Tumor Microenvironment and Immune Suppression

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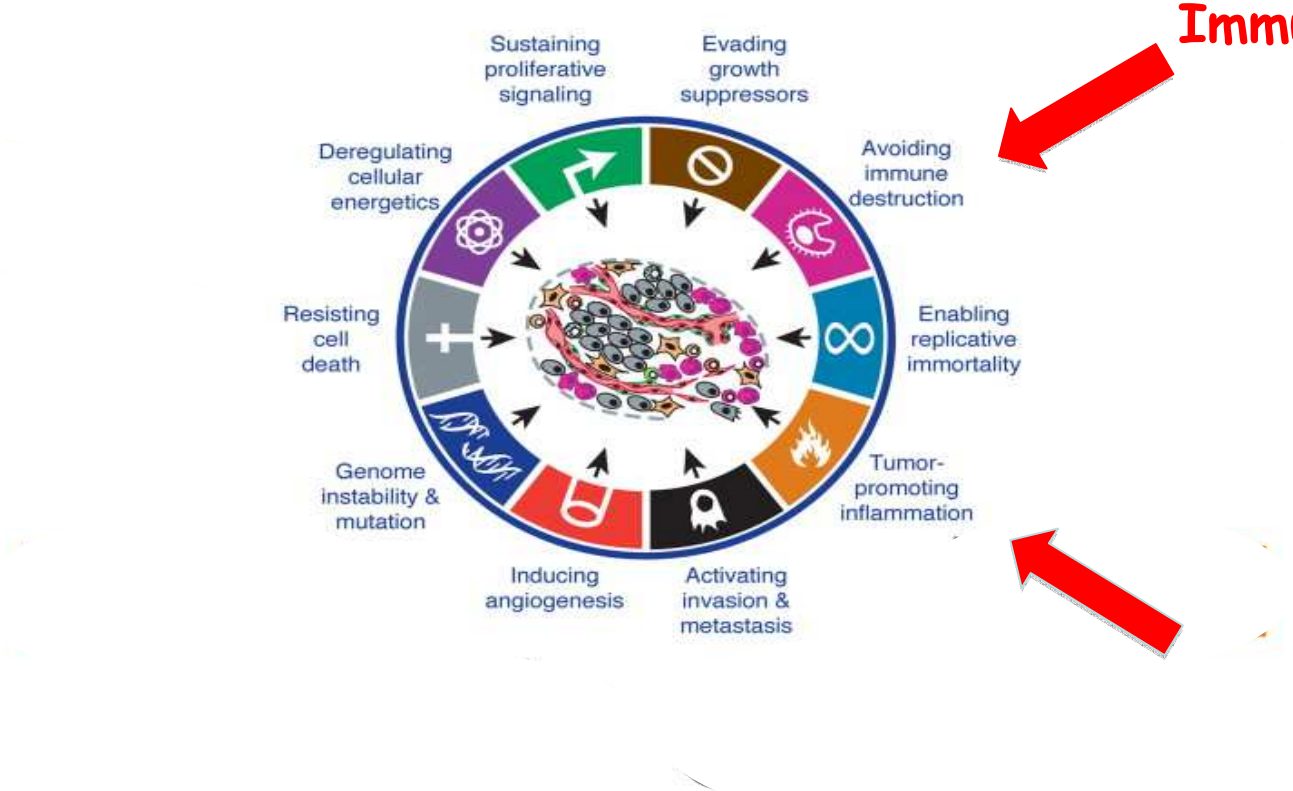
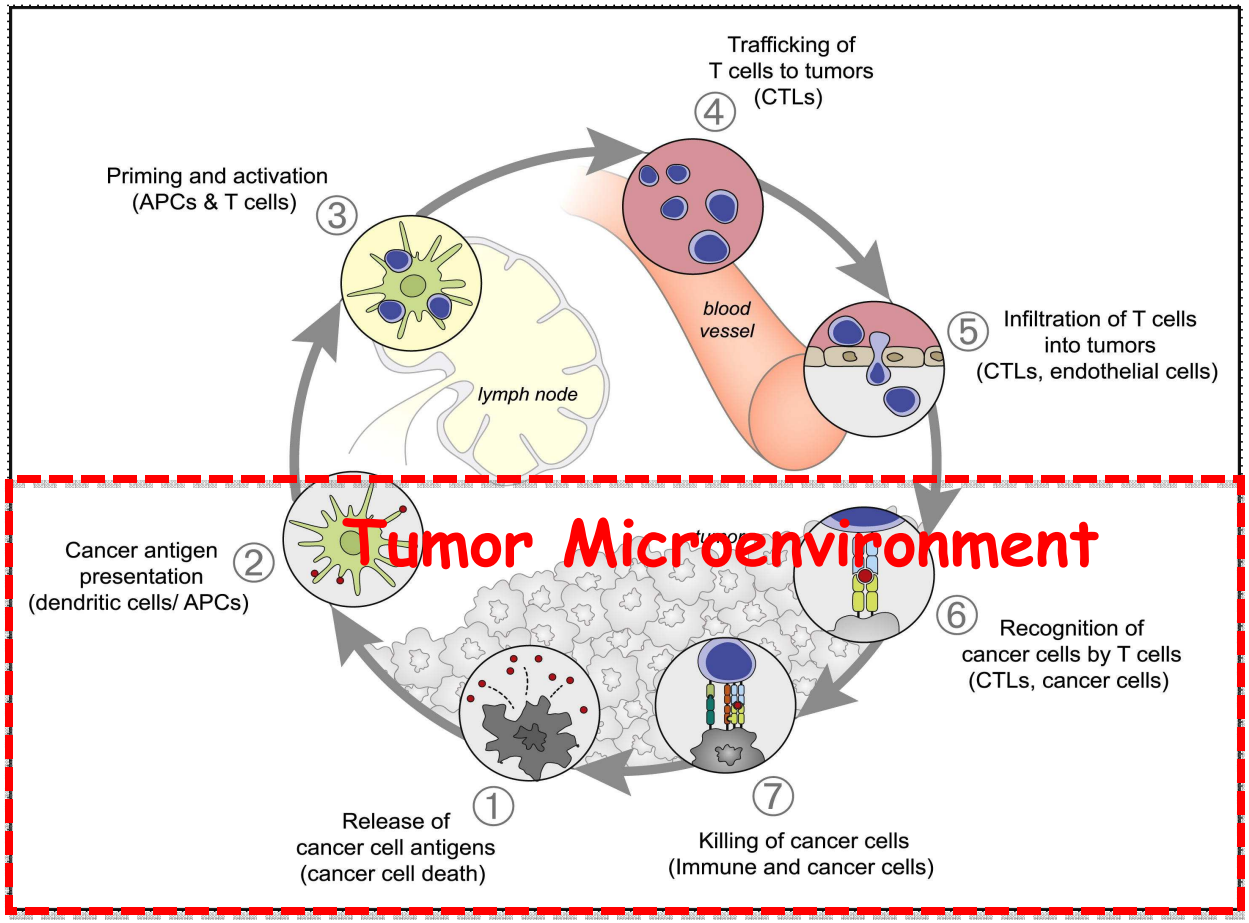
Hallmarks of Cancer: The Next Generation

Role of the Immune System



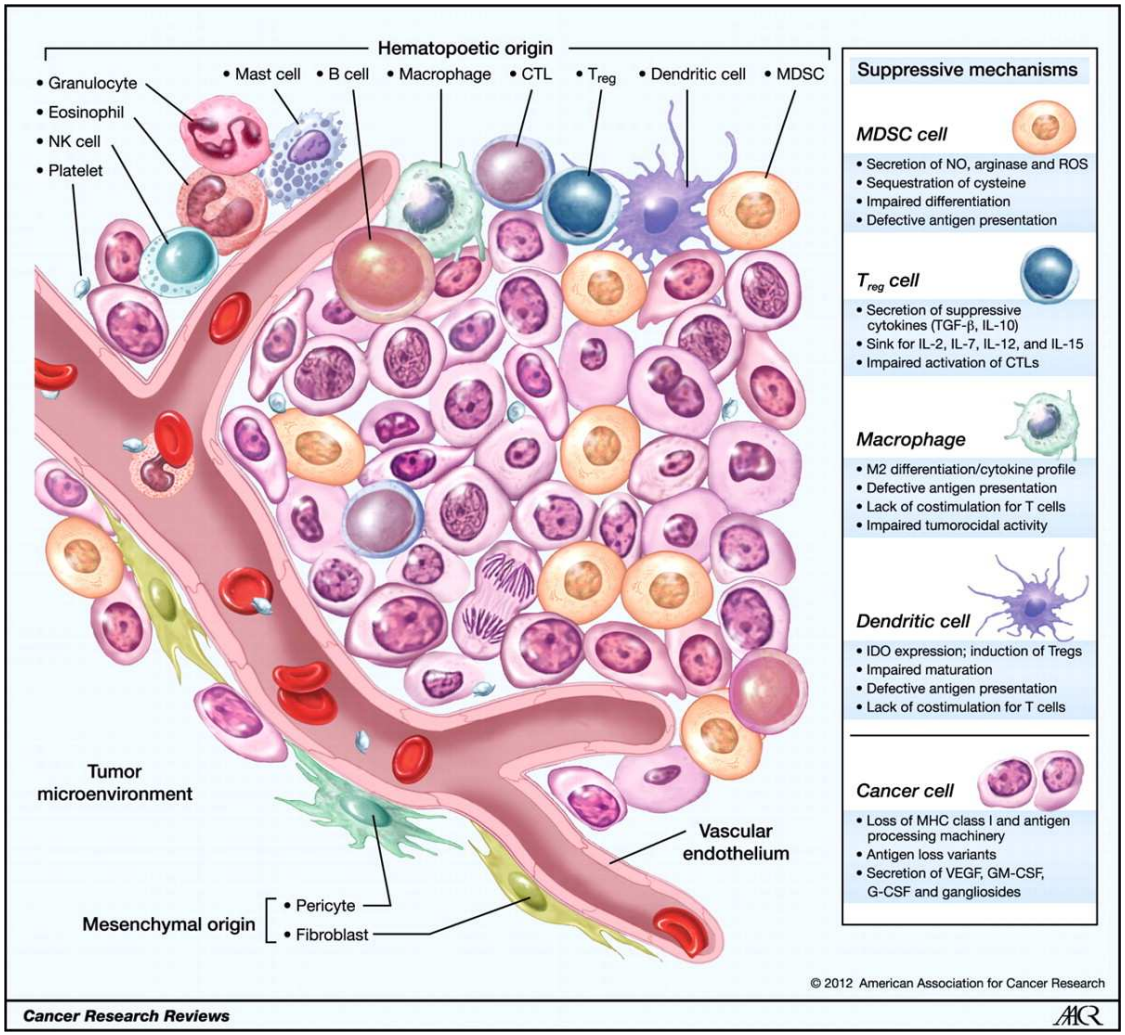
Douglas Hanahan , Robert A. Weinberg, Cell, 2011, 244: 646 - 674

The Cancer-Immunity Cycle and Tumor Microenvironment (TME)



Daniel S. Chen and Ira Mellman, Immunity, 2013, 39, 2013: 1 - 10

Cellular Infiltrates Within the TME



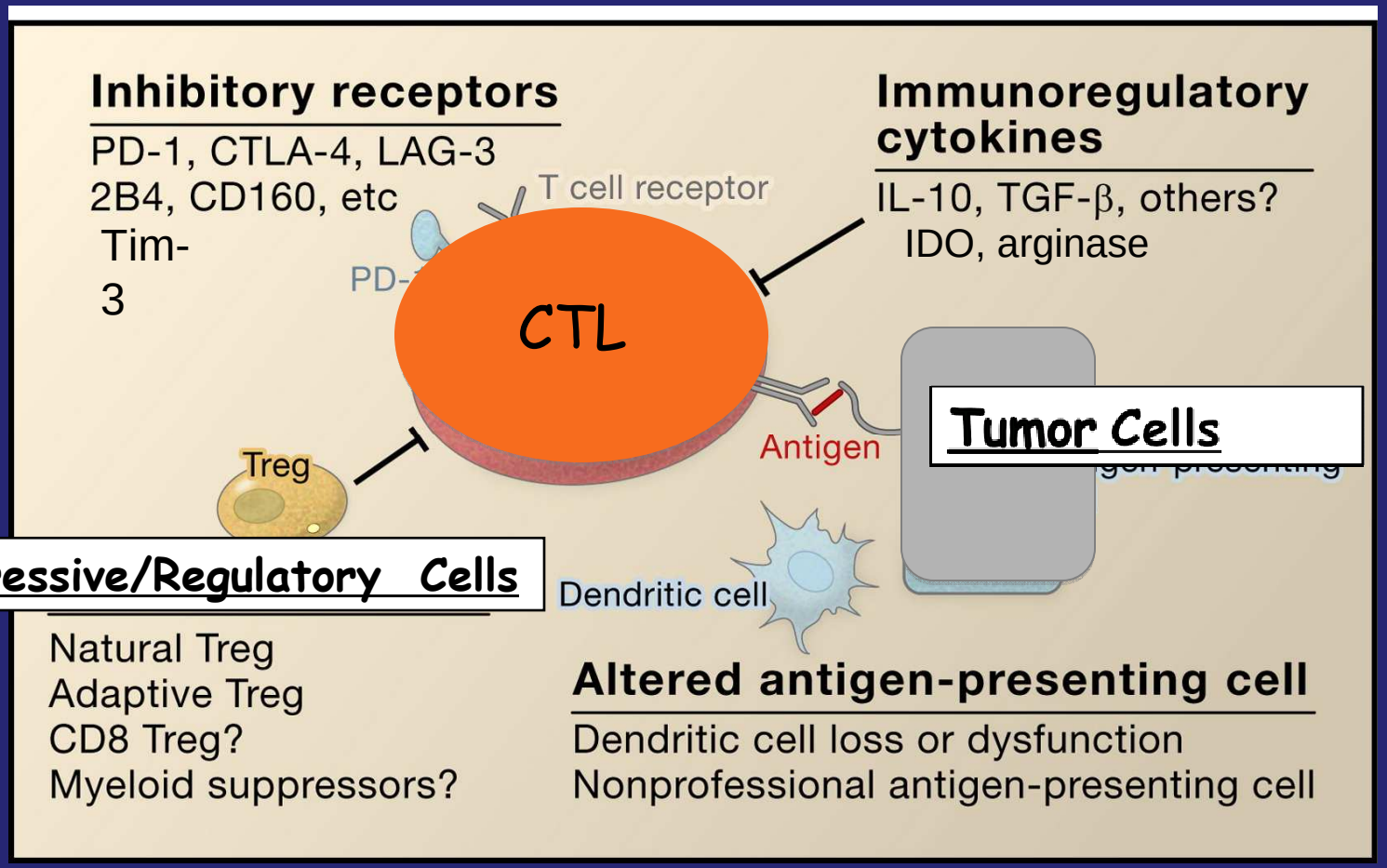
Stromal Cells
- Tumor-associated Fibroblasts
- Endothelial Cells
- Pericytes

Effector T cells
- Cytotoxic T cells: CTL
- CD4+ T cells

Others
- Granulocytes
- Eosinophils
- Mast cells
- Platelets

Kerkar S P , and Restifo N P Cancer Res 2012;72:3125-3130

Immunoregulatory Pathways Inhibit antigen-specific T Cell Function during Chronic antigen exposure

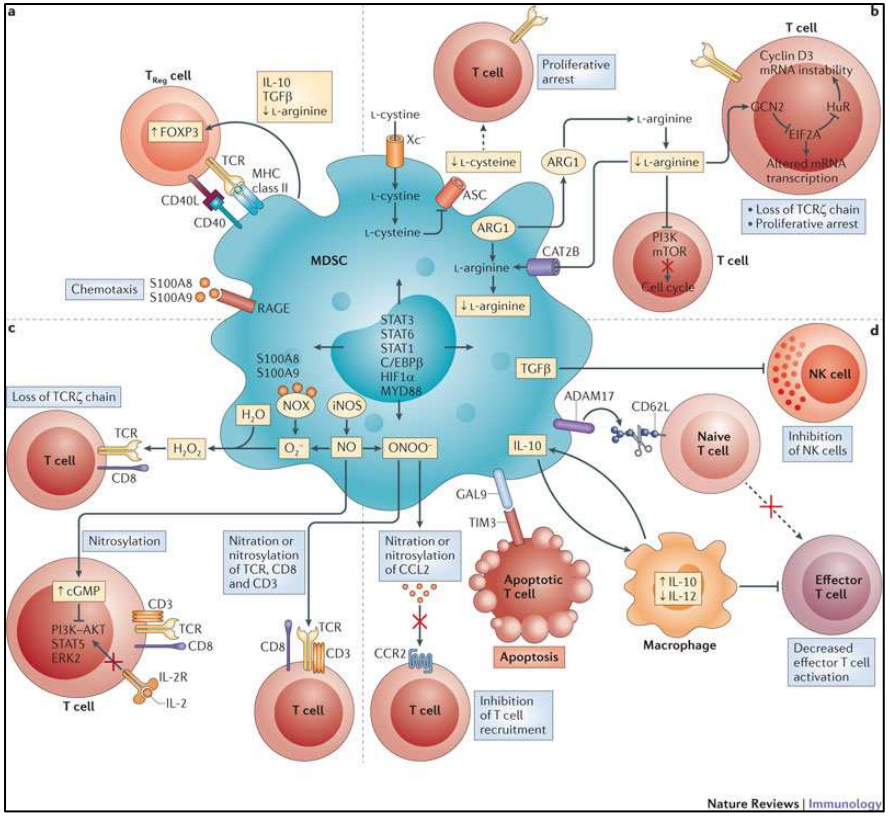


Regulatory T cells: Tregs

- Natural and Induced Tregs (tumor antigen-specific Tregs)
- Can produce IL-10 and TGF-β
- Markers:
  - Transcription factor forkhead box Foxp3,
  - CTLA-4, GITR, CD39, Tim-3, VEGFR…
- Suppress T and NK functions through multiple mechanisms (IL-2 deprivation, IL-10 and TGF-b secretion, granzyme-dependent cytolysis, adenosine production, DC crosstalk).
- Targeting Tregs: anti-CD25, anti-CTLA-4 (ADCC), anti-GITR, TKis

Myelosuppressive Dendritic Cells: MDSCs

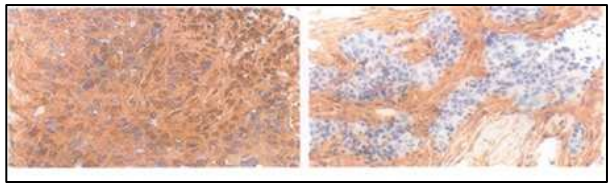
- Immature dendritic cells
- Lin-, HLA-DR-, CD33+ cells ?
- Suppress T cell
  - though cell-to-cell contact
  - Produce NO (➔ nitration and nitrolysation of aa) and arginase 1 (➔ arginine depletion)
  - IL-10 and reactive oxygen species production
  - Favor Treg differentiation



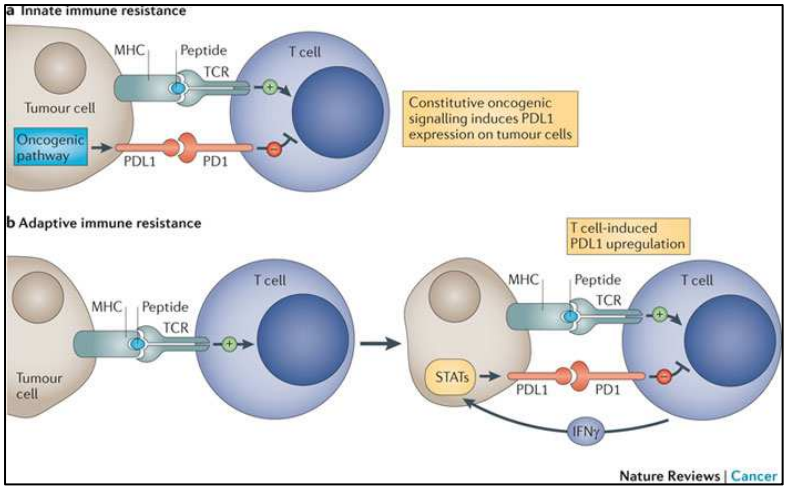
Tumor cells and Immune Escape

- Loss of peptide-MHC complexe expression with downregulation of antigen processing machinery
- Express surface molecules that can kill CTLs: FasL, Trail
- Secrete immunosuppressive cytokines/molecules promoting T cell dysfunction:IL-10, TGF-β, IDO, TDO, adenosine, PGE2, galectin 3
- Hypoxia and tumor lactic acidosis can suppress CTLs
- They can upregulate inhibitory receptor ligands including PD-L1, HVEM, galectin 9
- and HLA-DR.

MHC class I+ MHC-Class I-



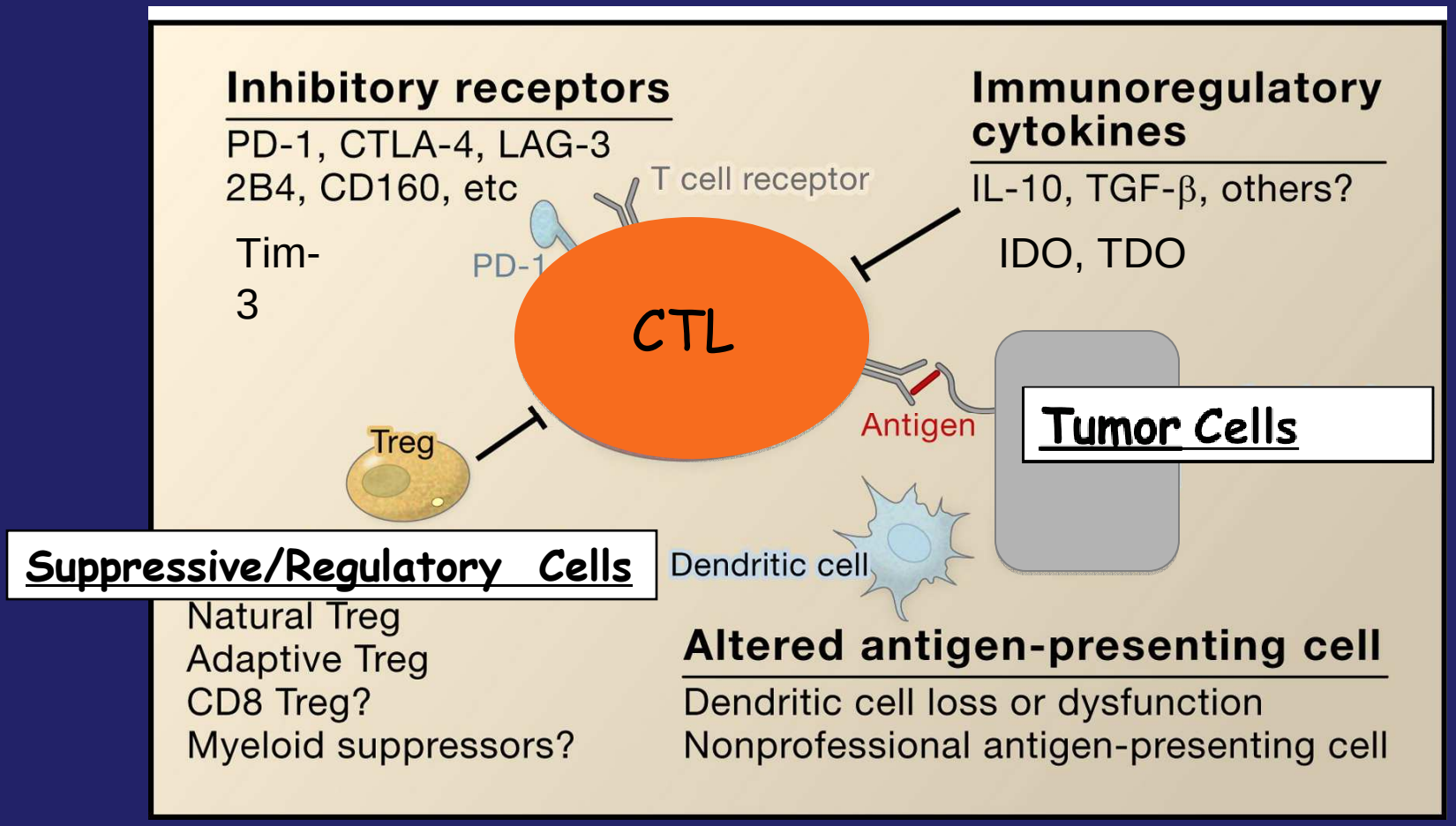
Breast Cancer



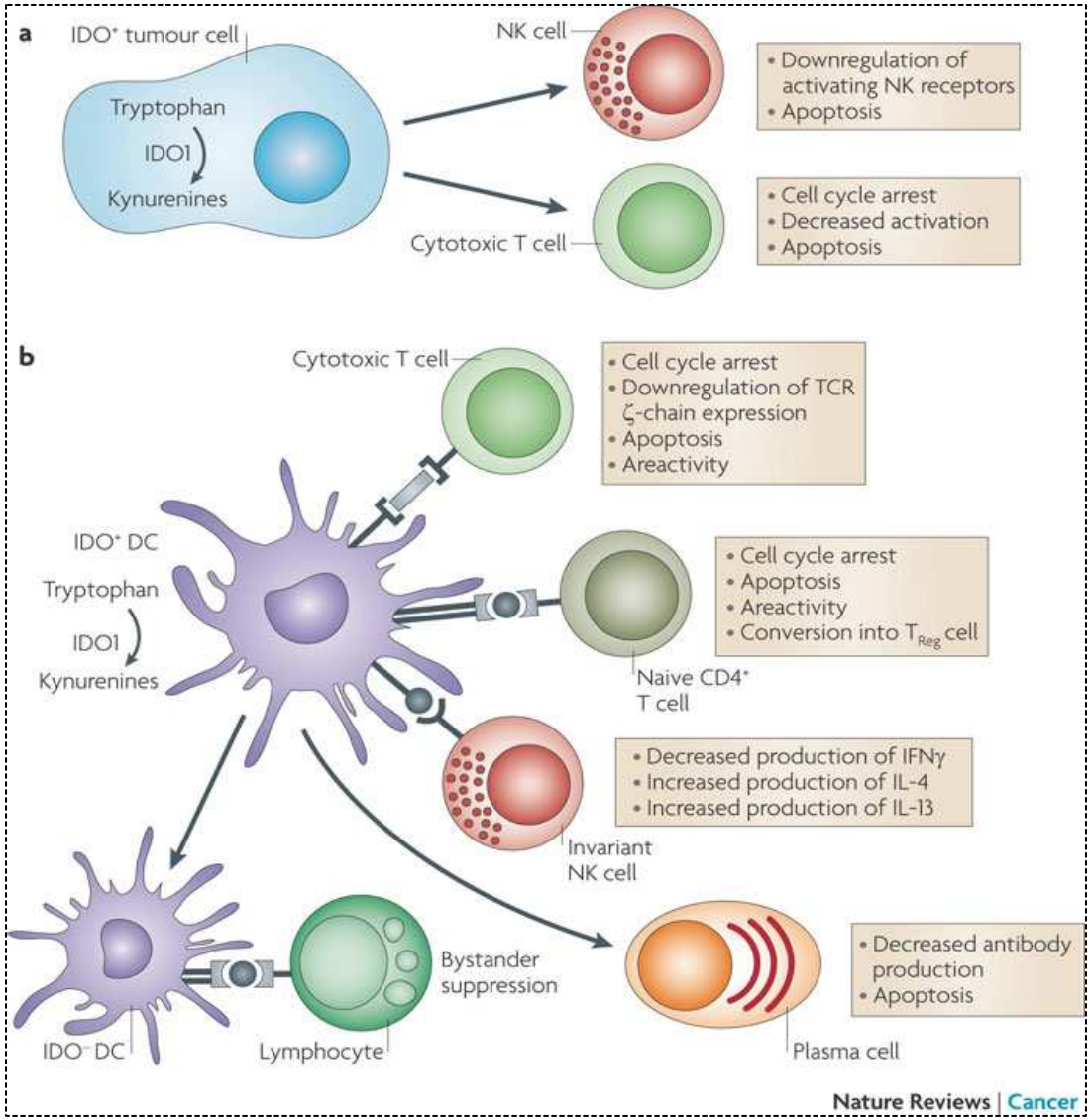
Other Tumor-infiltrating Cells

- **Tumor-Associated Macrophages**
  - Secrete immunosuppressive factors
  - Recruit Tregs via CCL2
  - Produce Arginase 1 and iNOS
  - **Mast cells recruit MDCS and Tregs**
- **Cancer-Associated Fibroblasts**
  - recruit MDSCS
  - Produce TGF-β
- **Abnormal tumor vasculature** with absence of high endothelial veinules limit mass transit of CTLs and represent an active barrier to tumor-reactive T cells
  - May express FasL, Trail, PD-L1, IL-10, TGF-β ….
  - Maintained by tumor cells through paracrine mechanisms
  - Targeting tumor microvasculature: VEGF blockade

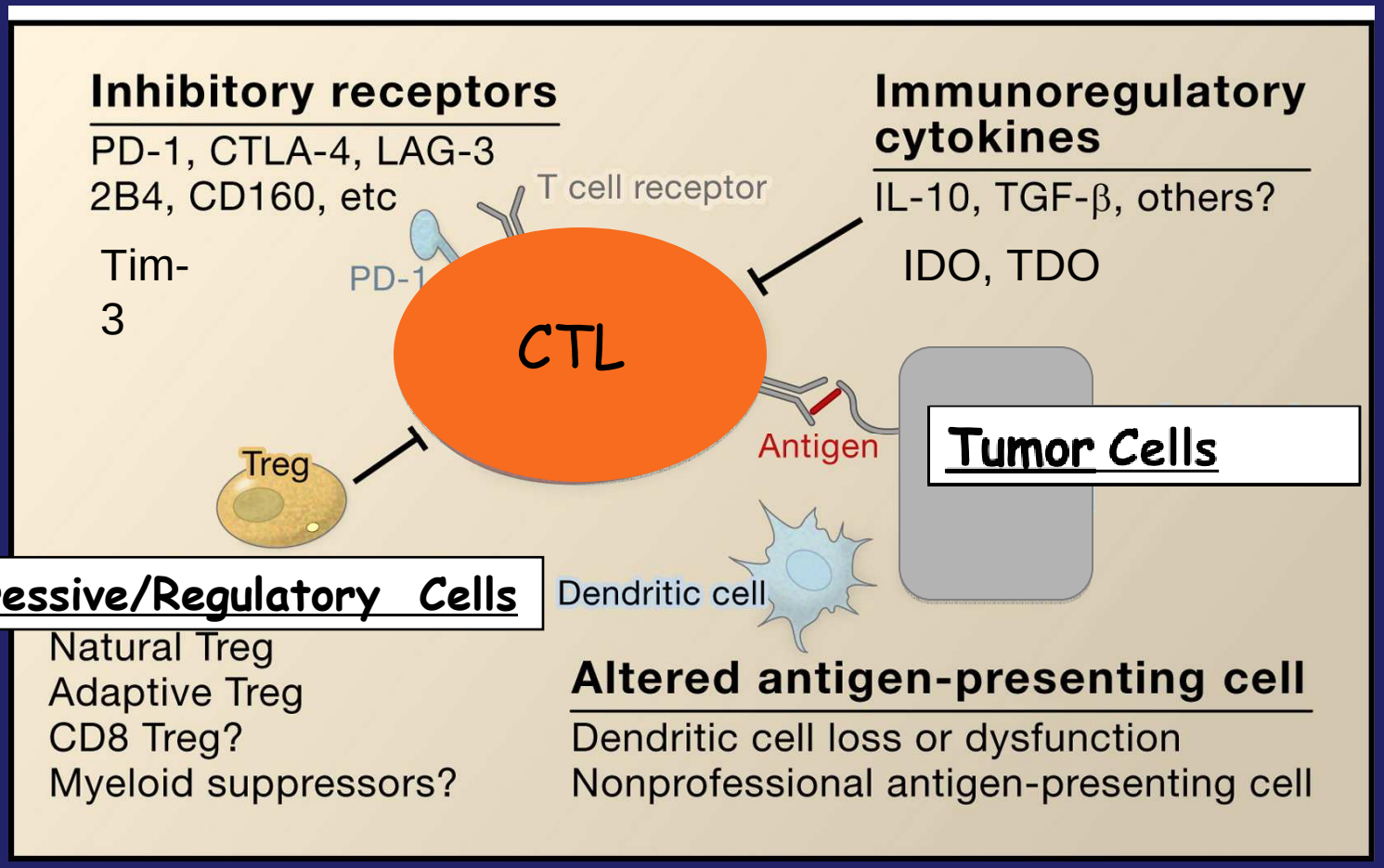
Immunoregulatory Pathways Inhibit T Cell survival and function in the TME



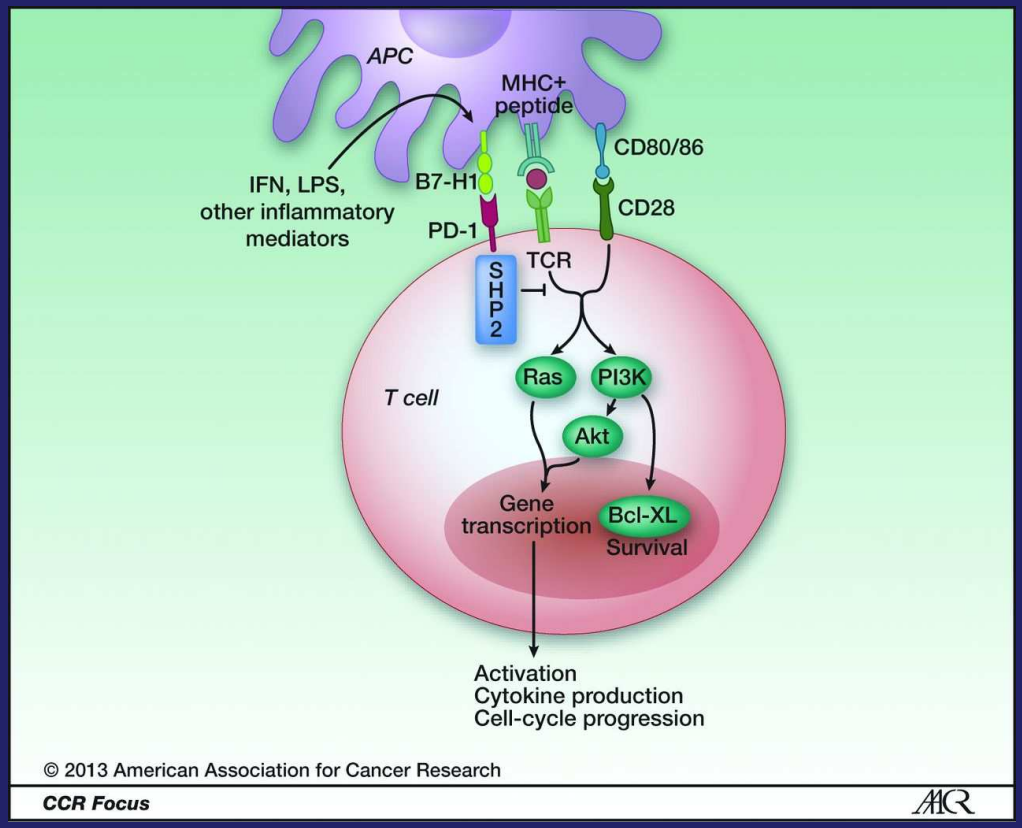
Immunosuppressive Effects of IDO in the TME



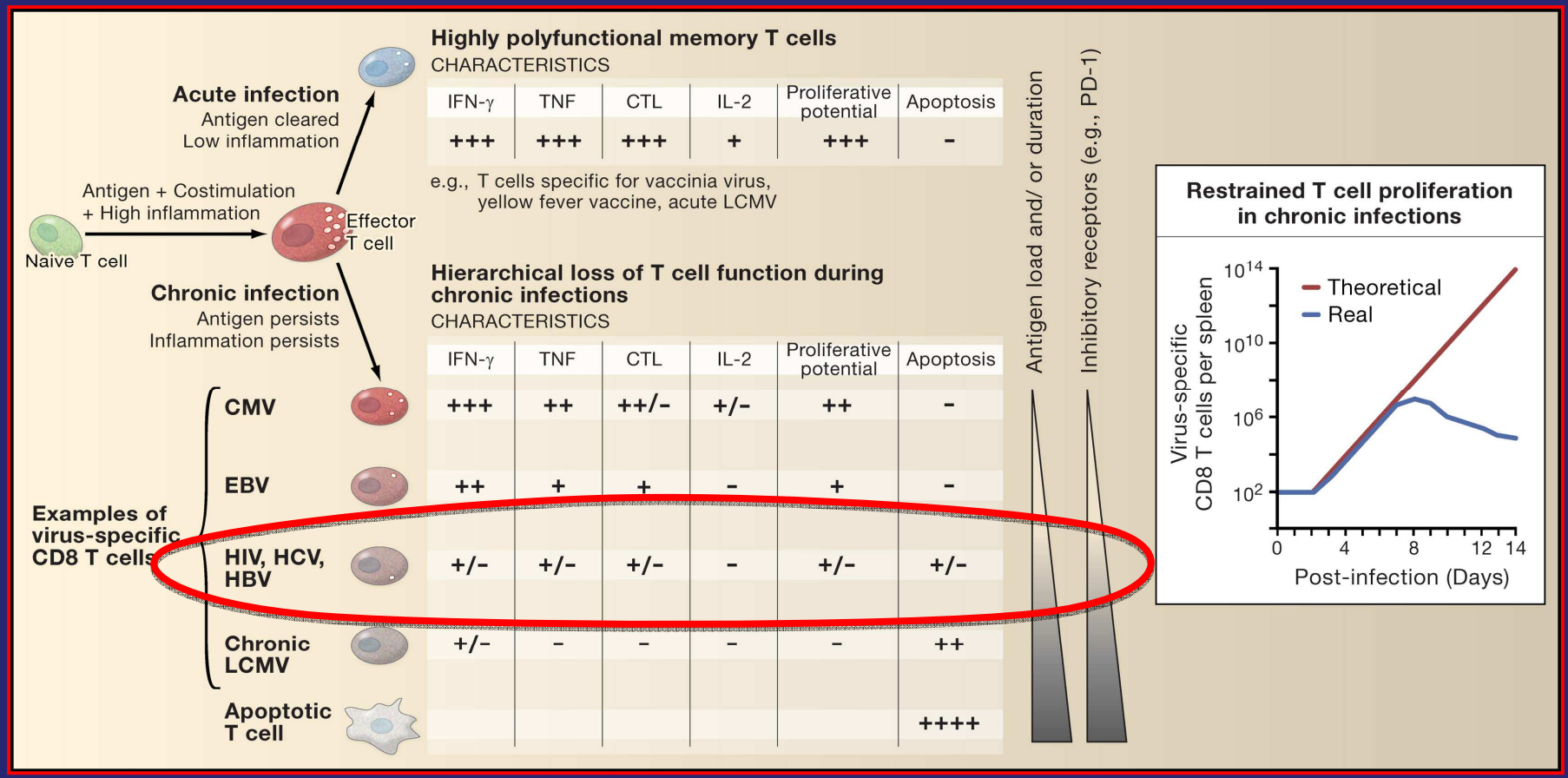
Immunoregulatory Pathways Inhibit antigen-specific T Cell Function during Chronic antigen exposure



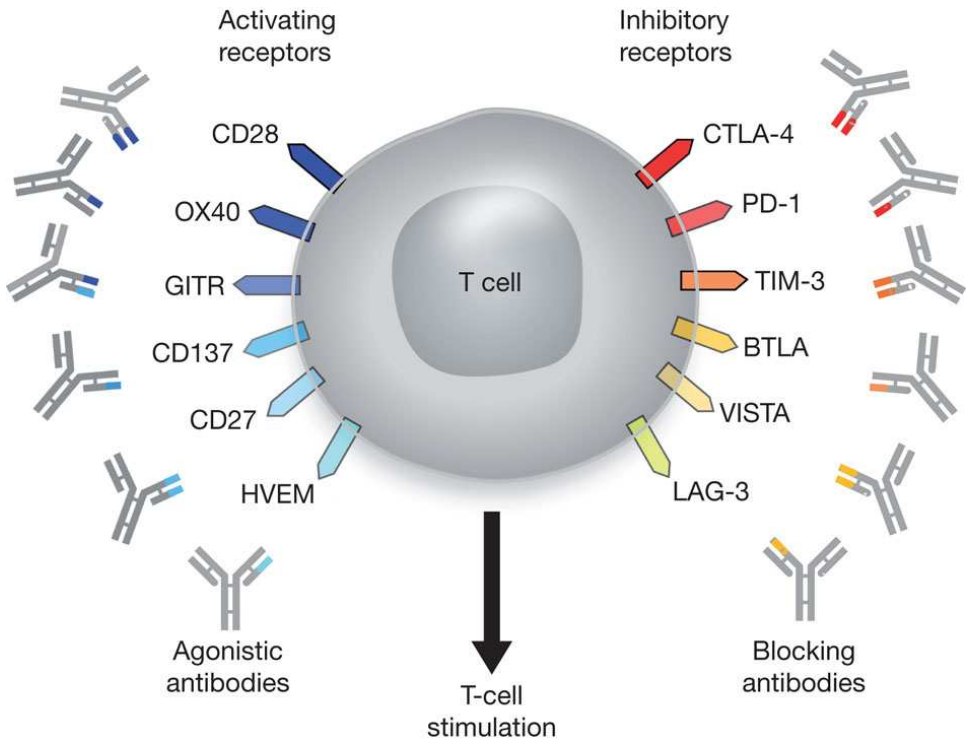
PD-1/B7-H1 (PD-L1) pathway



T Cell Dysfunction/Exhaustion Upon Chronic Antigen Exposure

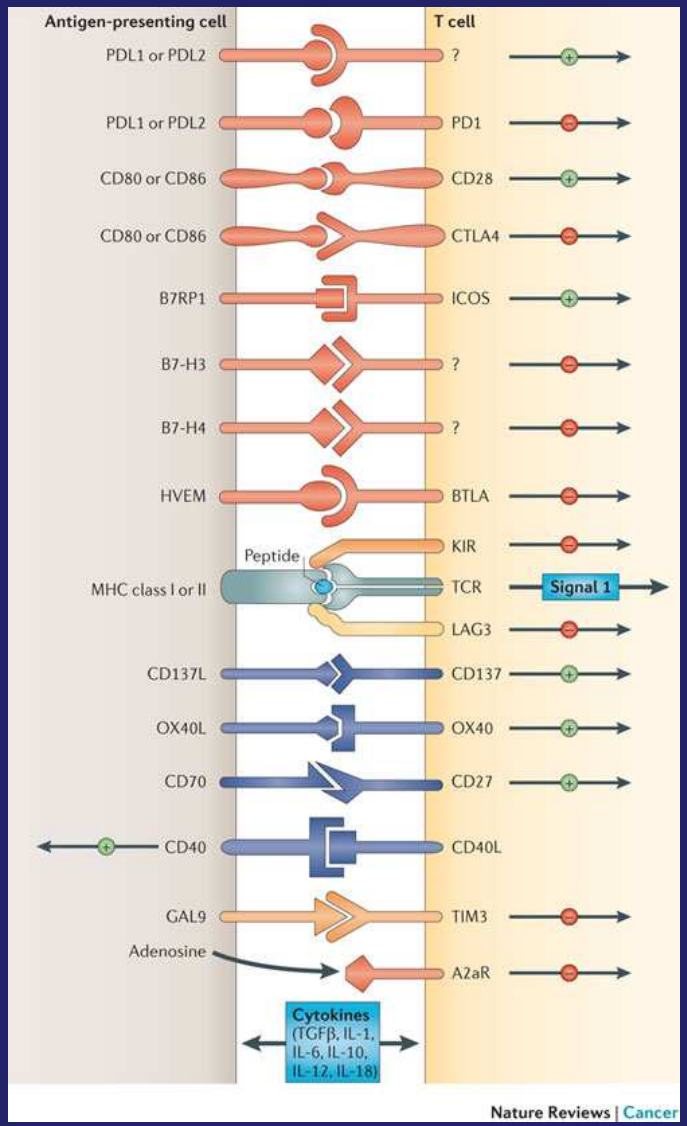


T Cell Targets for Immunoregulatory Antibody Therapy

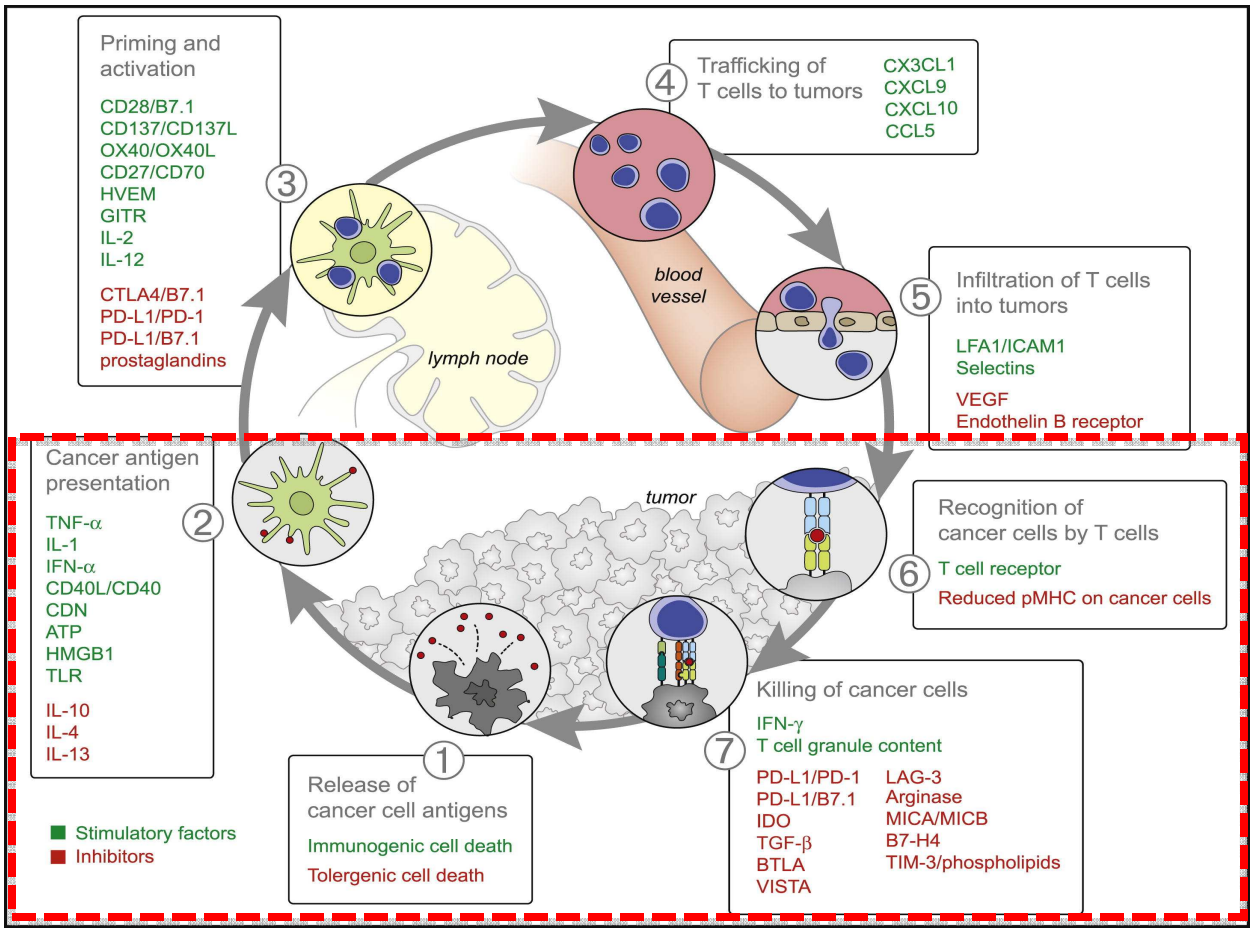


I Mellman *et al. Nature* **480**, 480-489 (2011)

Multiple co-stimulatory and inhibitory interactions regulate T cell responses.

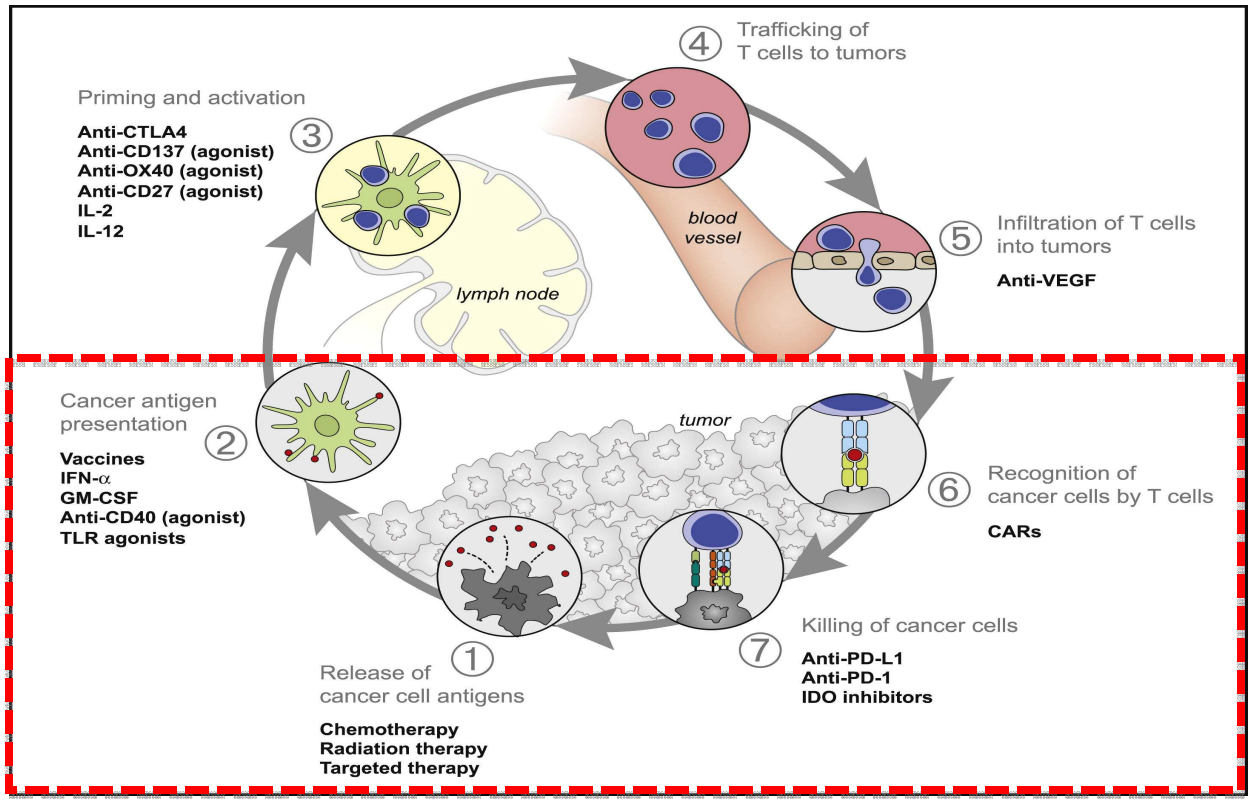


Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle and Tumor Microenvironment



Cytotoxic T cell (CTL) Cell Death or CTL Dysfunction

Manipulating the TME with Potent Immunotherapies of Cancer



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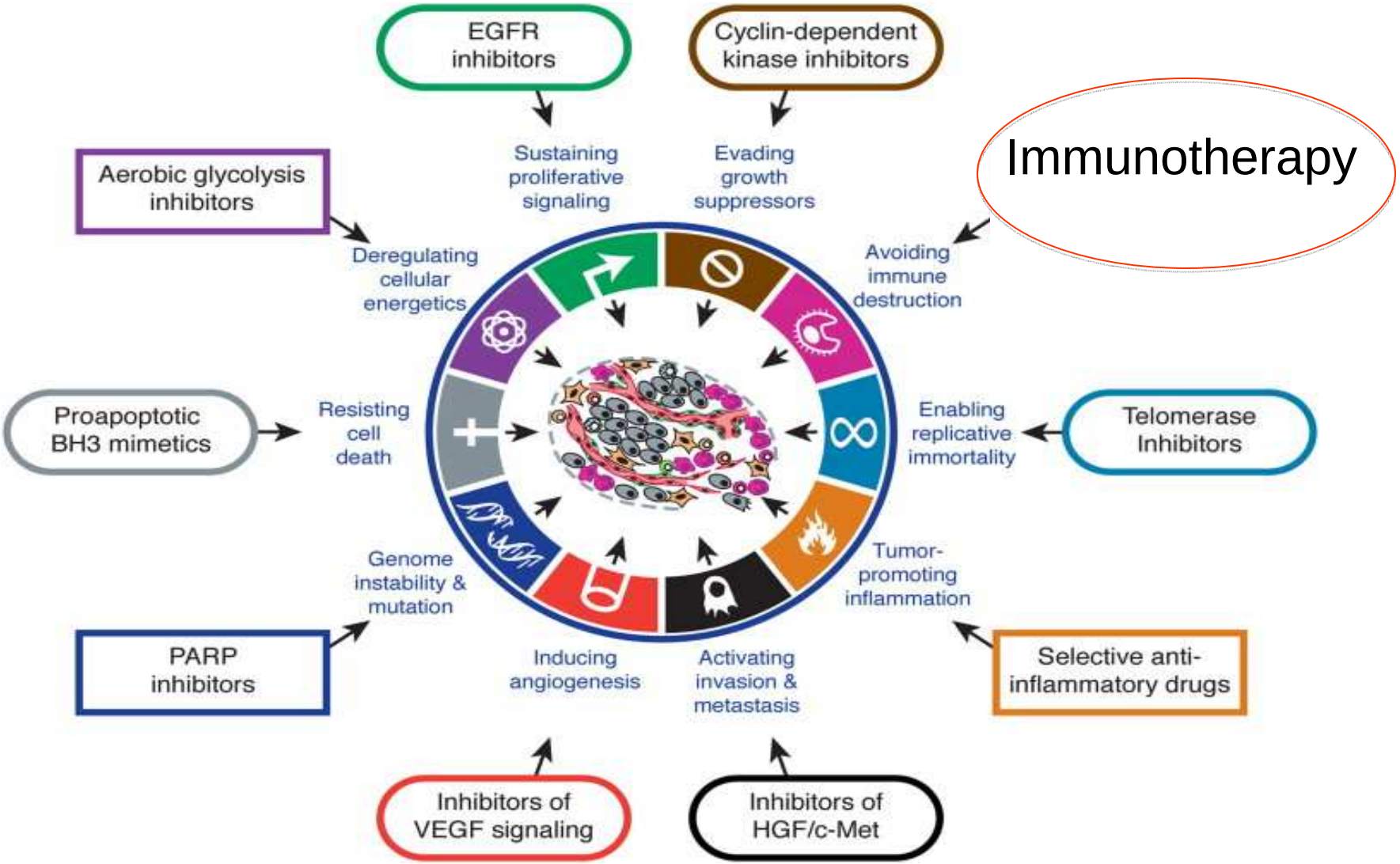
Manipulating the TME with Therapeutic Targeting of the Hallmarks of Cancer



Question 1

What receptor in the list below is not an inhibitory receptor expressed by T cells in the TME ?

- PD-1?
- BTL-A
- Tim-3
- LAG-3
- CD28

Question 2

Please indicate the wrong answer:

Dysfunctional/exhausted CTLs in the TME

- Upregulate PD-1 expression
- Loose their capacity to produce cytokines
- Loose their capacity to proliferate
- Occur in the TME upon chronic antigen stimulation
- Can potently lyse tumor cells

Question 3

Please indicate the wrong answer:

Tregs in the TME

- Express Foxp3
- Upregulate CD39
- Suppress T cell functions
- Do not express CTLA-4

Question 4

Please indicate the wrong answer below

Tumor cells in the TME may escape T cell destruction by the following mechanisms:

- Loss peptide-MHC complex expression with downregulation of antigen processing machinery
- PD-L1 expression
- Production of IL-10, TGF-β and galectin 3
- Expressing MHC class I molecules