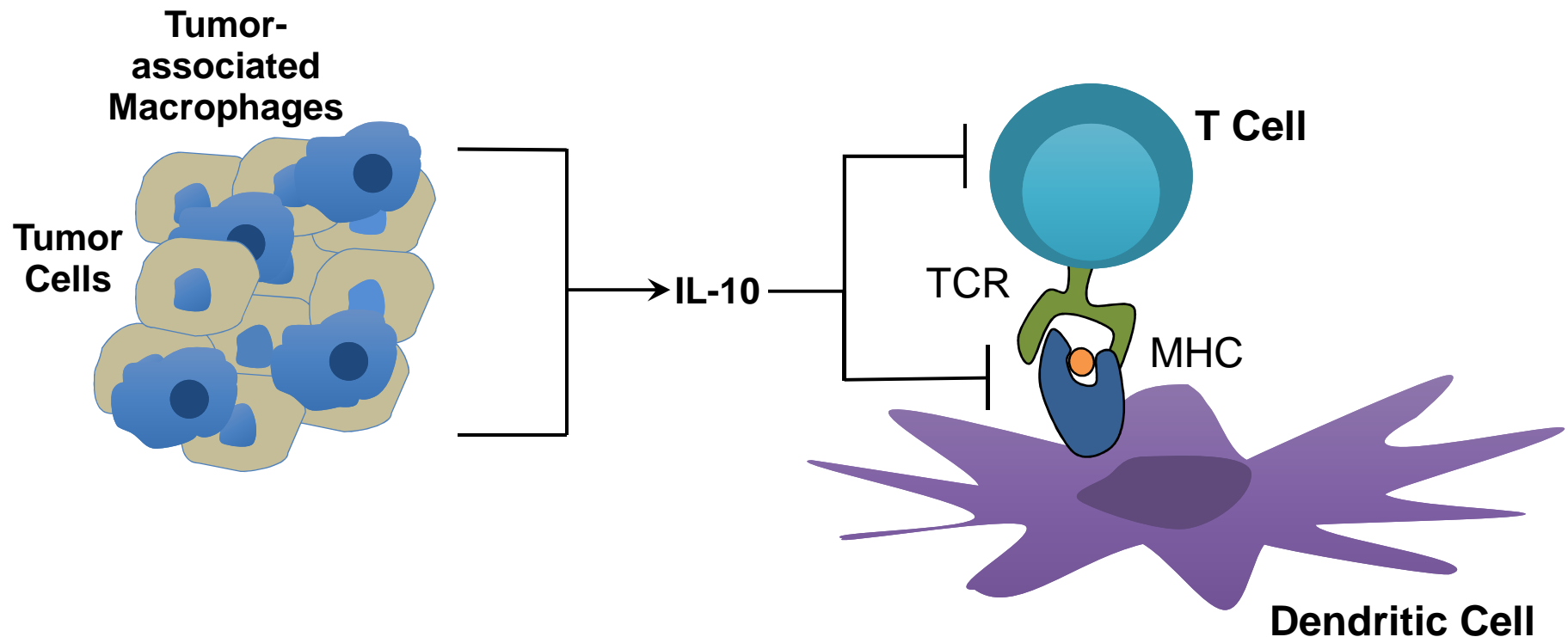
# TGF- $\beta$ : Transforming Growth Factor- $\beta$

- TGF- $\beta$  is a soluble cytokine expressed by several tumor types in addition to cancer-associated fibroblasts (CAFs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs) in the tumor microenvironment
- TGF- $\beta$  potently suppresses the proliferation and activation of CD8<sup>+</sup> cytotoxic T cells, CD4<sup>+</sup> T helper cells, and Natural Killer (NK) cells while promoting the differentiation of regulatory T cells



# IL-10

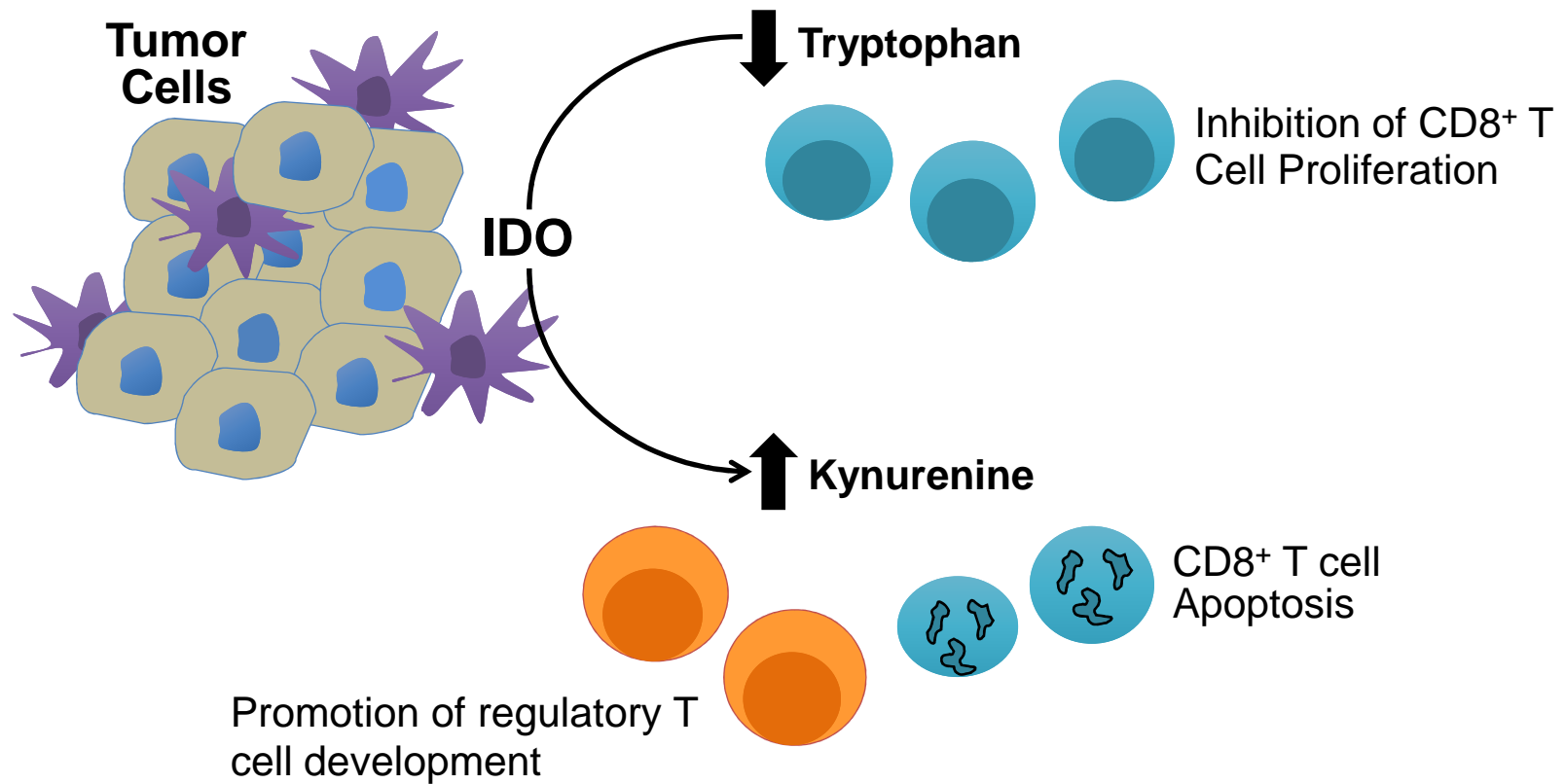
- IL-10 is expressed by a variety of cell types within the tumor microenvironment including macrophages, CD4<sup>+</sup> T cells, and regulatory T cells
- IL-10 suppresses the activation, proliferation, and effector function of naïve T cells while also suppressing the function of antigen-presenting cells such as dendritic cells; promotes regulatory T cell function
- IL-10 enhances the expression of TGF- $\beta$  and its receptor



\* *In some contexts, IL-10 has also been shown to be immunostimulatory*

# IDO: Indoleamine 2,3-dioxygenase

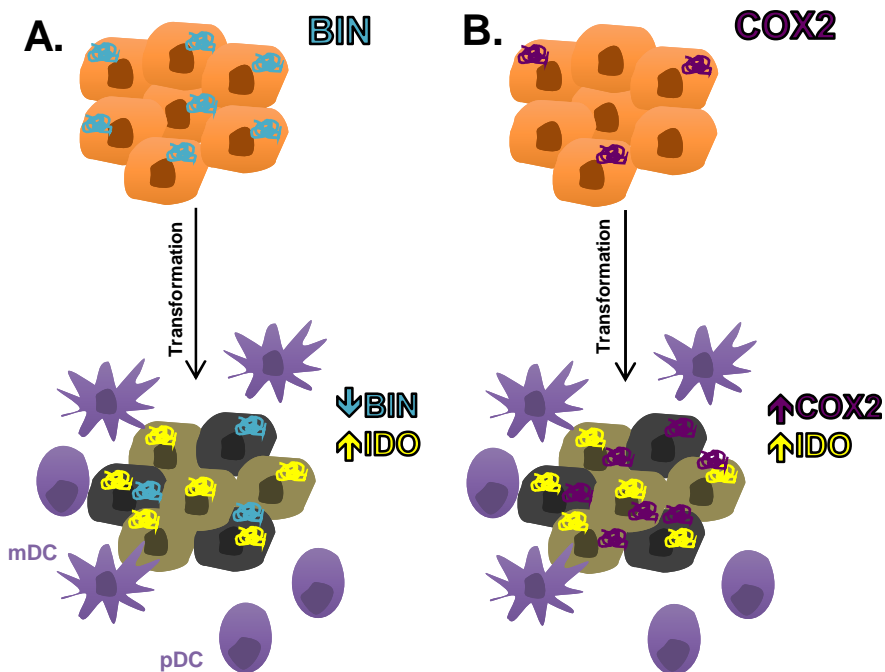
- IDO is expressed by dendritic cells, macrophages, and tumor cells
- IDO catalyzes the conversion of the essential amino acid tryptophan to kynurenine
- Suppresses T cell proliferation/activation and promotes T cell apoptosis
- Promotes regulatory T cell differentiation and activation



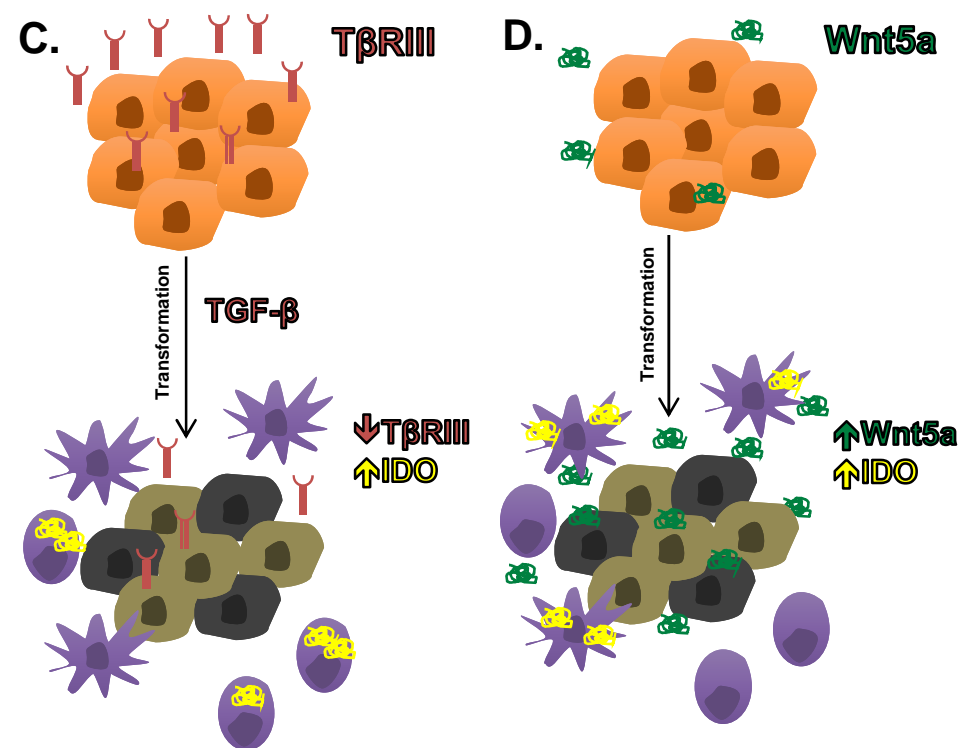
# Regulation of IDO During Tumorigenesis

- Pathways which drive carcinogenesis have also been shown to stimulate IDO expression both intrinsically (by the tumor itself) and extrinsically (within dendritic cells in the tumor microenvironment)

## Intrinsic Regulation

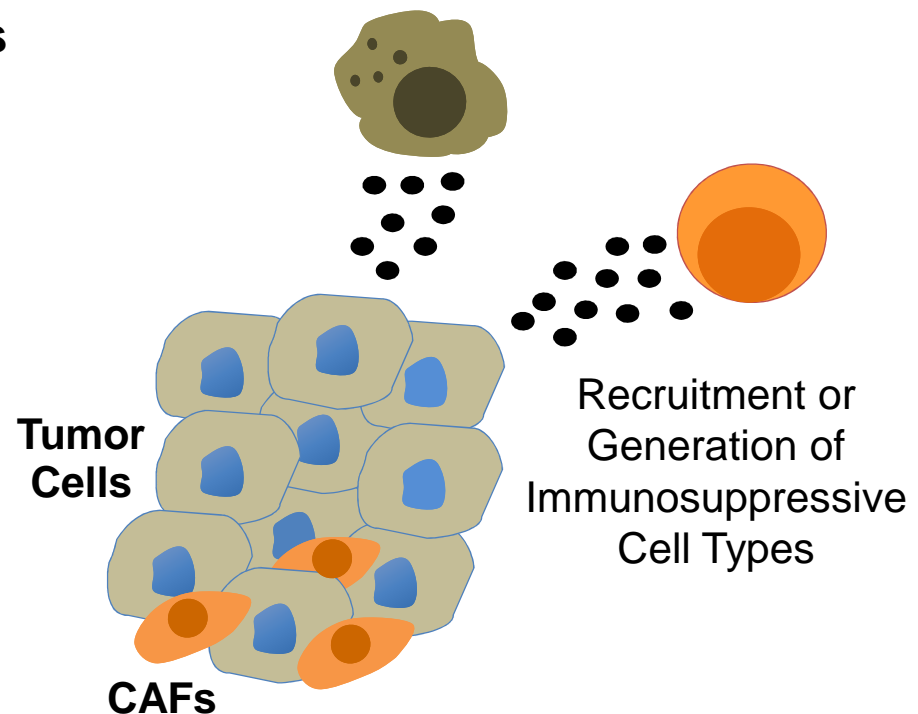


## Extrinsic Regulation



# Outline: Basic Mechanisms of Tumor Immune Suppression

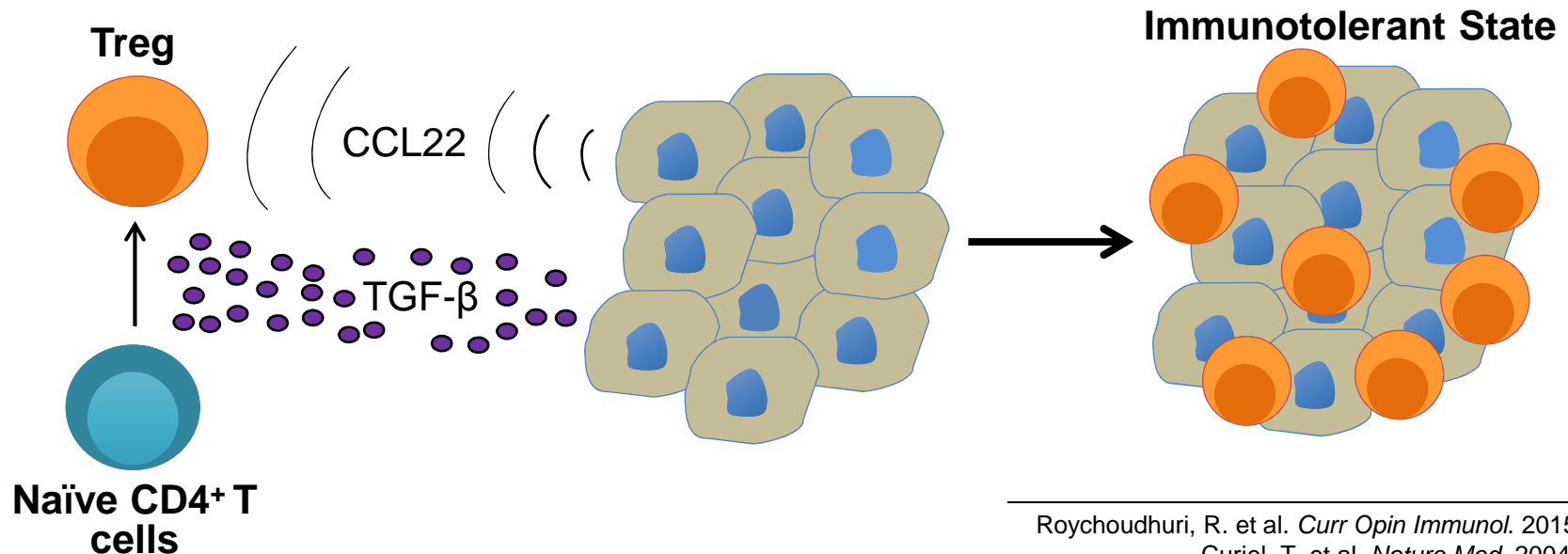
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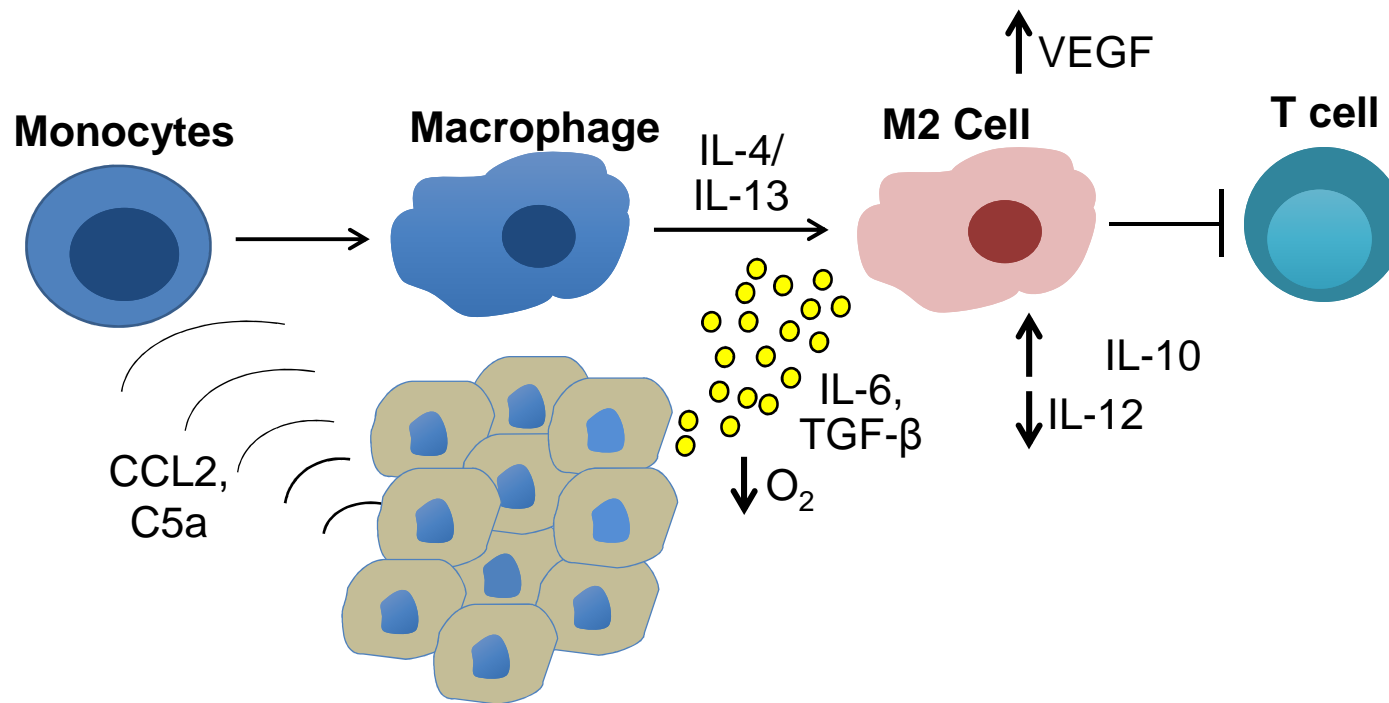
# Tregs: Regulatory T Cells

- CD4<sup>+</sup> FoxP3<sup>+</sup> Tregs 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
- Tregs mediate effector T cell suppression via cell-cell contact-dependent mechanisms (CTLA-4, PD-L1) and the production of soluble cytokines (TGF- $\beta$ , IL-10)
- Low T<sub>effector</sub>/Treg ratios are associated with a poor prognosis in multiple cancer types
- TGF- $\beta$  and IDO promote the differentiation and activation of Tregs within the tumor microenvironment
- Tumors also recruit Tregs to the tumor bed via expression of soluble chemokines



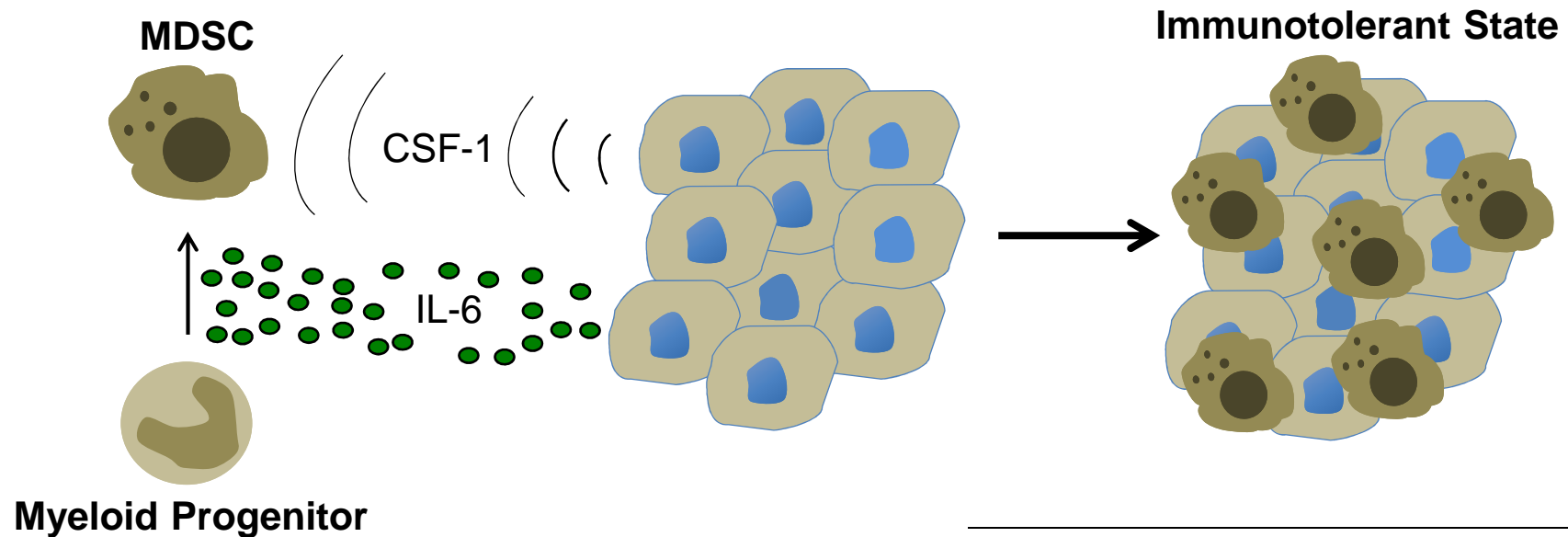
# TAMs: Tumor-associated Macrophages

- 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



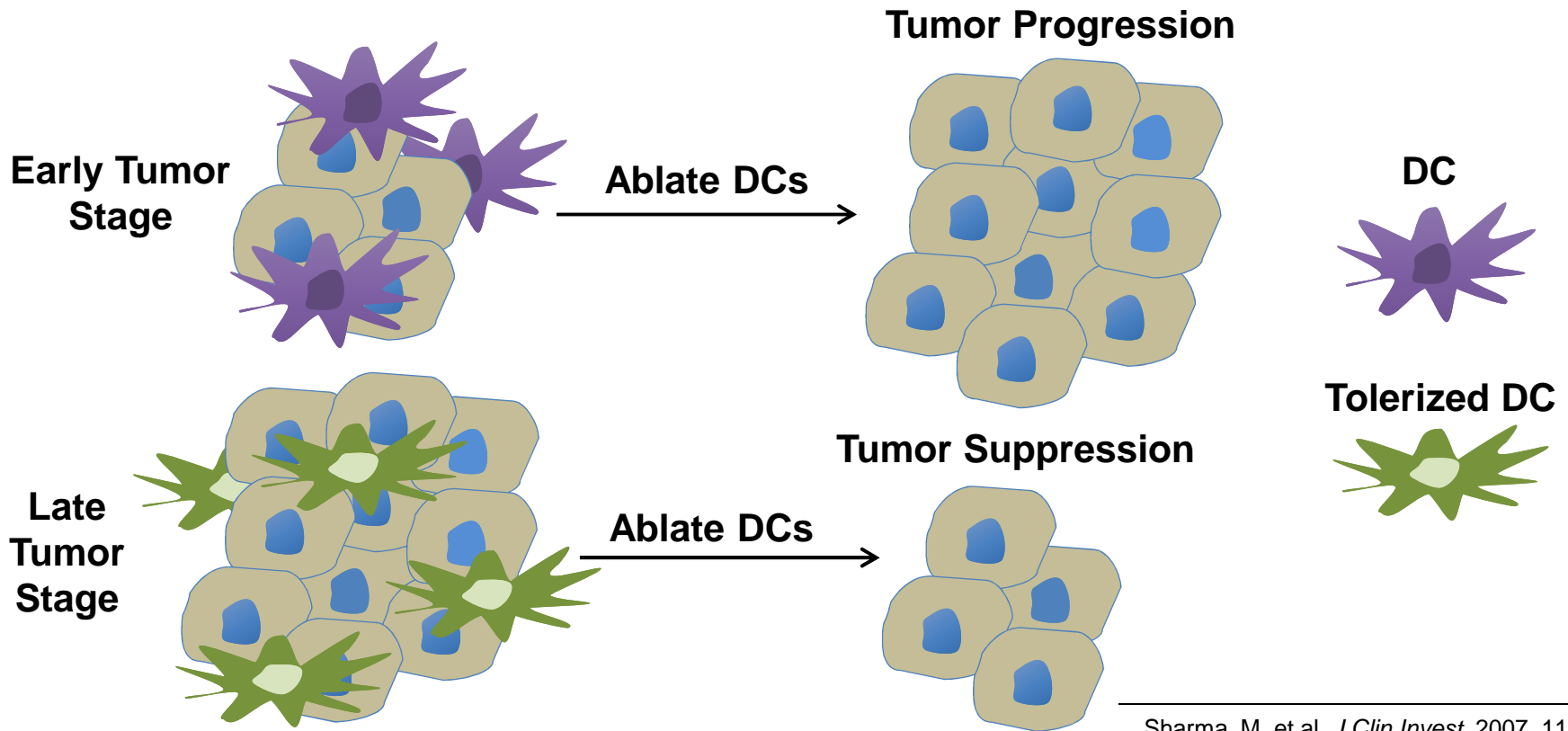
# MDSCs: Myeloid-derived Suppressor Cells

- MDSCs represent a heterogeneous population of immature myeloid cells that develop due to defective differentiation in the bone marrow
- MDSC numbers expand in the setting of cancer and inflammation; tumor-mediated signaling via STAT3 (e.g. IL-6, VEGF) 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- $\beta$



# 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 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
- IDO seems to significantly contribute to the immunosuppressive function of tolerized DCs



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 Immunoediting Hypothesis provides the intellectual framework for understanding the evolution of cancer-mediated immune suppression
- Developing cancers actively suppress the host immune system through a variety of mechanisms which are ultimately necessary for cancer progression
- Understanding these mechanisms of cancer-mediated immune evasion promises to lead to the identification of novel immunotherapeutic approaches which will likely involve combinatorial regimens
- Understanding which immune evasion mechanism is dominant for which individual cancer type or individual patient will facilitate the development of personalized immunotherapy regimens

Celebrating 30 Years of Advancing  
Cancer Immunotherapy Worldwide



# The Society for Immunotherapy of Cancer (SITC) Presents its 30<sup>th</sup> Anniversary Annual Meeting & Associated Programs

**November 4 – 8, 2015 | National Harbor, Maryland**

- **SITC 30<sup>th</sup> Anniversary Annual Meeting**
- **Workshop: New Perspectives on Target Antigens in the Changing Cancer Immunotherapy Landscape**
- **Primer on Tumor Immunology and Cancer Immunotherapy™**
- **Global Regulatory Summit**  
Featuring Regulatory Agency Representatives from Around the World
- **International Symposium on Cancer Immunotherapy**  
Led by Innovators in the Field from Around the Globe
- **Predictive Biomarkers in Cancer Immunotherapy: Oasis or Mirage?**  
An Open Debate Organized by SITC's Industry Committee
- **Cancer Immunotherapy Patient Forum**  
Presented by Global Resource for Advancing Cancer Education, Melanoma Research Alliance and SITC

## Conference Highlights

- Keynote address to be given by **Professor Tasuku Honjo, 2015 Richard V. Smalley, MD Memorial Award Recipient**
- *Milestones in Immunotherapy* session featuring talks by Dr. James P. Allison, Dr. Cornelis J.M. Melief, Dr. Steven A. Rosenberg & Dr. Robert Schreiber
- Dedicated Early Career Scientist Activities & Awards
- Special 30<sup>th</sup> Anniversary Programming & Celebratory Events

Learn more at [www.sitcancer.org/2015](http://www.sitcancer.org/2015)

The 30<sup>th</sup> Anniversary Annual Meeting, Workshop and Primer are jointly provided by the Annenberg Center for Health Sciences at Eisenhower and the Society for Immunotherapy of Cancer in collaboration with Postgraduate Institute for Medicine.

