Immunology Basics Relevant to Cancer Immunotherapy:

Regulation of T Cell Responses by Checkpoint Inhibitors and Regulatory T Cells

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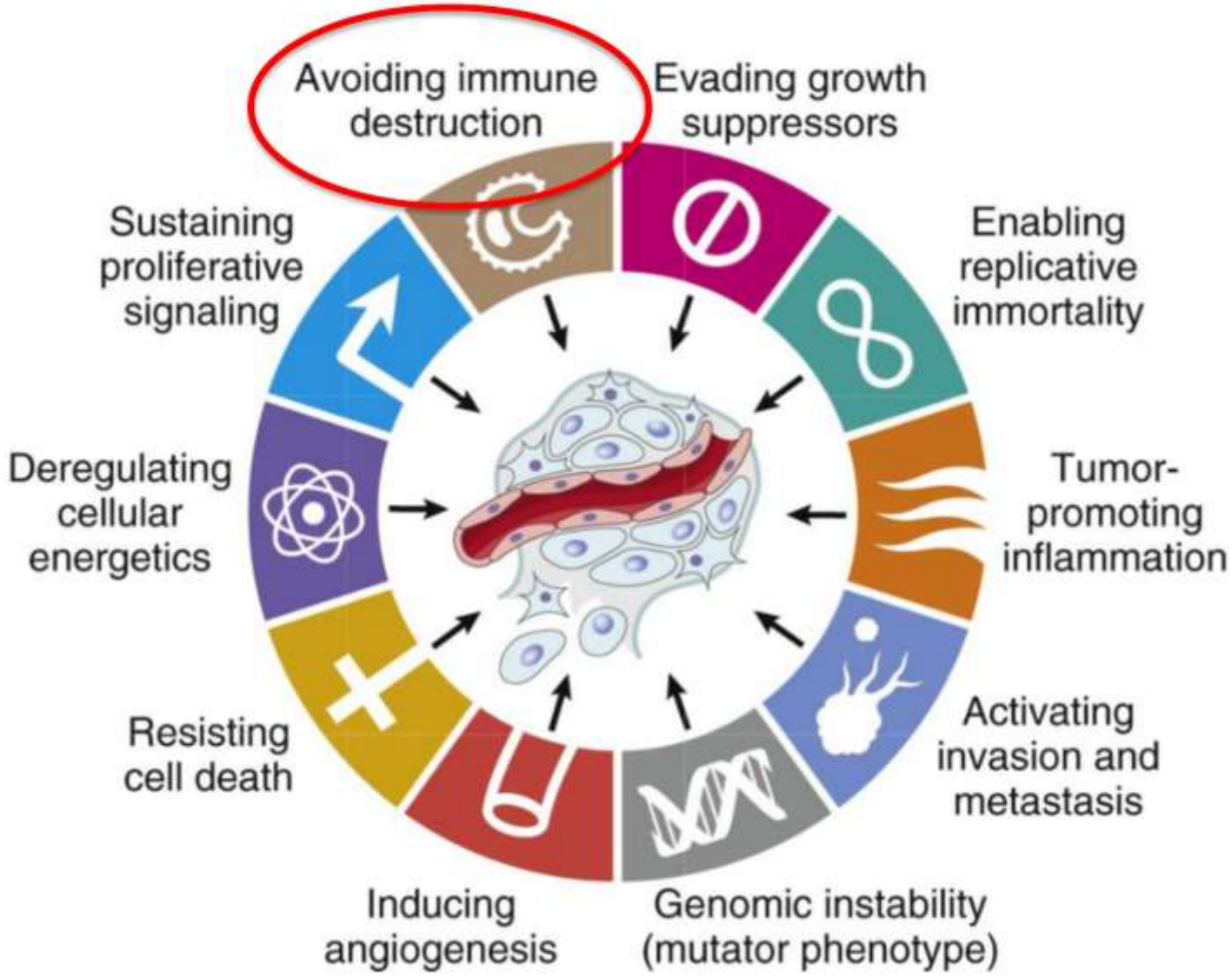
Lecture Outline

- Tumor immune evasion mechanisms
- T cell tolerance
- Mechanism of peripheral tolerance
- Inhibitory receptors on T cells
- Regulatory T cells
- Myeloid derived suppressor cells
- The immunosuppressive tumor microenvironment

Hallmarks of Cancer



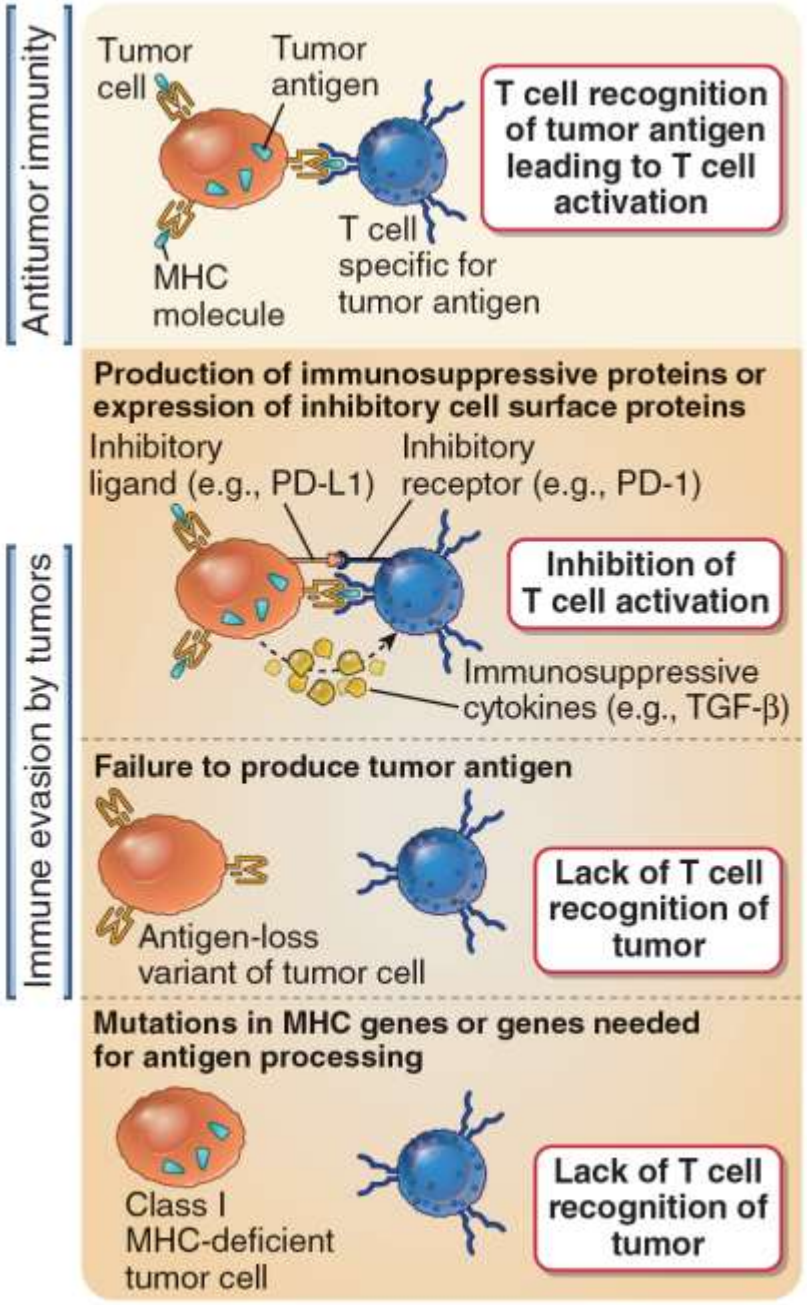
Hanahan and Weinberg *Cell* 2011

General principles

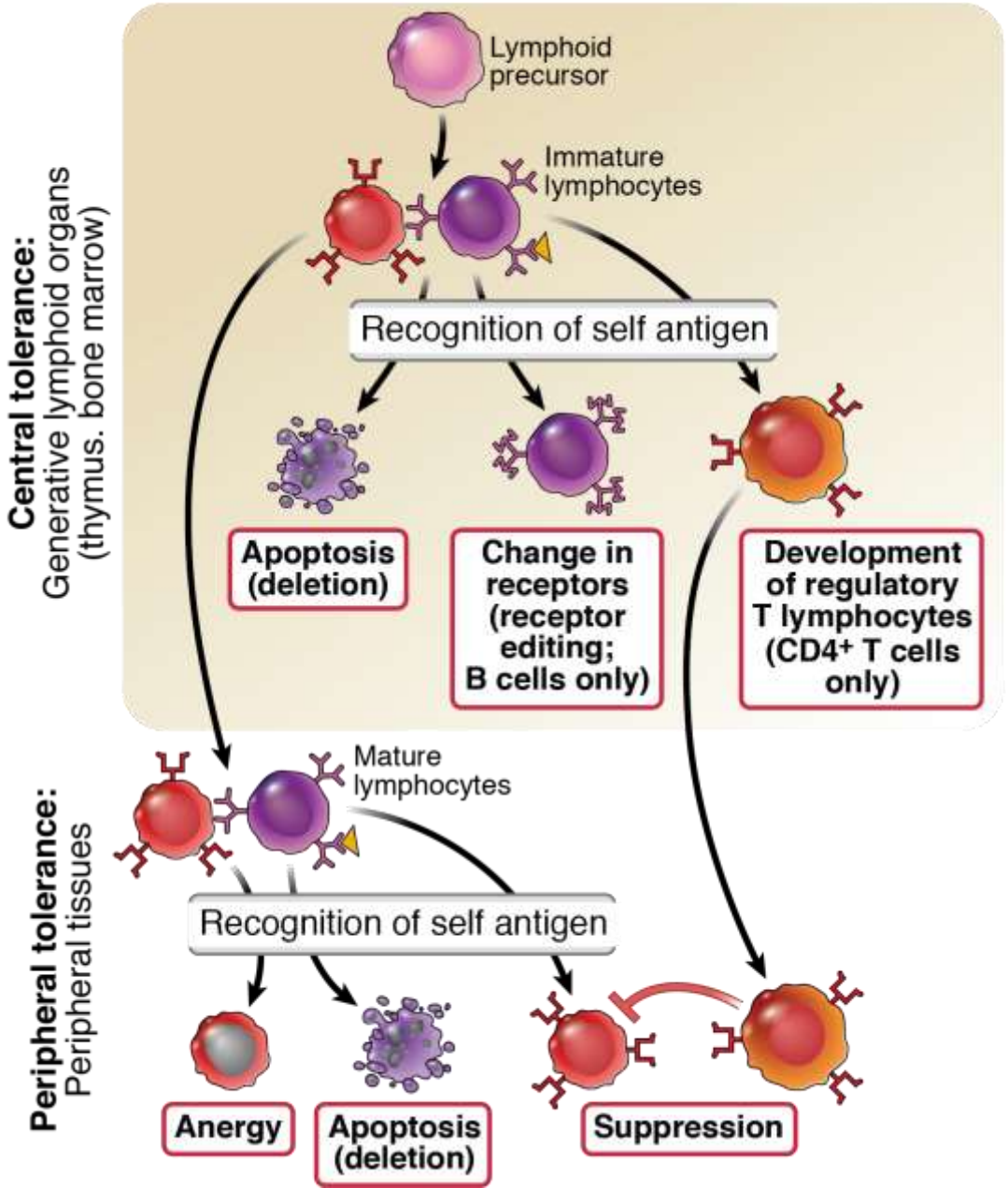
- The immune system recognizes and reacts against cancers
- The immune response against tumors is often dominated by regulation or tolerance
  - Evasion of host immunity is one of the hallmarks of cancer
- Some immune responses promote cancer growth
- Better characterization of the immune responses against cancers will help in developing new immunotherapies

Mechanisms by Which Tumors Escape Immune Defenses

- Same mechanisms microbes use to evade immunity
- Same mechanisms of peripheral self tolerance



Central and Peripheral Tolerance to Self

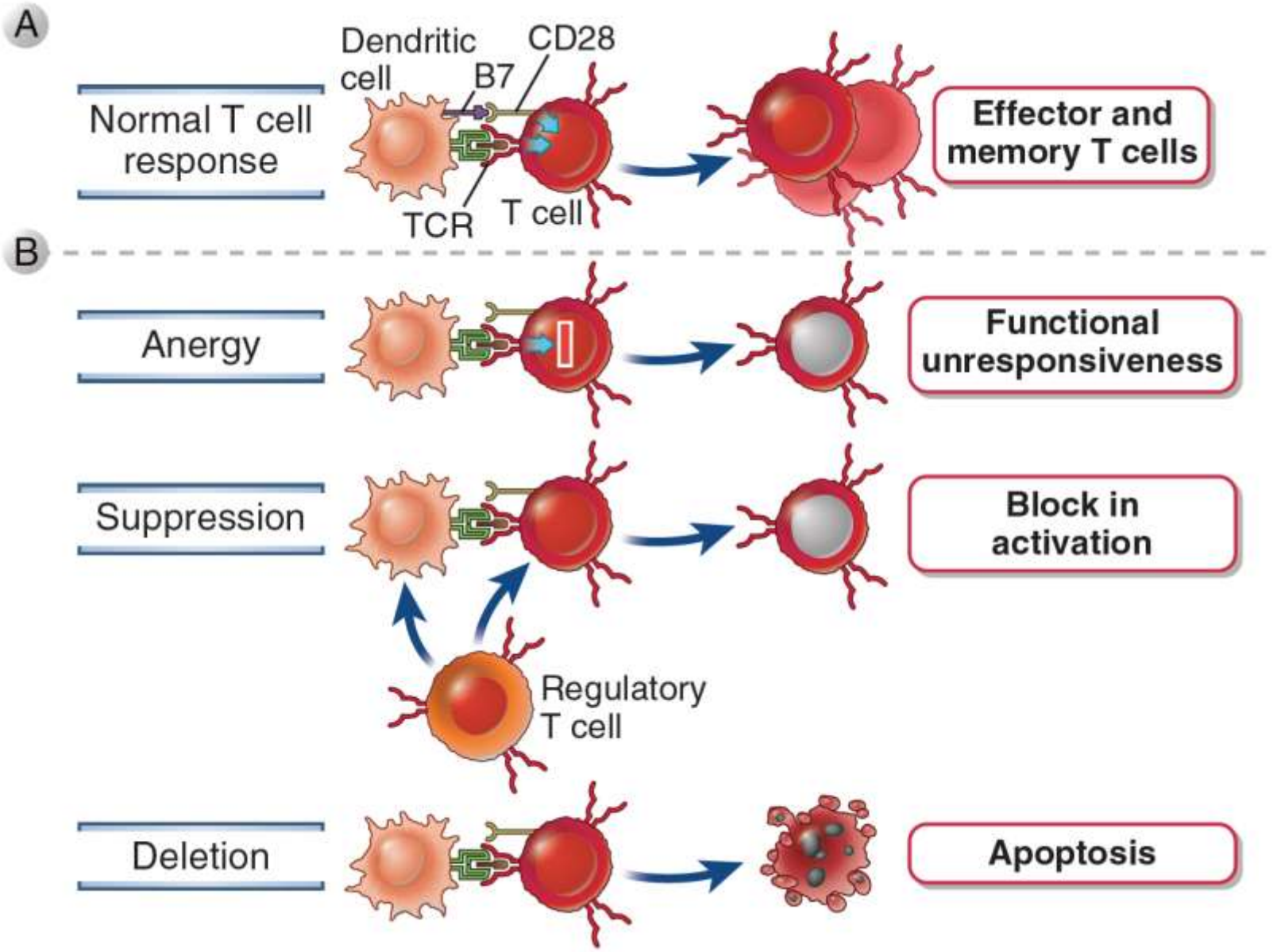


The principal fate of lymphocytes that recognize self antigens in the generative organs is death (deletion), BUT:

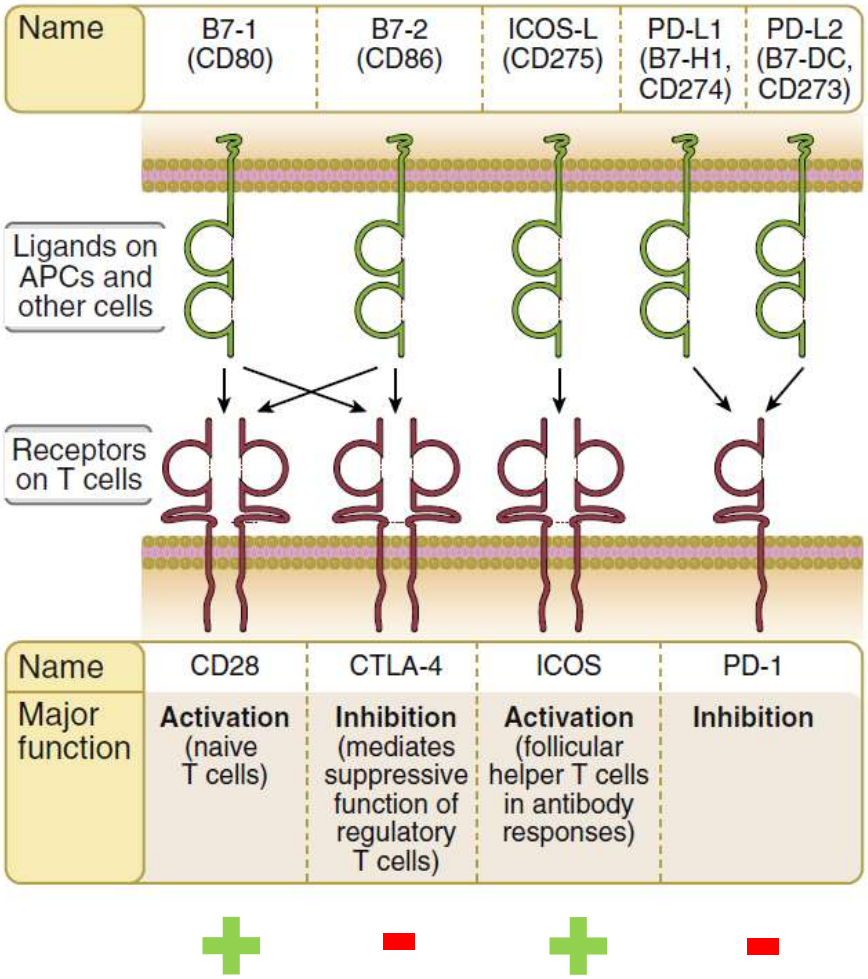
Some B cells may change their specificity (called "receptor editing")

Some T cells may differentiate into regulatory (suppressor) T lymphocytes

Mechanisms of Peripheral Tolerance

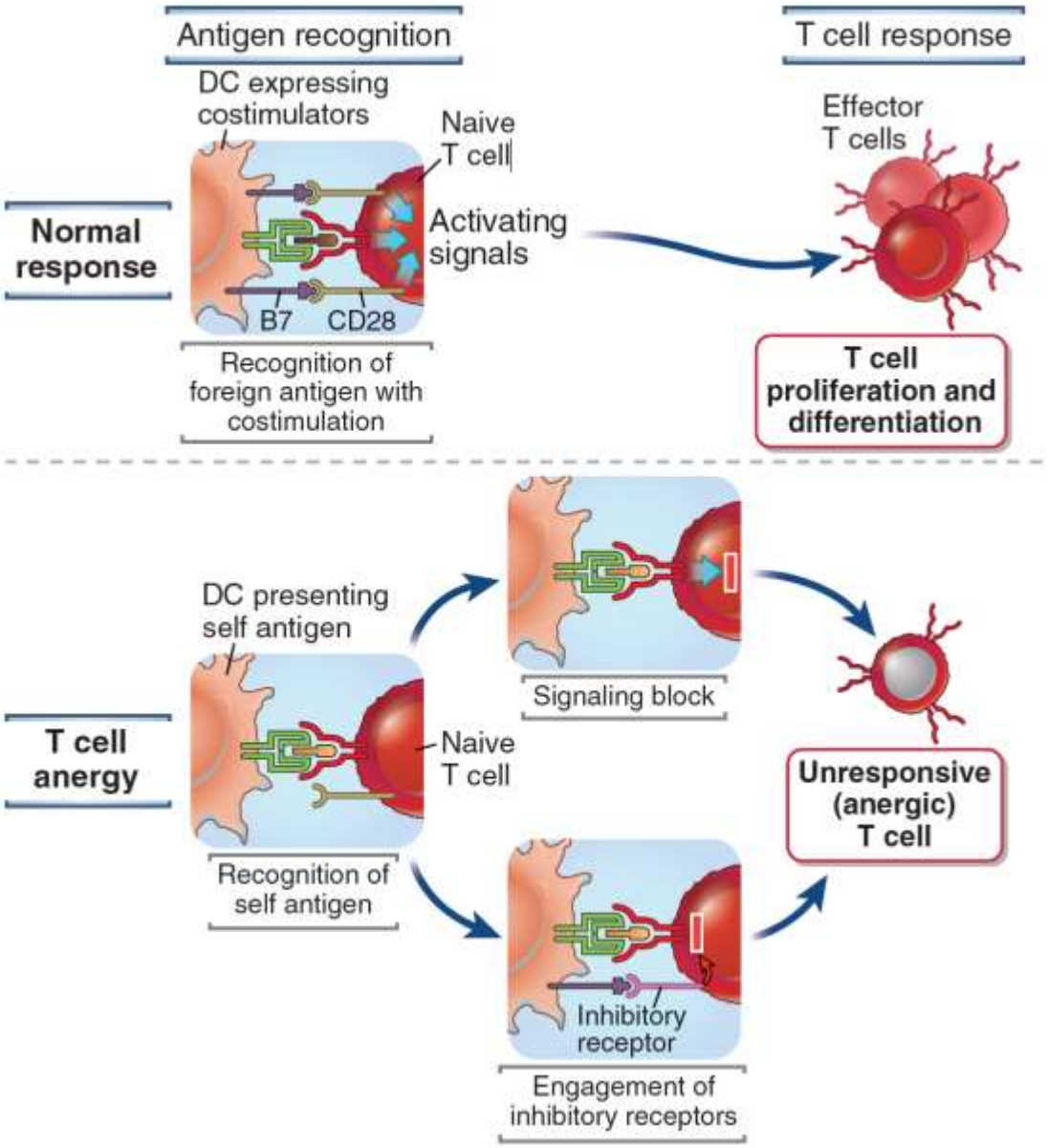


Peripheral Tolerance Depends on B7-CD28 Family Proteins

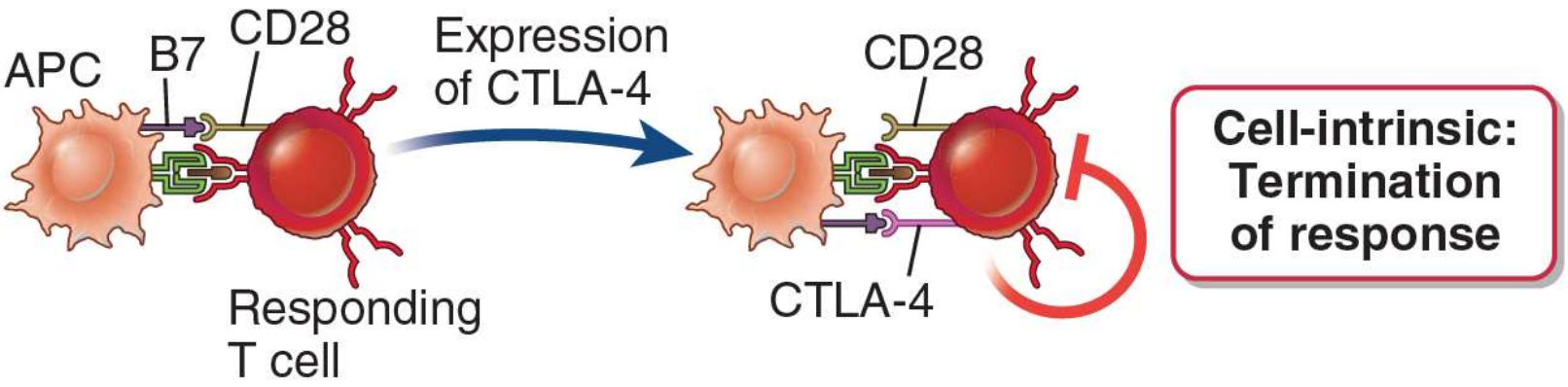


- Antigen recognition in absence of B7's
- CTLA-4 blocking of B7
- CTLA4 inhibitory signals into the T cells
- PD-L1/2 binding to PD-1, generating inhibitory signals into T cells

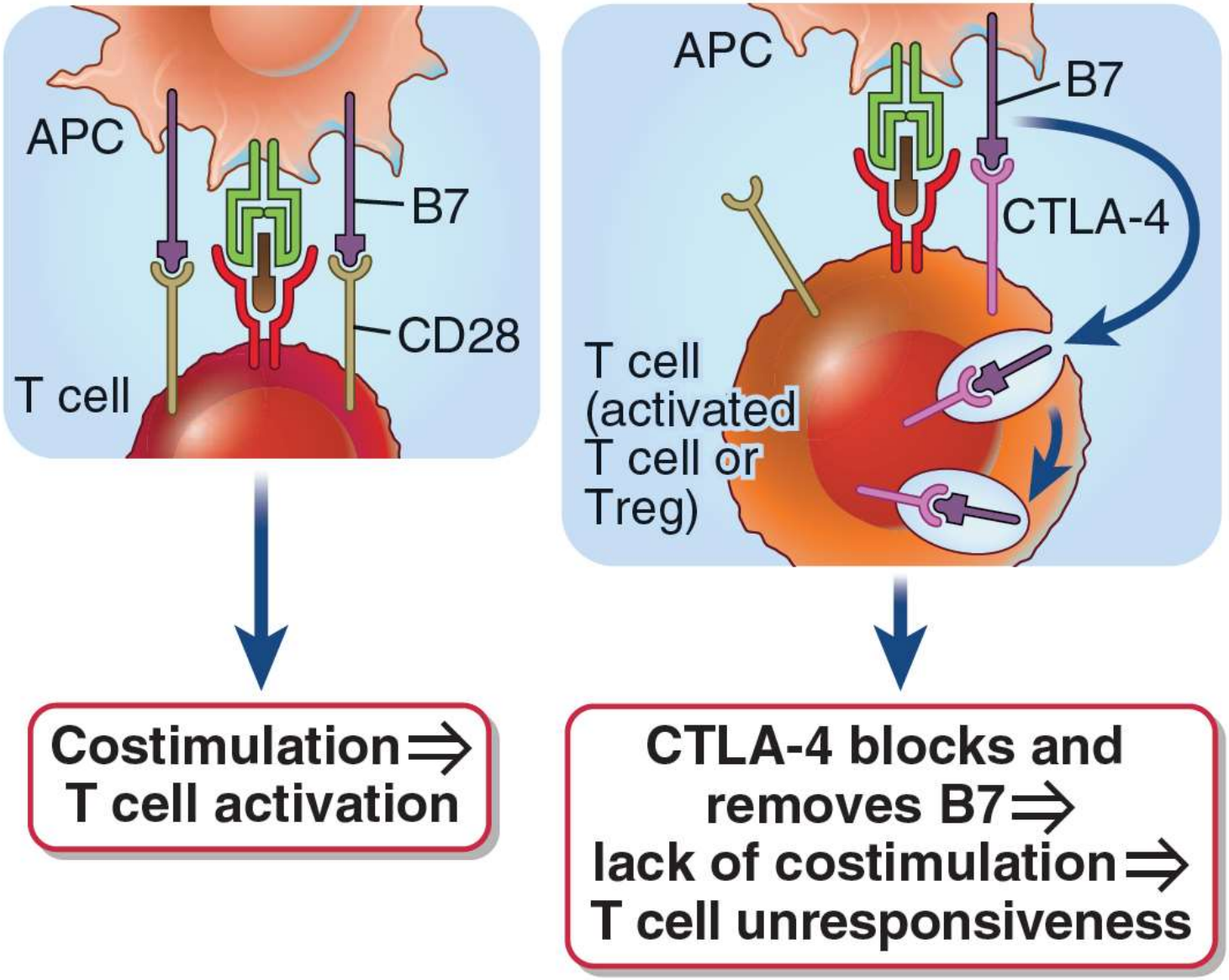
Mechanisms of T Cell Anergy



One Mechanism of Action of CTLA-4

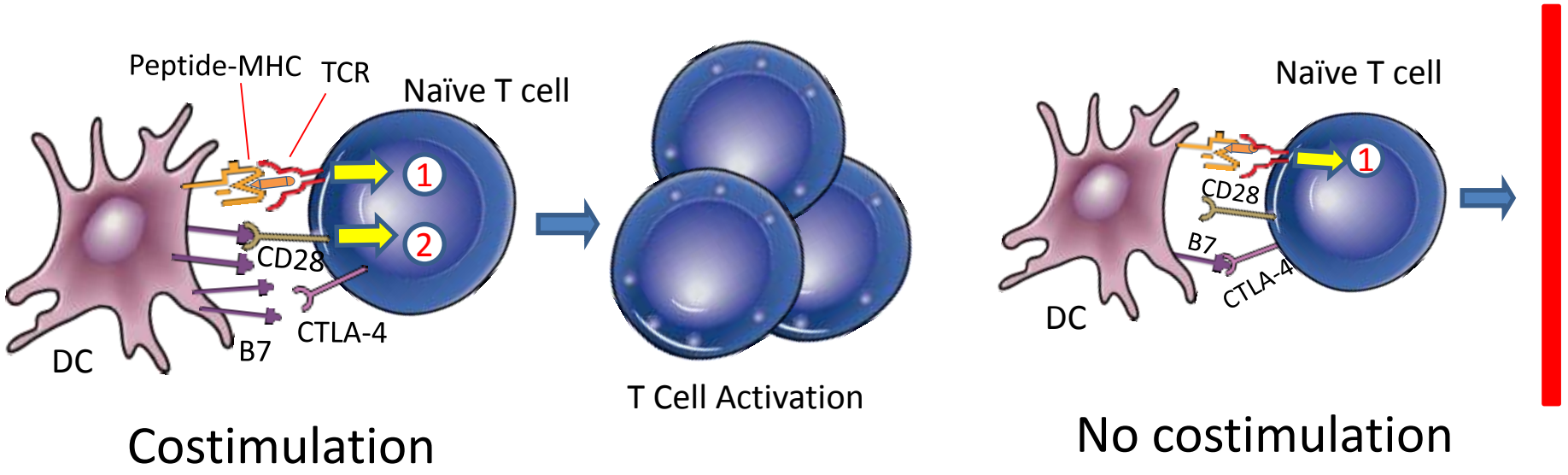


Mechanisms of Action of CTLA-4



CTLA-4 Inhibits T cell Activation:

Competitive Blockade of CD28 –B7 Costimulation

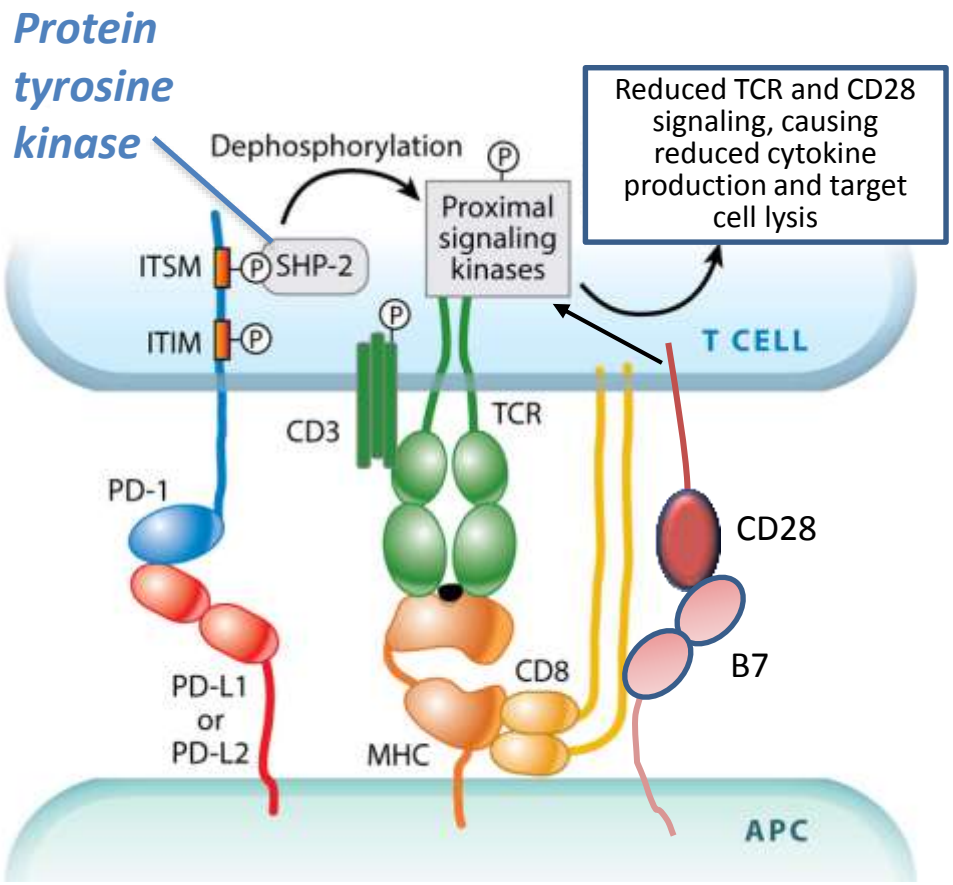


Costimulation

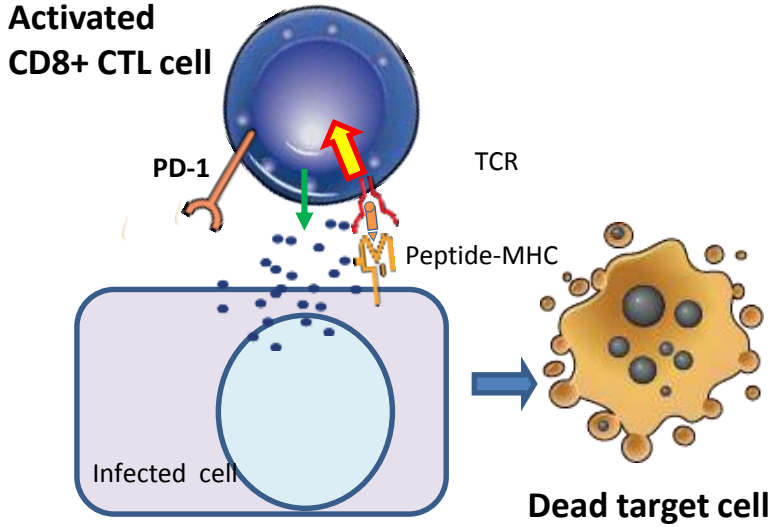
No costimulation

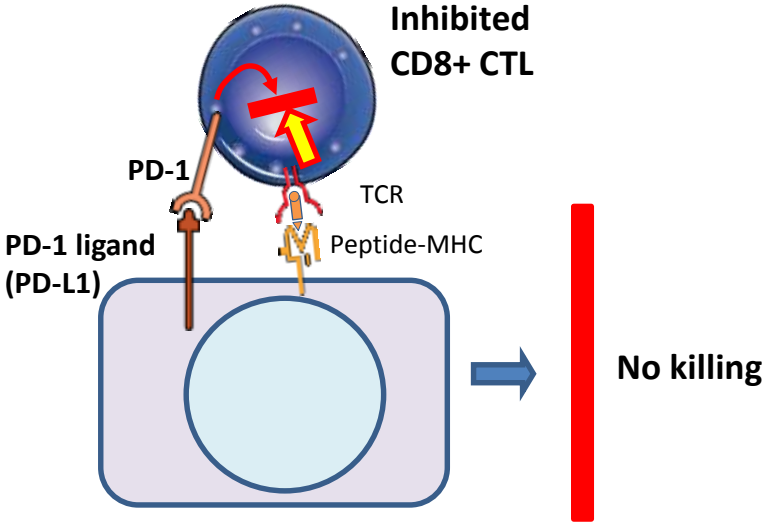
How PD-1 Inhibits T cell Activation:

Inhibitory Signals Block Effector T Cell Activation



Baumeister SH, et al. 2016.
Annu. Rev. Immunol. 34:539–73





Actions and Functions of CTLA-4 and PD-1

	CTLA-4	PD-1
Major site of action	Secondary lymphoid organs	Peripheral tissues
Stage of immune response that is inhibited	Induction (priming)	Effector phase
Cell type that is inhibited	$CD4^+$ and $CD8^+$	$CD8^+ > CD4^+$
Cellular expression	Tregs, activated T cells	Activated T cells
Main signals inhibited	Competitive inhibitor of CD28 costimulation (by binding to B7 with high affinity and removing B7 from APCs)	Inhibits kinase-dependent signals from CD28 and TCR (by recruiting and activating phosphatase following binding to its ligands PDL-1 or PDL-2)
Role in Treg-mediated suppression of immune responses	Yes	Probably no

CyTOF analysis of T cells in anti-CTLA-4 treated tumors show expansion in CD4+ and CD8+ effectors, but expansion of only CD8+ effectors in anti-PD-1 treated tumors

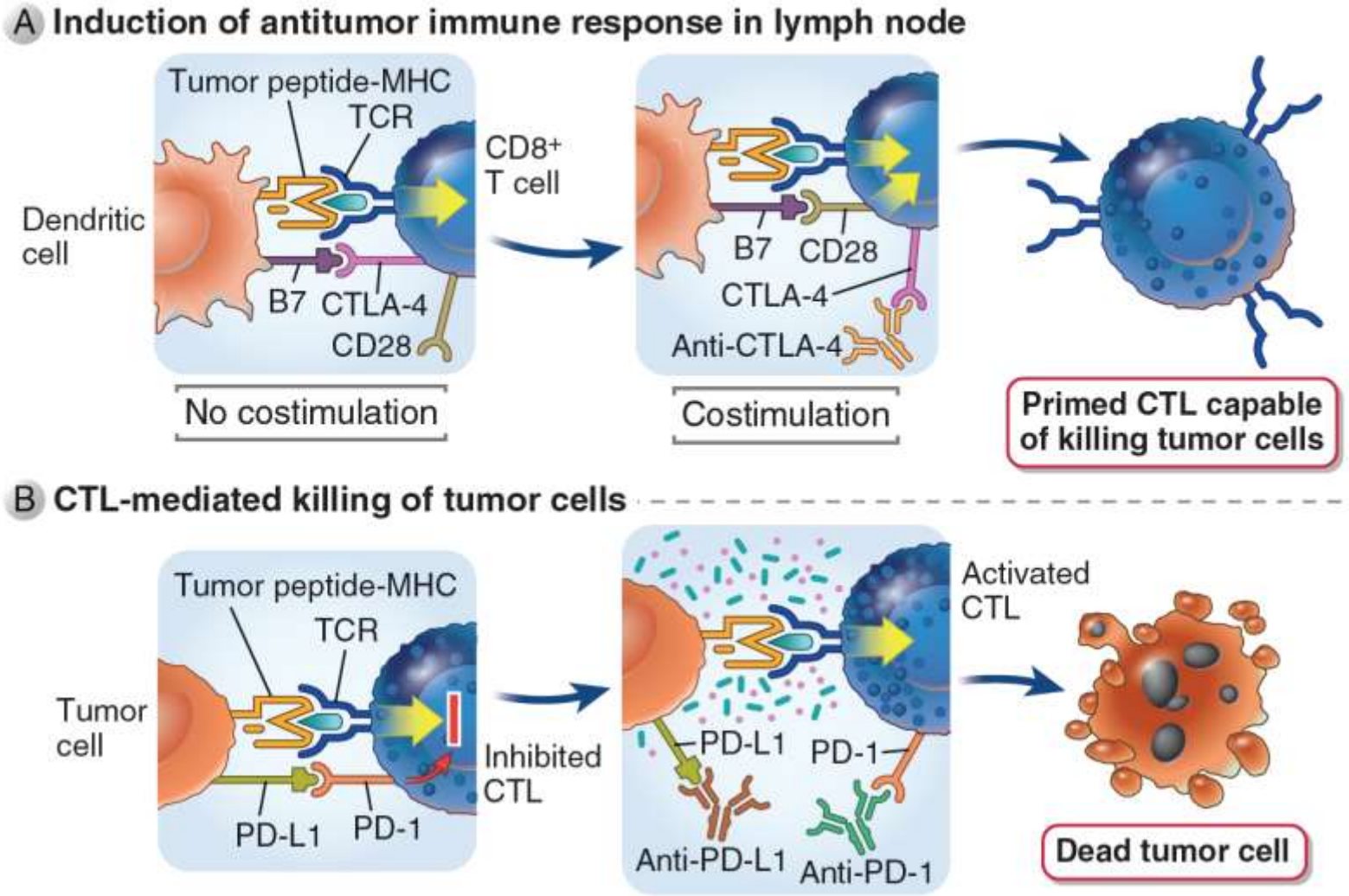
Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017

Why do Tumors or Tumor-Specific T cells Engage PD-1 and CTLA-4?

- CTLA-4:
  - Tumor cause low levels of B7 expression, which permits preferential engagement of the high-affinity receptor CTLA-4
- PD-1:
  - Many tumors may upregulate PD-L1
    - Gene amplification; increased recycling; increased transcription
  - Many tumors induce PD-1 on tumor-specific T cells
    - Chronic antigen exposure leads to effector T cell "**exhaustion**", characterized by high PD-1 , high CTLA-4, decreased cytokine production and decreased cytotoxicity

Relevance of Inhibitors of T Cell Activation to Cancer Immunotherapy:

"Immune Checkpoint blockade":
Inhibit the inhibitors and increase anti-tumor immunity



Immune Checkpoint Blockade (ICB) Counteracts a Common Tumor Evasion Mechanism

- Only 30-50% of patients respond to ICB therapy… why ?
- Tumors with more mutations (more neoantigens) are more responsive to checkpoint blockade than similar tumors less mutations.
  - Tumors with mismatch repair (MMR) mutations generate large numbers of random point mutations, and are generally more immunogenic than other tumors.
  - Tumors with MMR mutations are more responsive to checkpoint blockade than similar tumors without MMR mutations.
- Other evasion strategies at work
  - LAG-3, TIGIT, other inhibitors
  - Treg to Teff balance

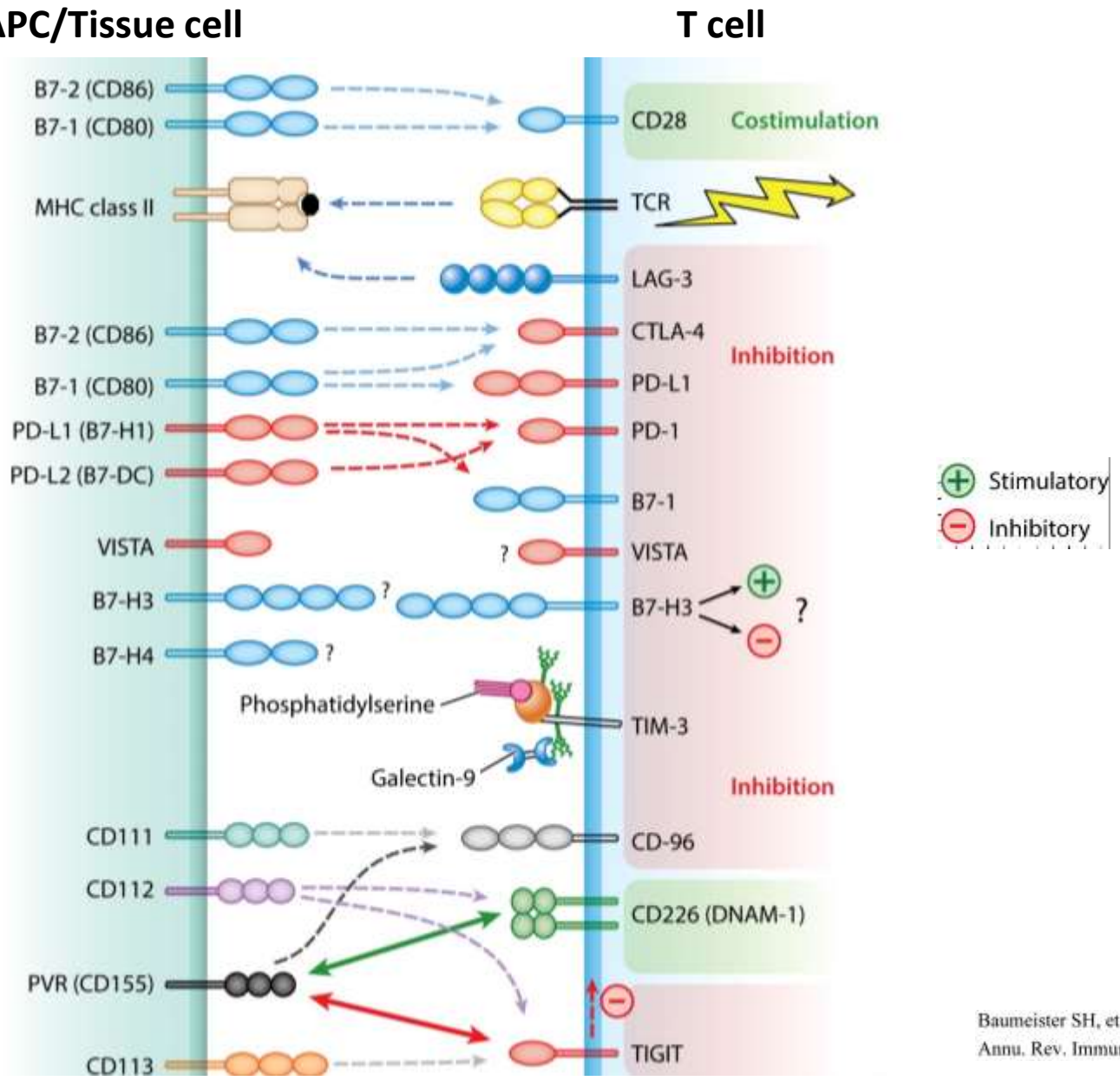
Checkpoint Blockade is More Effective than Tumor Vaccines

- Tumor vaccines have been tried for many years with limited success

- Immune evasion is a hallmark of cancer
  - Multiple regulatory mechanisms

- Vaccines have to overcome regulation
  - Tumor vaccines are the only examples of therapeutic (not prophylactic) vaccines
  - Vaccination after tumor detection means regulatory mechanisms are already active

Many inhibitory/regulatory molecules on T cells



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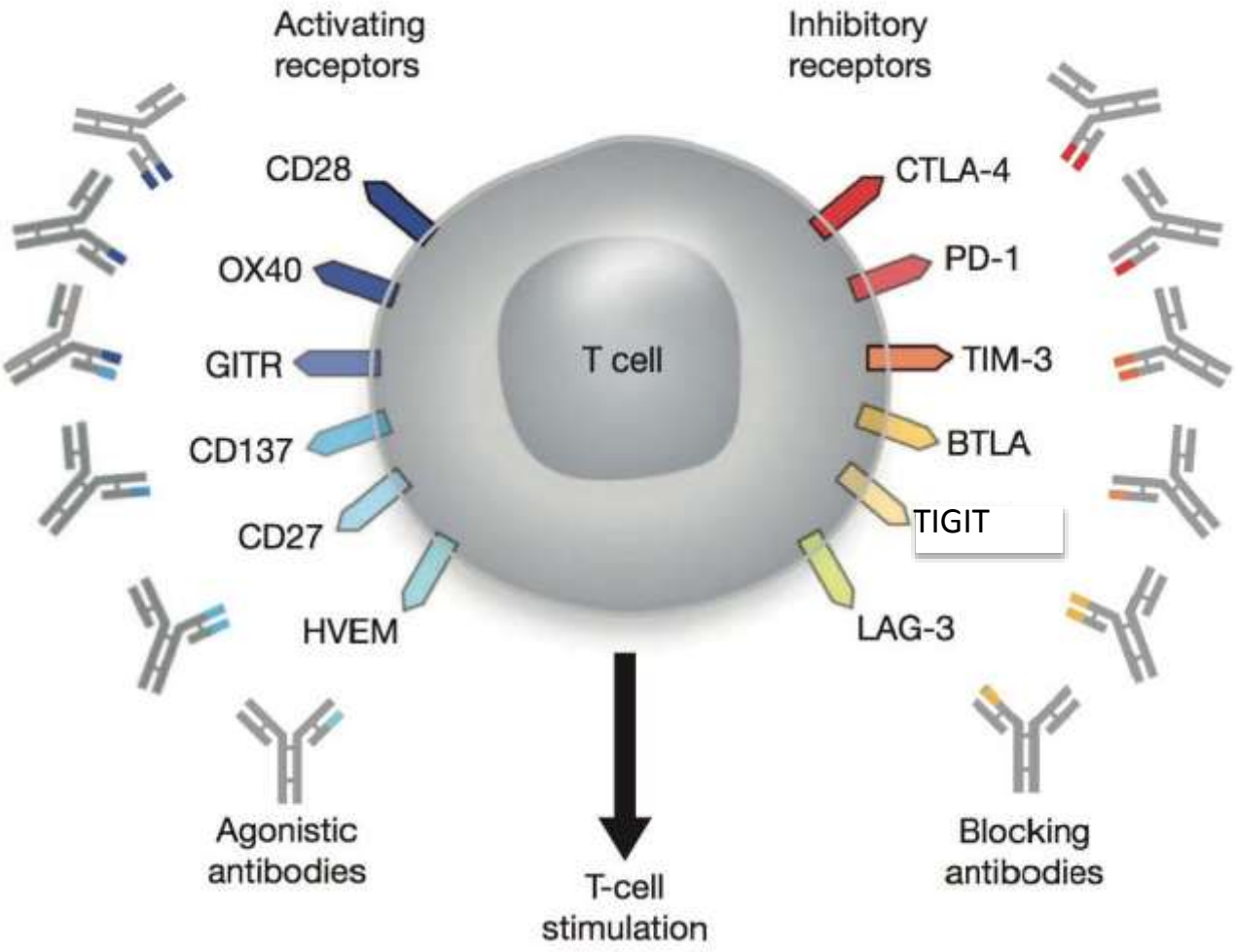
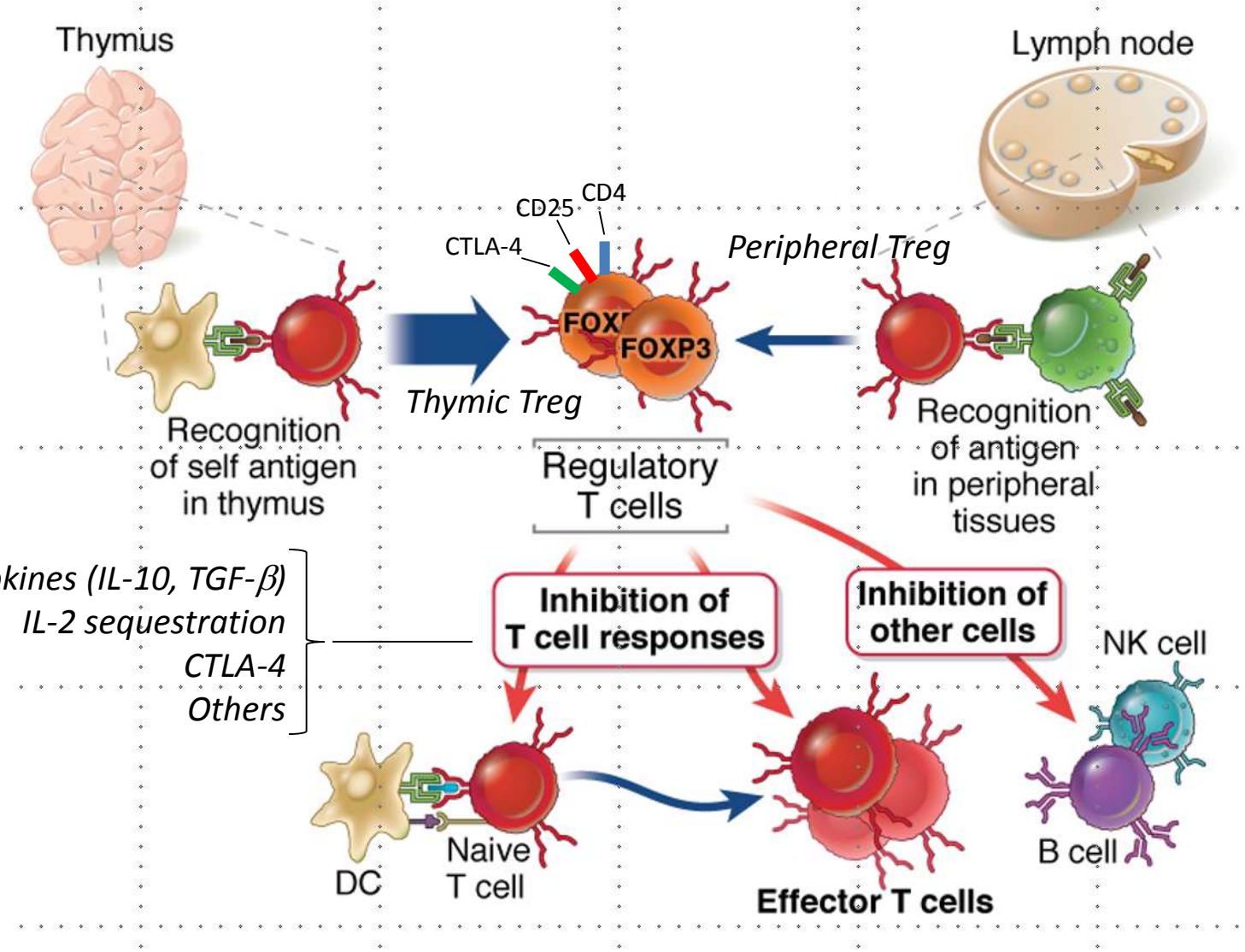
Both Activating and Inhibitory Receptors on T cels are Potential Immunotherapy "Targets"

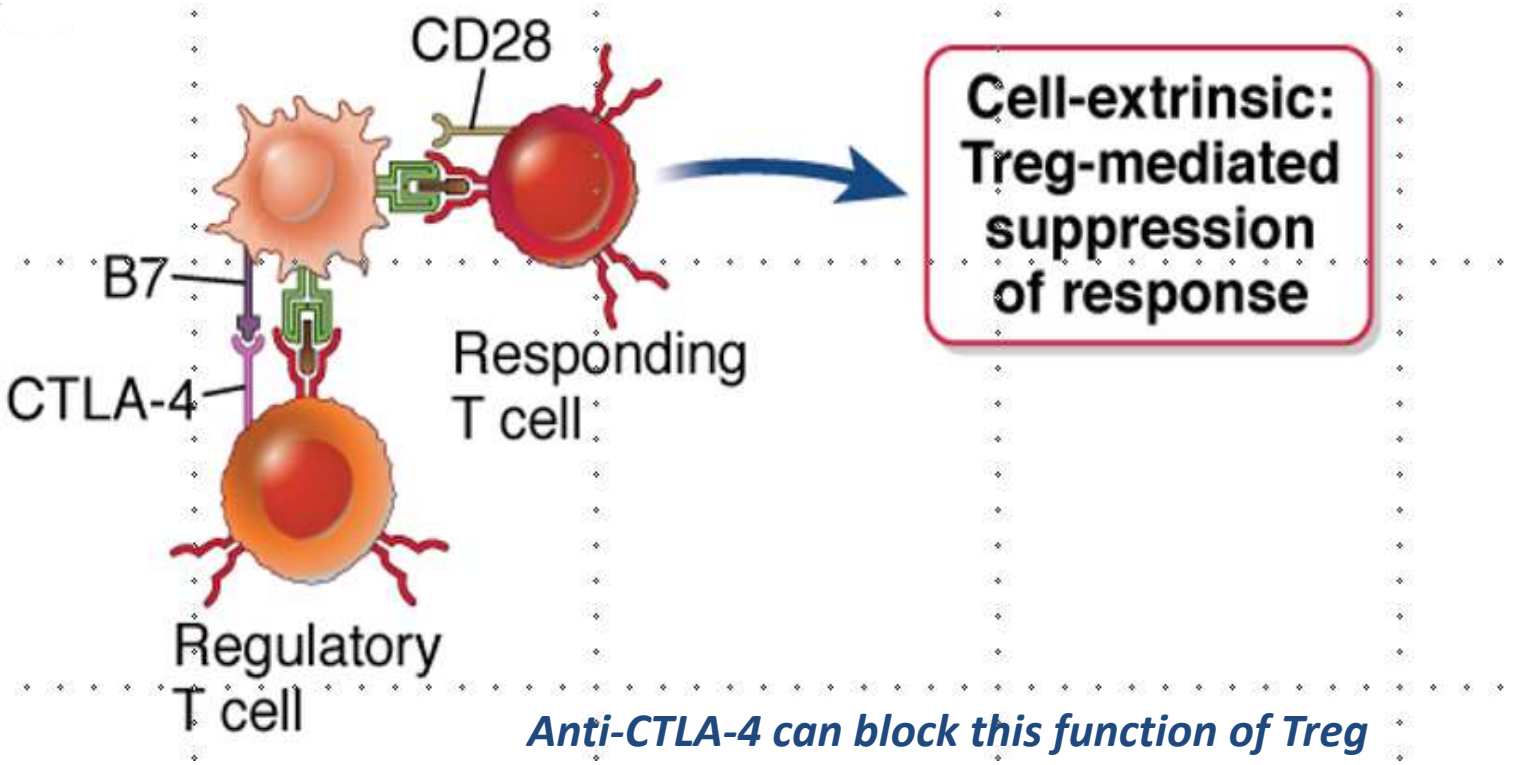


Regulatory T Cells



Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017

Regulatory T Cells and CTLA4



Anti-CTLA-4 can block this function of Treg
Anti-CTLA-4 may also deplete Treg

Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017

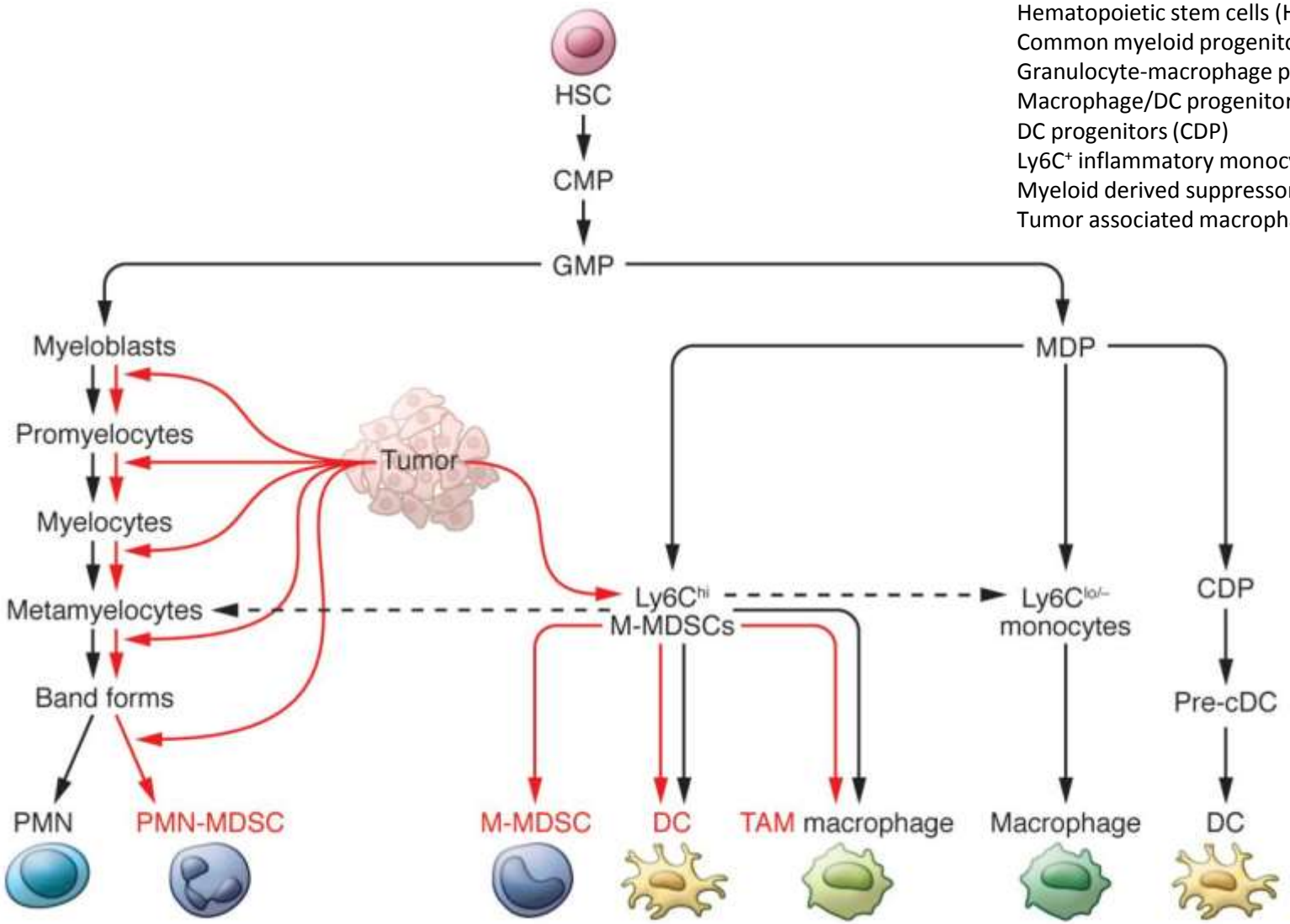
Myeloid Derived Suppressor Cells

- MDSCs have potent immunosuppressive activity
- MDSC are formed in the bone marrow and, migrate to secondary lymphoid organs and the tumor
- MDSCs suppress immune cell function by multiple mechanisms.
  - Expression of arginase, inducible NOS , TGF-β, IL-10 , and COX2
  - Sequestration of cysteine
  - Decreased expression of L-selectin by T cells
  - Induction of Tregs

- *Myeloid-derived suppressor cells are prominent in the tumor microenvironment*

Myeloid Derived Suppressor Cells

Hematopoietic stem cells (HSC)
Common myeloid progenitors (CMP)
Granulocyte-macrophage progenitors (GMP)
Macrophage/DC progenitors (MDP)
DC progenitors (CDP)
Ly6C^{+} inflammatory monocytes
Myeloid derived suppressor cells (MDSC)
Tumor associated macrophage (TAM)



Marvel D, Gabrilovich DI. J Clin Invest. 2015 125:3356-64. PMID: 2616821

Relevance of Treg and MDSC to Immunotherapy

- Treg and possibly MDSCs are important “targets” for enhancement of anti-tumor immunity
- Checkpoint blockade drugs may directly impair Treg or MDSC function

Take Home Points

The Immunosuppressive Tumor Microenvironment:
A Major Challenge