Advances in Cancer Immunotherapy

Immunology 101 for the Non-Immunologist

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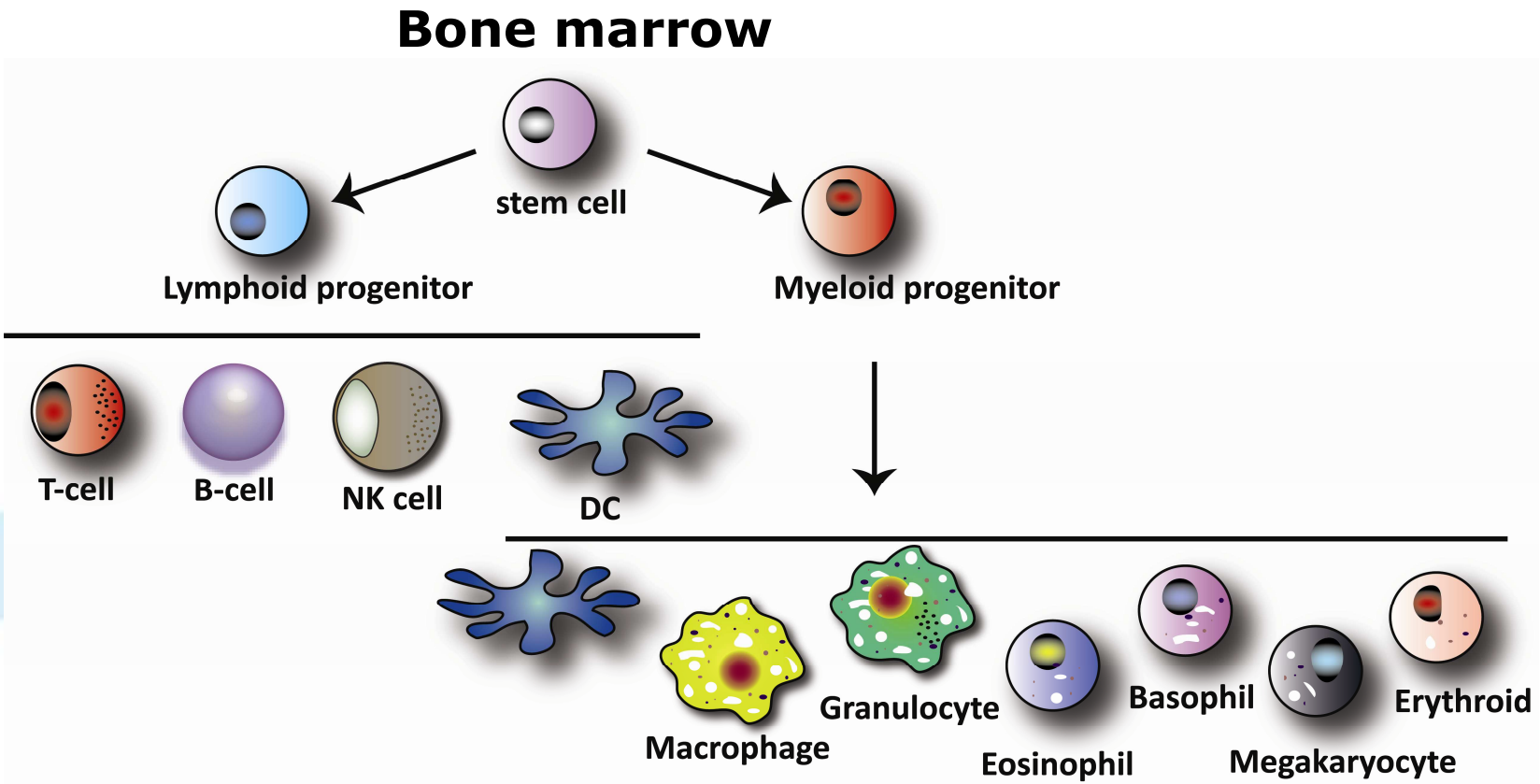
Cellular Origin of Immune Cells



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Innate vs Adaptive

- **Innate immunity:**
  - Resistance that exists before infection
  - First line of defense
  - Broad specificity
    - Macrophages
    - Neutrophils
    - Eosinophils
    - NK cells

Most potential pathogens are checked before they establish an infection.

Innate vs Adaptive

- **Adaptive Immunity**
  - Antigen specific receptors
  - Responds to antigen stimulation with proliferation and differentiation
  - Gives rise to immunologic memory
    - T lymphocyte
    - B lymphocyte – antibody producing cells
    - Professional Antigen Presenting Cells (APC)

Antigen: Molecule (usually a protein) that react with an antibody (**anti**body **gen**erating)

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General Immune Responses

	Innate	Adaptive
Type of Response	Antigen-Independent	Antigen-Dependent
Time to max response	Immediate	Lag between exposure and response
Specificity	Broad	Antigen-specific
Memory	None	Yes
Evolutionary Origin	Early (vertebrates)	Recent (mammals)
Examples	Inflammation, macrophages	Antibodies, T cell mediated immunity

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Adaptive Immunity

- **Cellular immunity:**
  - Mediated by T lymphocytes
  - Require antigen presentation by a professional antigen presenting cell
  - $CD4^+$ (helper) T cells: Produce cytokines for activation of other immune cells
  - $CD8^+$ (cytotoxic) T cells: Recognizes and kills specific target cells: virus-infected cells, tumor cells

- **Humoral immunity:**
  - Antibody-mediated immunity
  - B cells with help from dendritic cells and T helper cells

Immune Tissues and Organs

Primary lymphoid organs – maturation

- Thymus: The site of T cell maturation.
- Bone marrow: The site of B cell maturation

Secondary lymphoid organs – activation

- Lymph nodes
- Spleen
- Mucosal immune system (mucosal-associated lymphoid tissue, MALT)

Antigen Presenting cells

Types of antigen presenting cells (APC)

B-cells

Macrophages

Dendritic cells

- Presents peptide derived from antigen to CD8 and CD4 T cells (signal 1)
- Provides co-stimulation signals (signal 2)
- Provides polarization signals

Signal 1 and 2 are required for T cell activation

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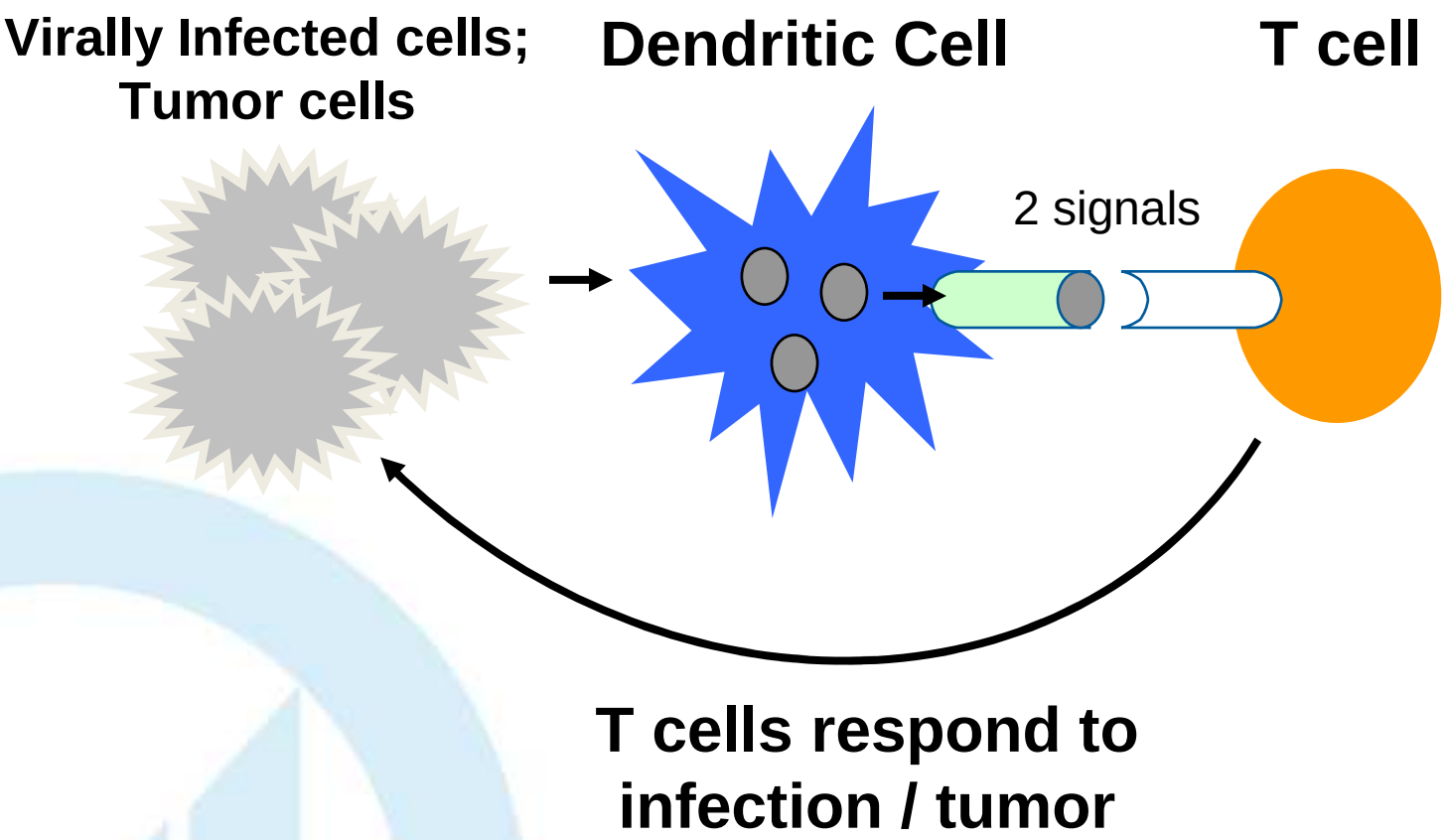
T cell Activation



Signal 1: Major Histocompatibility Complex

Presents peptide antigens to the T cell receptor (TCR)

- **MHC class I (HLA-A/B/C)**
  - Presents peptide to CD8 T cells
  - Typically peptides derived from endogenous proteins
  - Restricted peptide size (8-11 aa)
  - Expressed on most cells

- **MHC class II (HLA-DR)**
  - Presents peptides to CD4 T cells
  - Typically peptides derived from exogenous proteins
  - Broader peptide size (18-20 aa)
  - Only expressed by APCs

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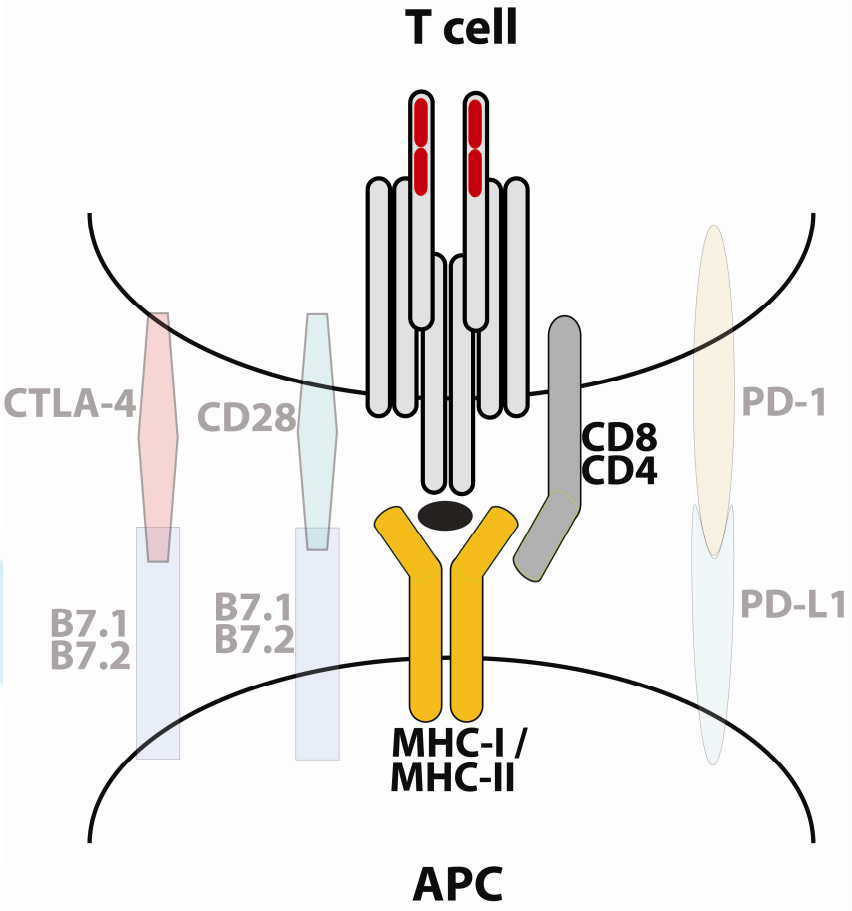
Signal 1: Antigen Presentation



- Initial signal for T cell activation
- In the absence of signal 2, T cells will not be activated, may undergo apoptosis

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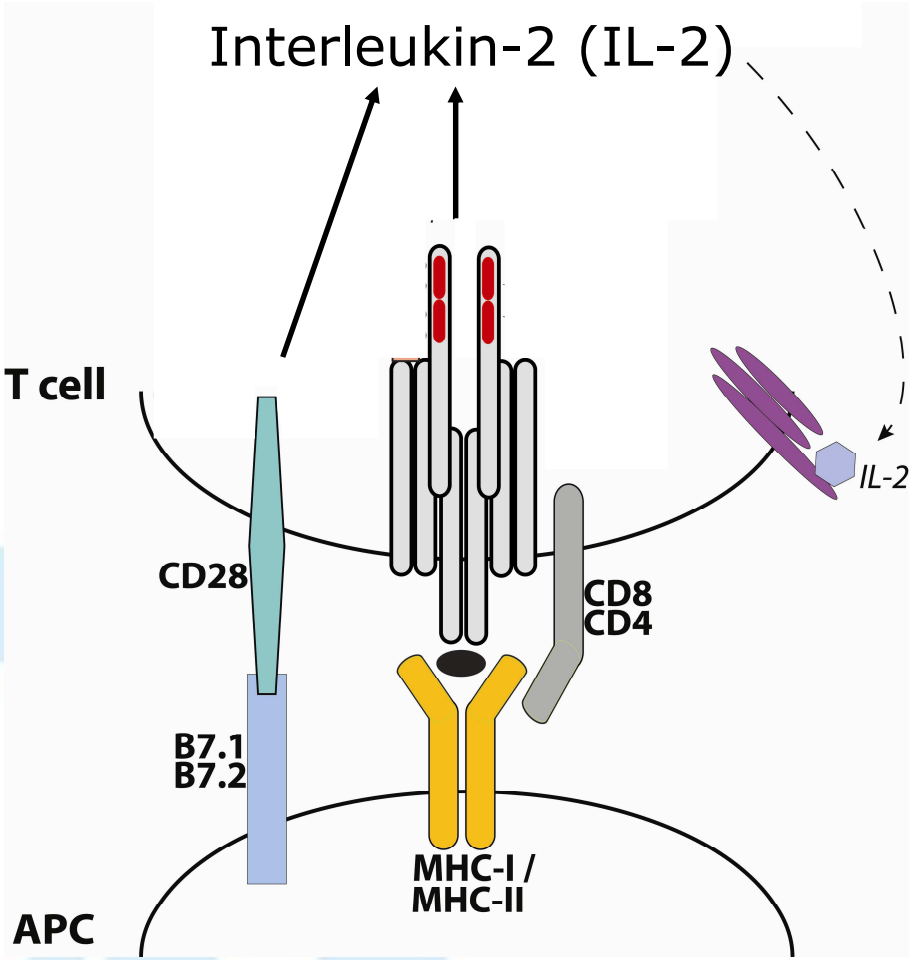
Signal 2: Co-stimulation



- Signaling between CD28 on T cells and B7.1/B7.2 on APC
- Leads to production of IL-2 required for T cell survival and proliferation

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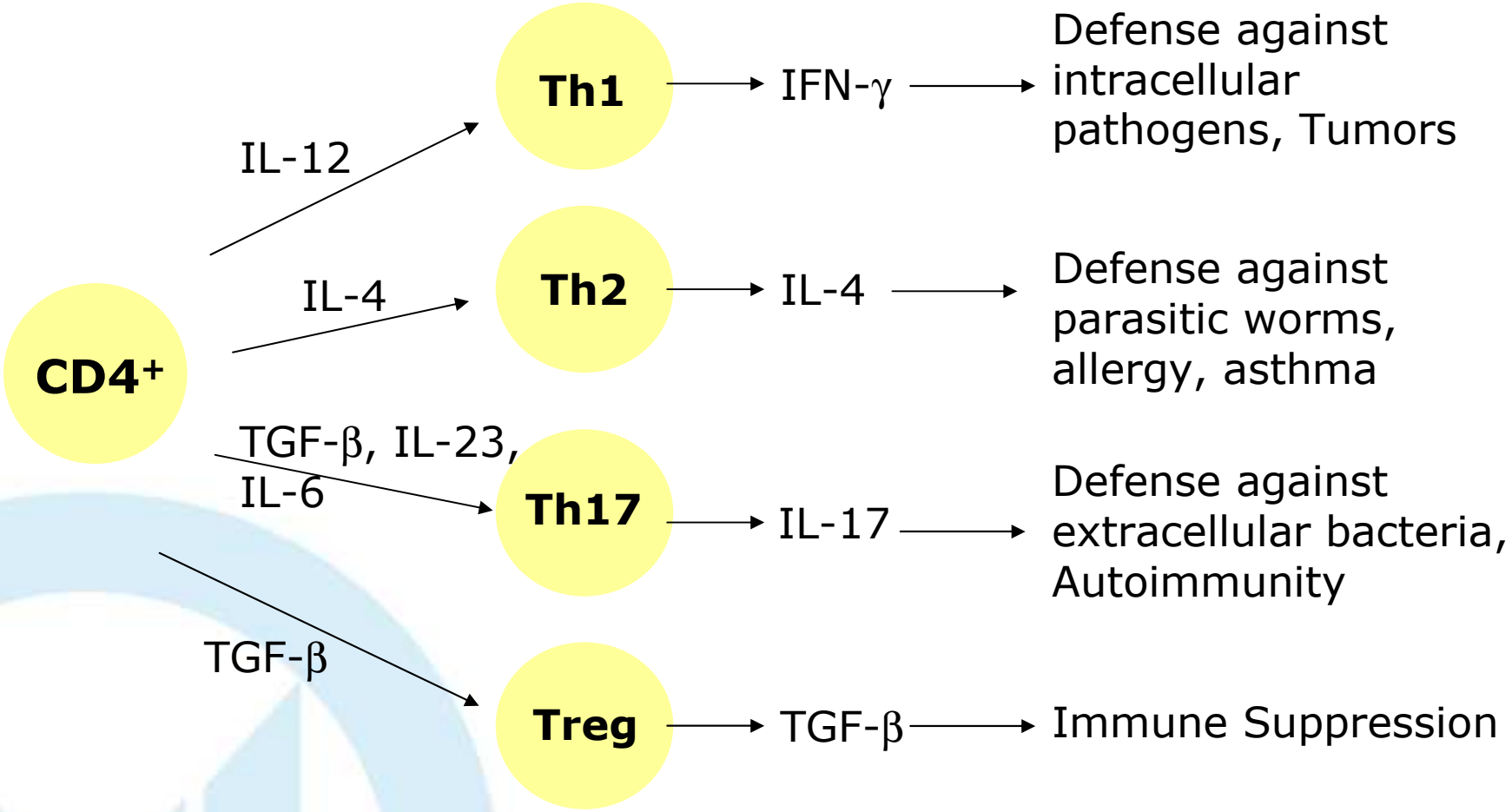
Polarization



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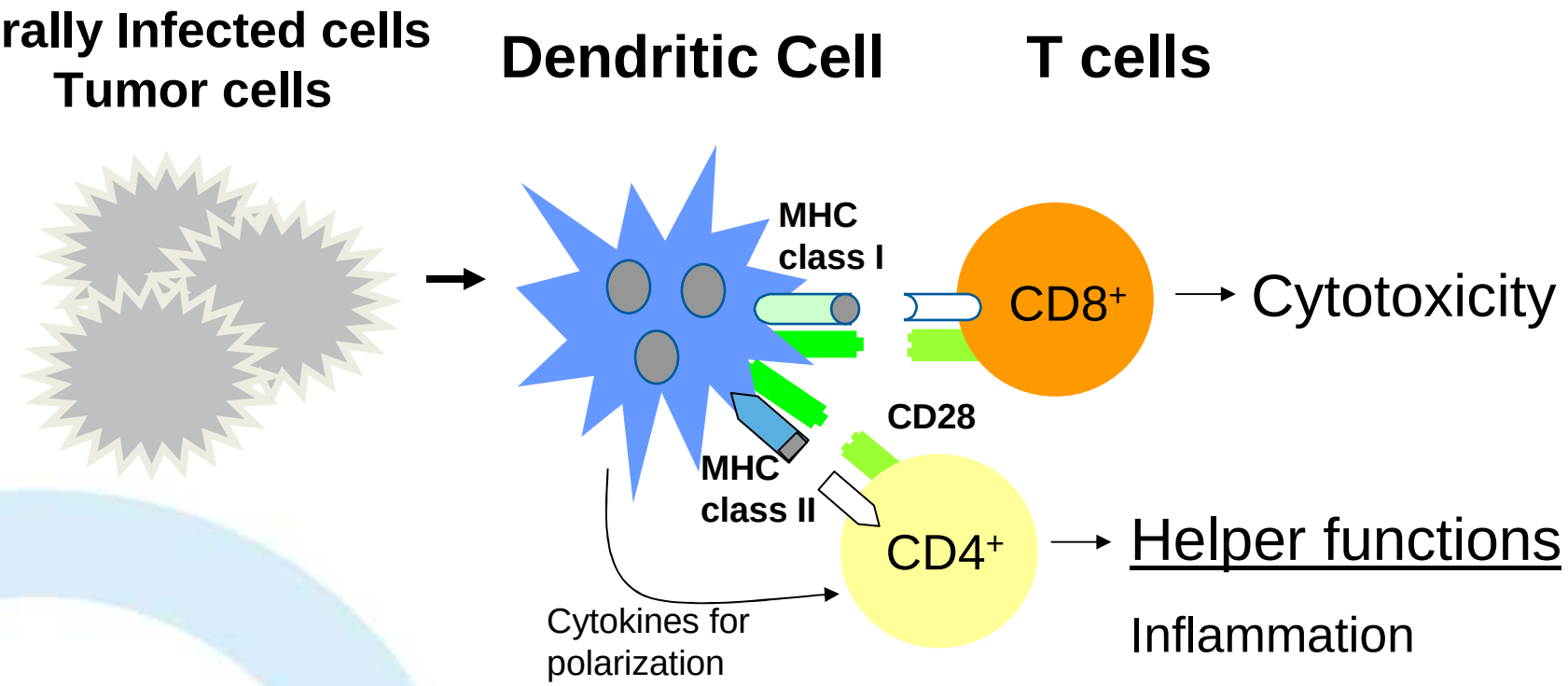
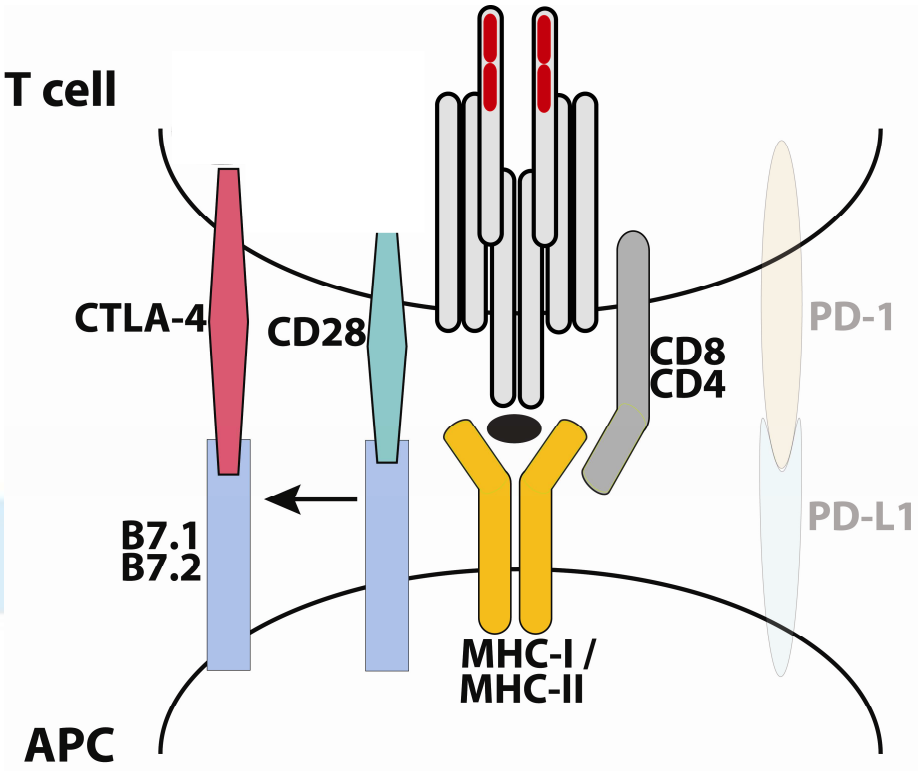
T cell activation



Regulation of T cell activity



CTLA-4

- Induced in activated T cells
- Also binds to B7.1 and B7.2
- Higher affinity than CD28
- Squelches the CD28 signal

Net effect of CTLA4 signaling is to shut off T cell activity

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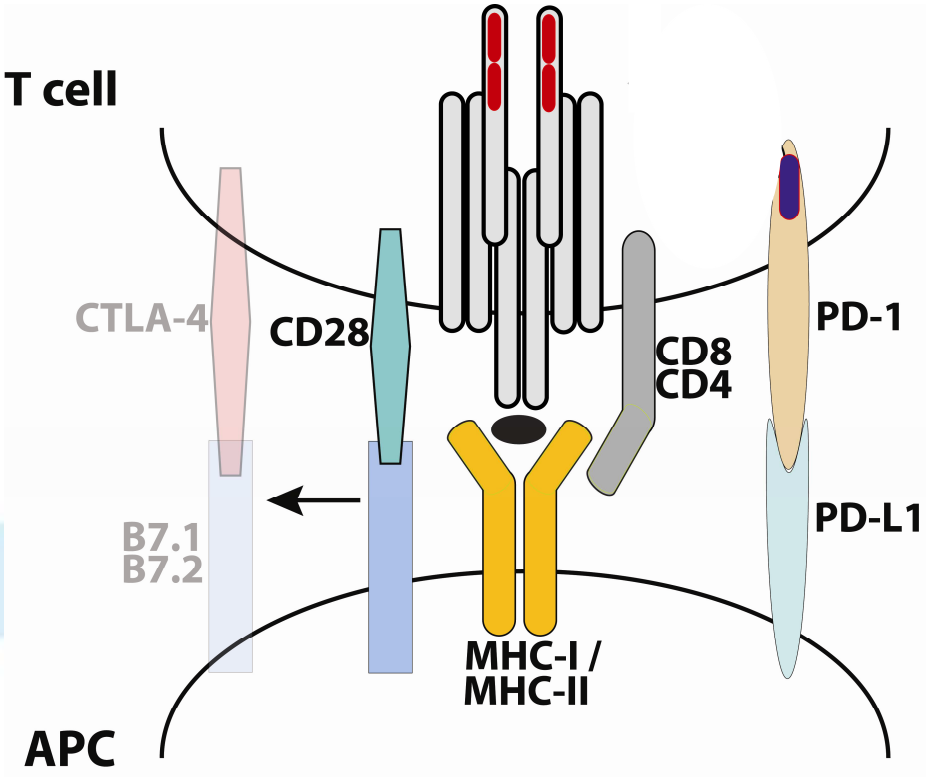
Regulation of T cell activity



PD-1

- Expressed on chronically activated T cells; marker of T cell exhaustion
- Binds to PD-L1/PD-L2
  - –Constitutively expressed on many cells (APCs, tumor cells)
- Blocking the PD-1/PD-L1 pathway can reverse T cell unresponsiveness in chronic viral infections

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Tolerance – Ignorance to Self Antigens

Mechanisms:

- **Clonal deletion of T cells that recognize "self"**

  Occurs in the thymus

- **Clonal inactivation of T cells in the periphery**

  Regulatory T cells (Tregs)

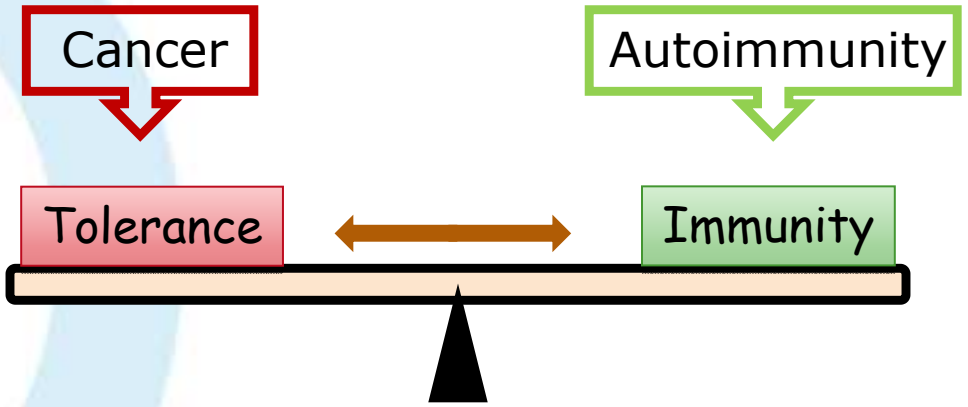
  Myeloid Derived Suppressor Cells (MDSC)

  These mechanisms also participate in the induction of tolerance to gut flora, fetus, and tumors.

Summary

Normal immune state is in balance

- Allows recognition of pathogens while avoiding reactivity to self
- Has built in mechanisms to limit the immune response
- Tumors tip the balance to a non-responsive state
- Approaches to enhance activation while blocking the suppression mechanisms can allow immune recognition of the tumor



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