Antigen Presentation and T Lymphocyte Activation

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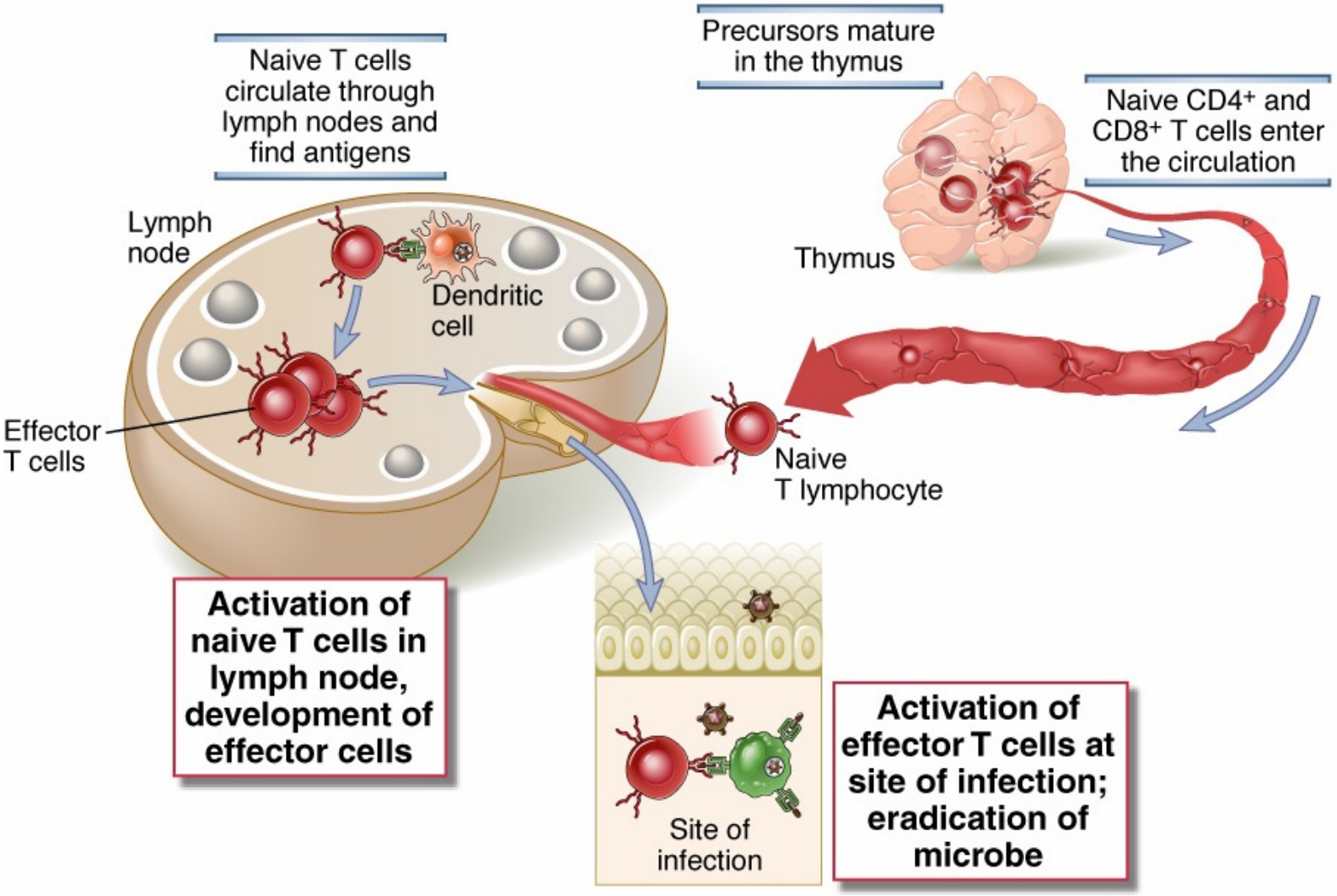
Lecture outline

- Dendritic cells and antigen presentation
- The role of the MHC
- T cell activation
- Costimulation, the B7:CD28 family

The life history of T lymphocytes



Abbas, Lichtman and Pillai. *Cellular and Molecular Immunology, 7th edition, 2011*

The challenge of finding antigens

- Very few lymphocytes in the body are specific for any one microbe (or antigen)
  - Specificity and diversity of antigen receptors: the immune system recognizes and distinguishes between 10^6 - 10^9 antigens; therefore, few lymphocytes with the same receptors

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  - **The small number of lymphocytes specific for each antigen cannot patrol all epithelia (routes of microbe entry) or tissues where the antigen may be present**

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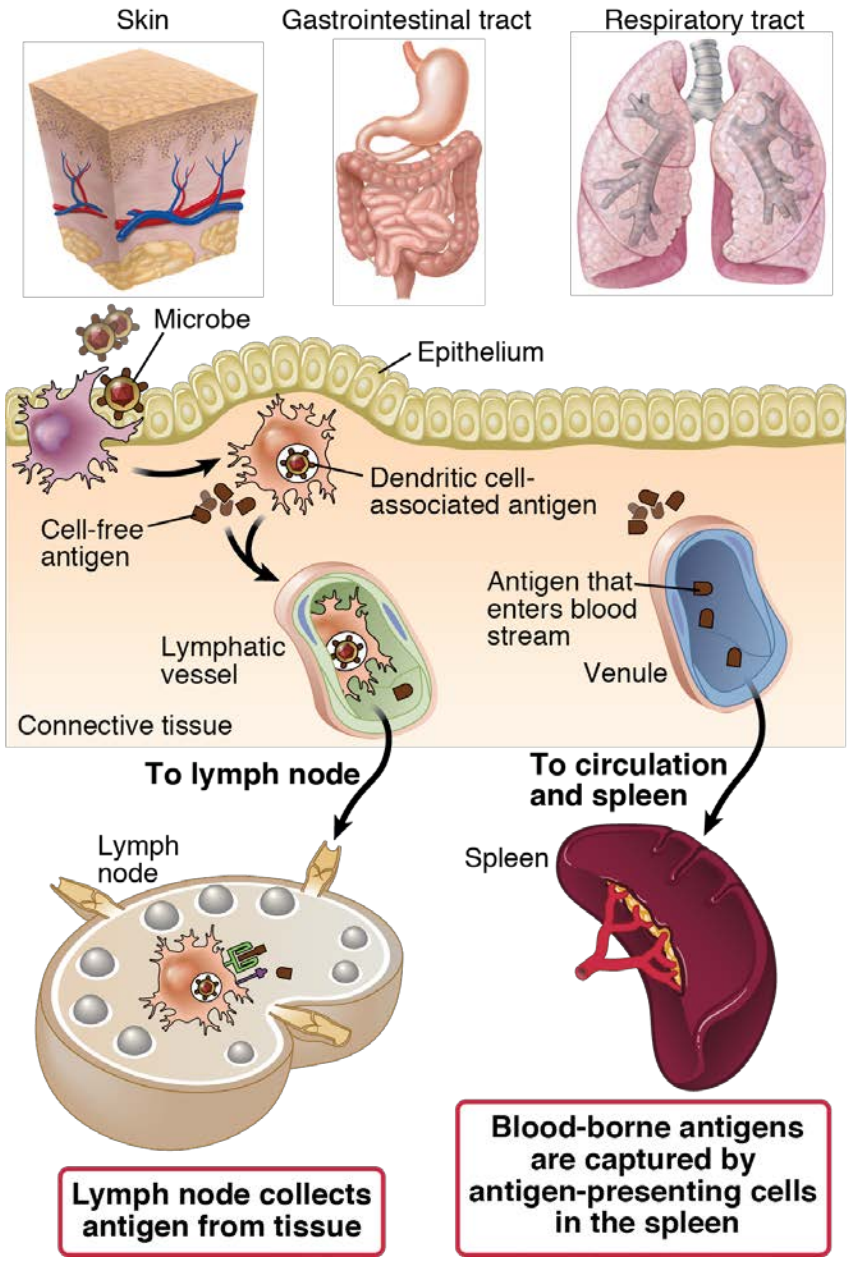
- **Therefore, antigens and lymphocytes have to be brought together**
  - **The function of lymphoid organs**

Capture of antigens

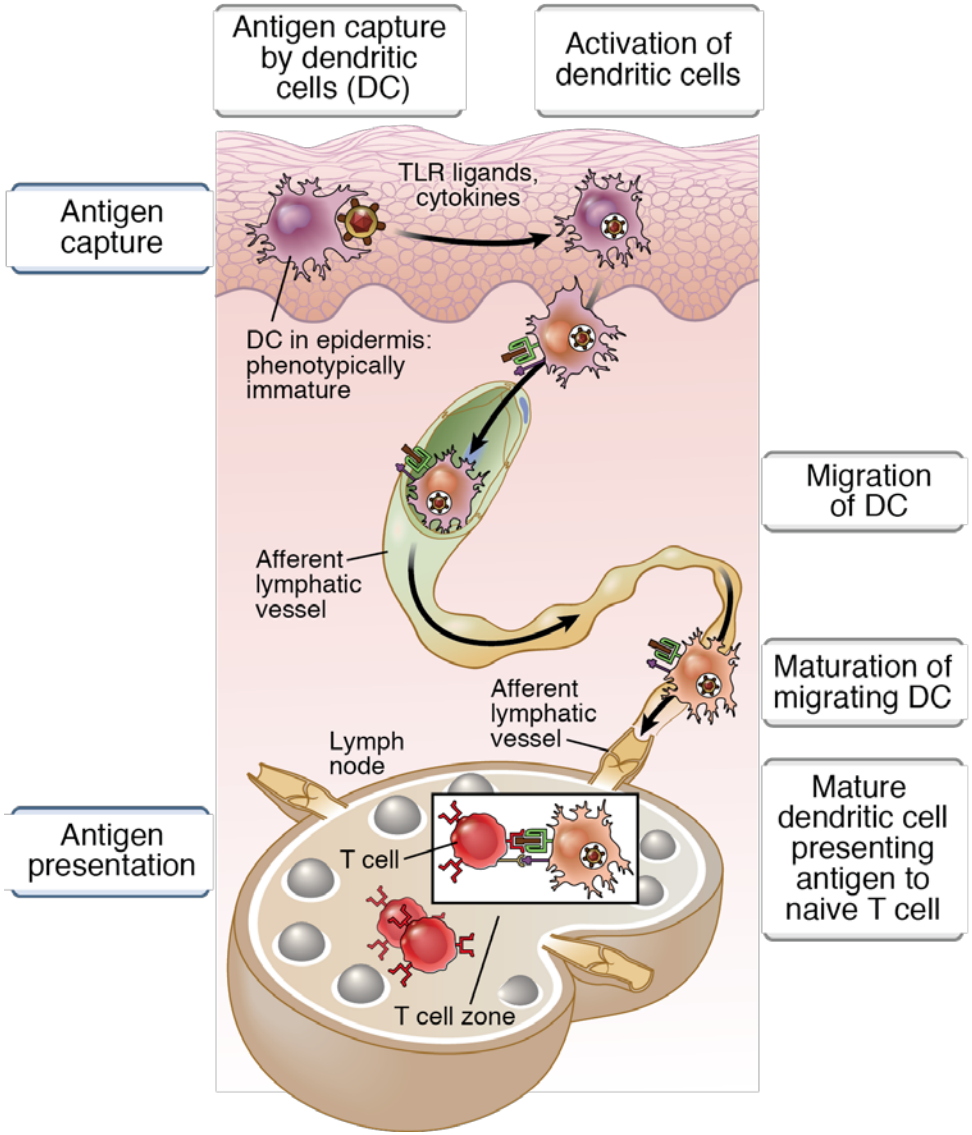
Sites of antigen entry

Sites of initial antigen capture

Sites of antigen collection and capture



Capture and presentation of antigens by dendritic cells



Abbas, Lichtman and Pillai. *Basic Immunology, 5th edition, 2016, Elsevier*

Sites of microbe entry: *skin, GI tract, airways (organs with continuous epithelia, populated with dendritic cells). Less often -- colonized tissues, blood*

Sites of lymphocyte activation: *peripheral lymphoid organs (lymph nodes, spleen), mucosal and cutaneous lymphoid tissues*

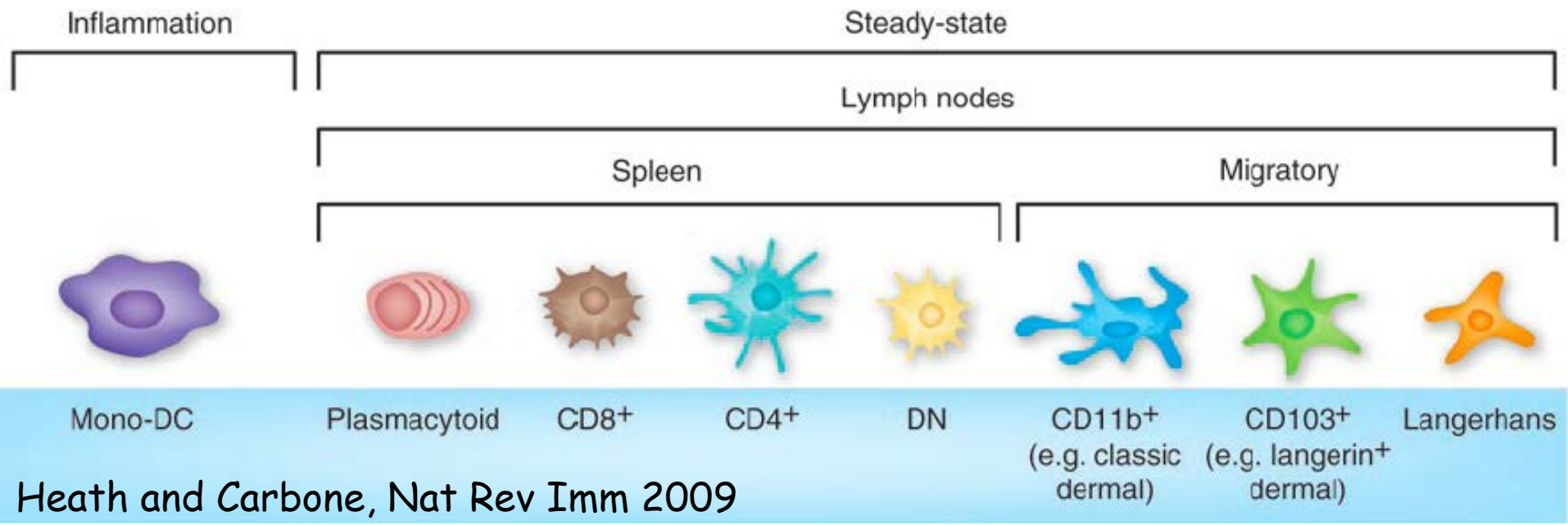
Antigens and T cells come together in the same organs

Dendritic cell subsets

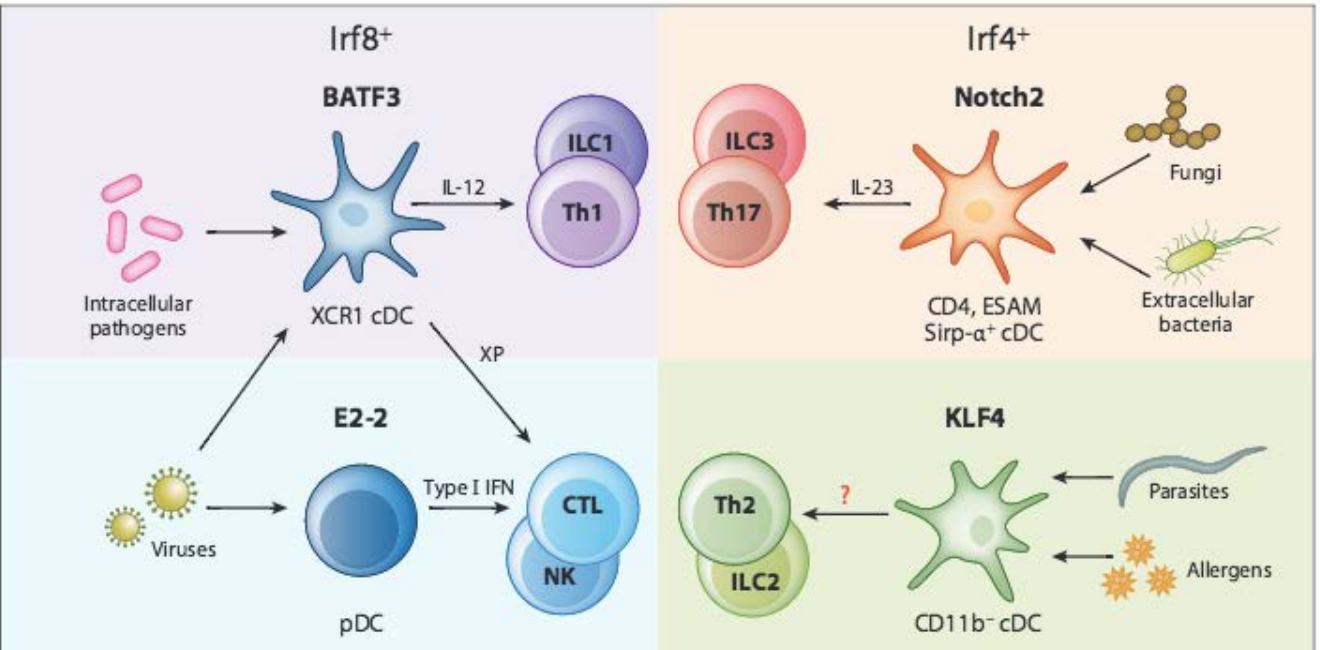
- **Classical**: CD11c+, located in epithelia (site of microbe entry), role in capture and presentation of most antigens
- **Plasmacytoid**: source of type I IFN; capture of blood-borne antigens, transport to the spleen

- **Immature**: in tissues; role in presentation of self antigens and maintenance of tolerance
- **Mature**: activated by TLR and other signals; role in T cell activation

Dendritic cell subsets



Heath and Carbone, Nat Rev Imm 2009



Murphy et al, Ann Rev Immunol 2015; classification based on transcription factors

Why are dendritic cells the most efficient APCs for initiating immune responses?

- **Location:** at sites of microbe entry (epithelia), tissues
- **Receptors for capturing and reacting to microbes:** Toll-like receptors, other receptors
- **Migration to T cell zones of lymphoid organs**
  - Role of CCR7
  - Co-localize with naïve T cells
- **Practical application:** dendritic cell-based vaccines for tumors

Take home messages

What do T cells see?

- All functions of T cells are mediated by interactions with other cells
  - Helper T cells "help" B cells to make antibodies and "help" macrophages to destroy what they have eaten
  - Cytotoxic (killer) T lymphocytes kill infected cells

- How does the immune system ensure that T cells see only antigens on other cells?

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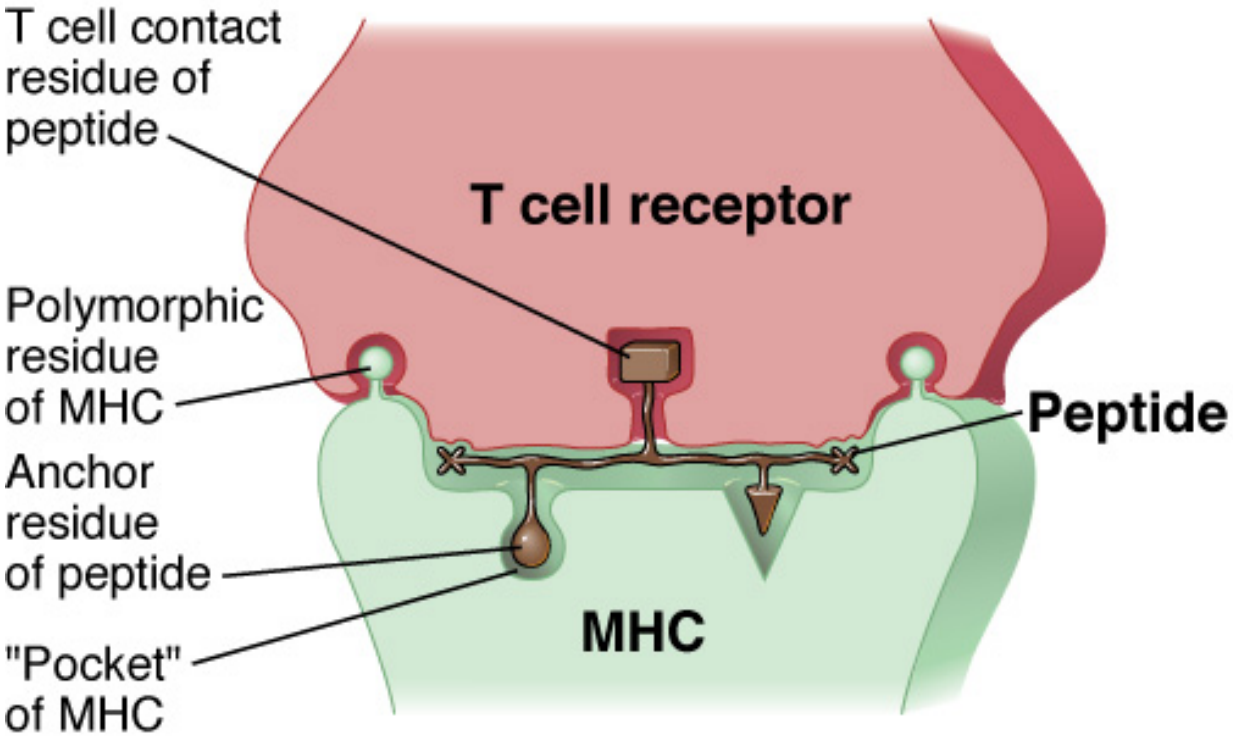
- To ensure cellular communications, T cells see antigens NOT in the circulation but only when displayed by molecules on the surface of other cells
  - These molecules are HLA (generic name: MHC) and the cells displaying the antigen are APCs

Take home messages

A model of T cell recognition of peptide displayed by an MHC molecule



Abbas, Lichtman and Pillai. *Cellular and Molecular Immunology, 7th edition, 2011* © Elsevier

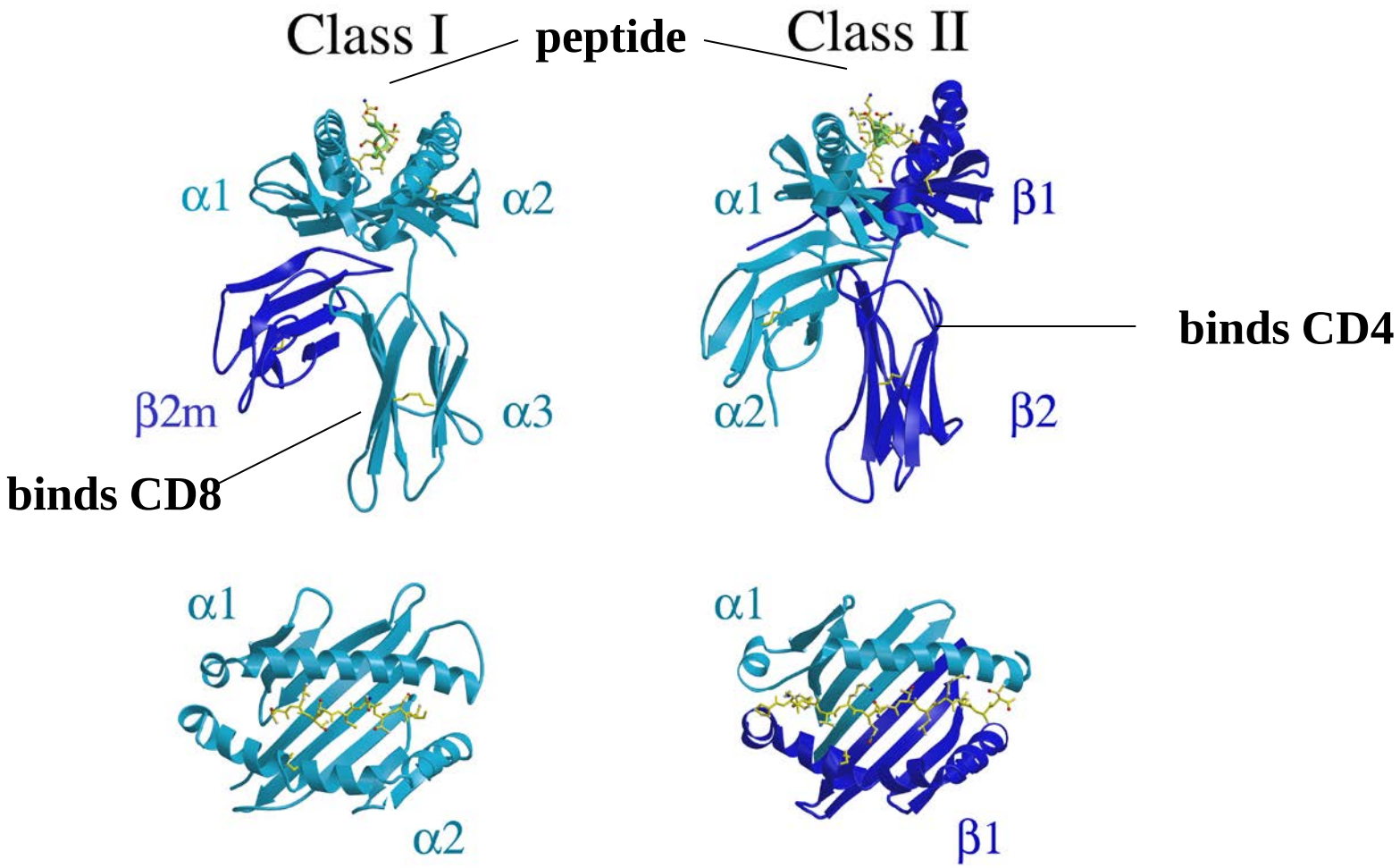
Human MHC = HLA

Because MHC molecules are on cells and can display only peptides, T lymphocytes can recognize only cell-associated protein antigens

MHC polymorphism

- Most polymorphic genes in biology
  - Large number of variants (alleles) in the population
  - Each variant presents only some peptides and is recognized by some T cells
- Polymorphism evolved to ensure recognition of any microbial peptide
- Polymorphism means unrelated individuals express different MHC molecules
  - Every person may recognize slightly different peptides
  - T cells from any individual recognize and react against MHC of any other individual

MHC Structures

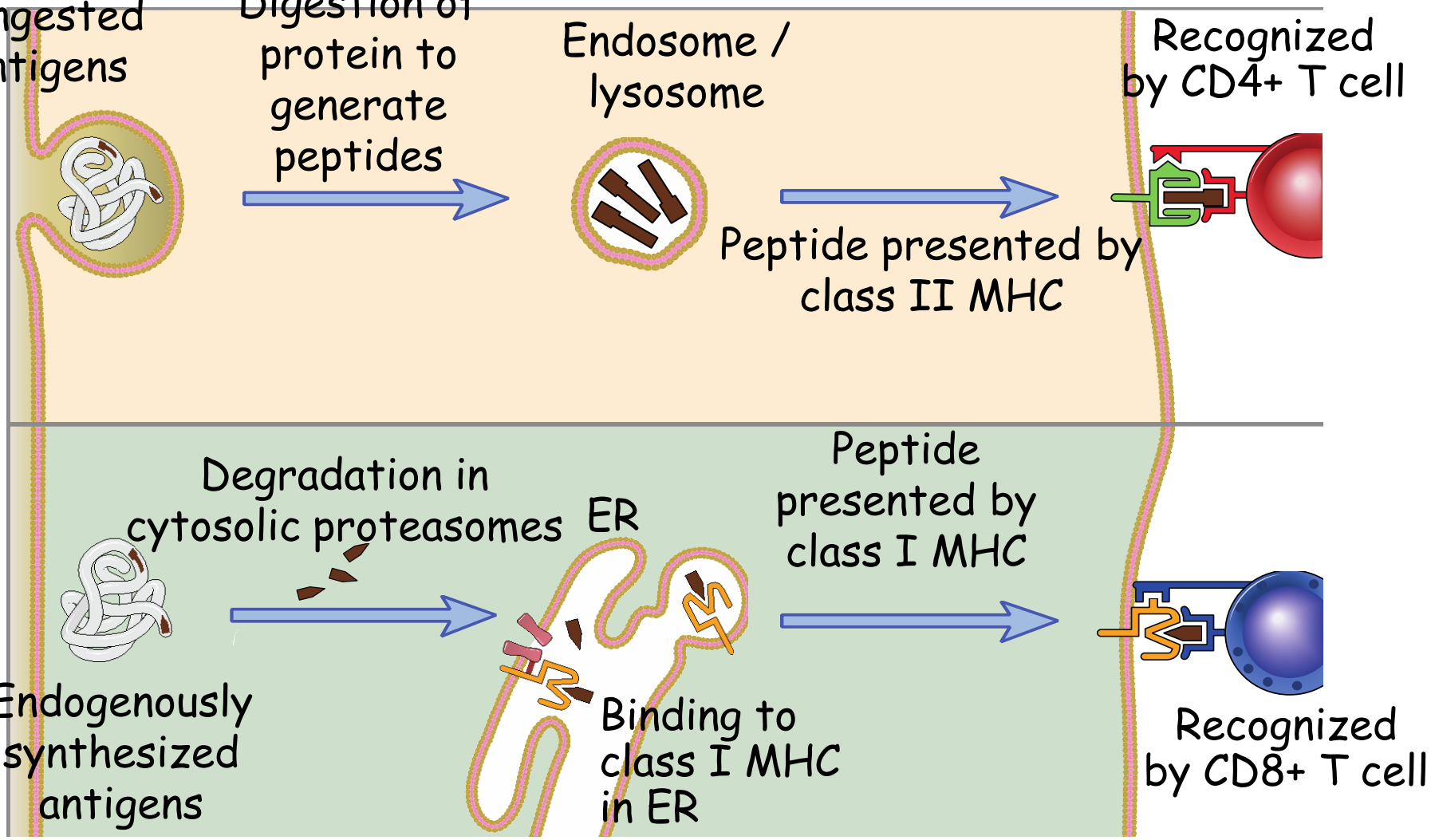


All MHC molecules have a similar basic structure: the cleft at the N-terminal region binds peptide antigens and is recognized by T cell receptors and the membrane-proximal domain binds CD4 or CD8.

What antigens do CD4+ and CD8+ T cells recognize?

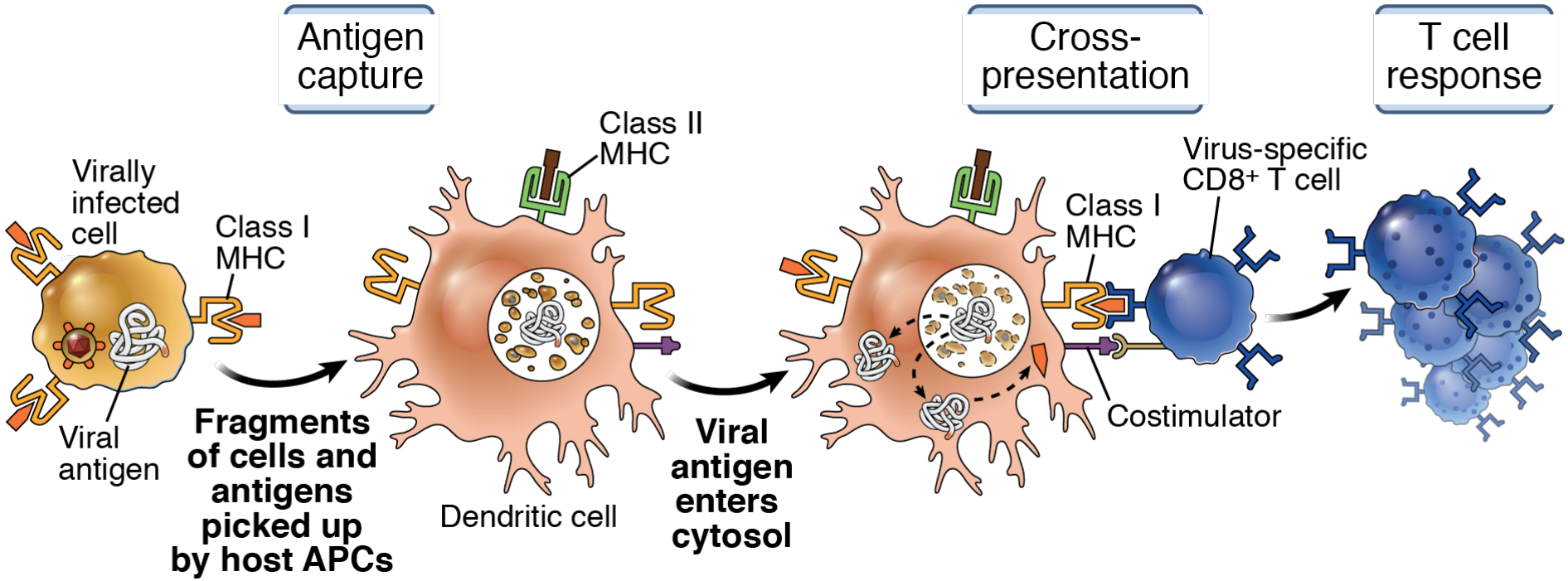
- Lymphocytes must respond to each microbe in ways that are able to eradicate that microbe
  - Extracellular microbes: antibodies; destruction in phagocytes (need helper T cells)
  - Intracellular microbes: killing of infected cells (need CTLs)
  - How do T cells distinguish antigens in different cellular locations?

Pathways of antigen processing

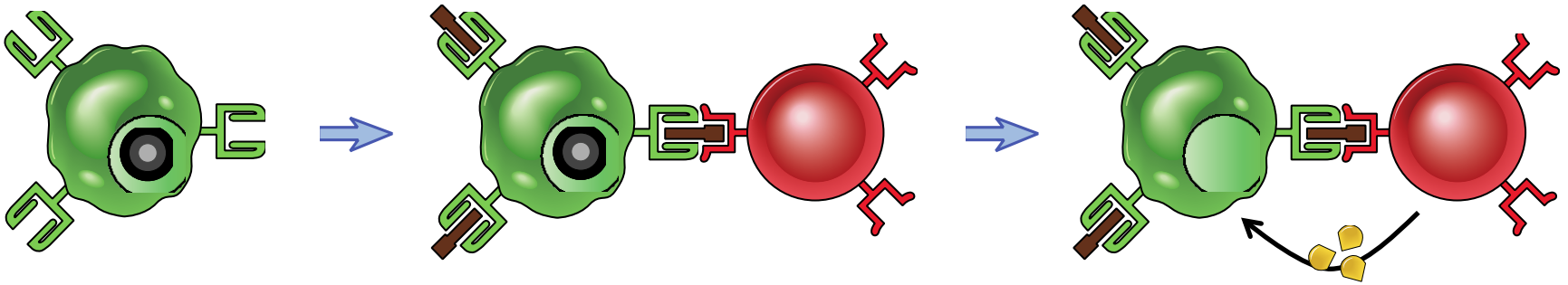


Protein antigen in cytosol (cytoplasm) --> class I MHC -- CTLs
Protein antigen in vesicles --> class II MHC --> helper T cells

Cross-presentation



Functional importance of class II MHC-associated antigen presentation

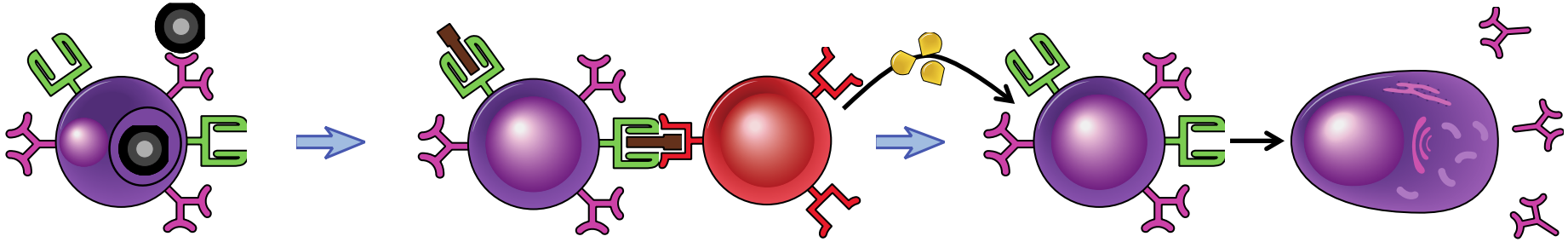


Macrophage ingests microbe

Microbial antigen is presented by class II MHC

Antigen is recognized by CD4+ T cell

CD4+ T cells secrete cytokines that activate macrophage to destroy ingested microbe



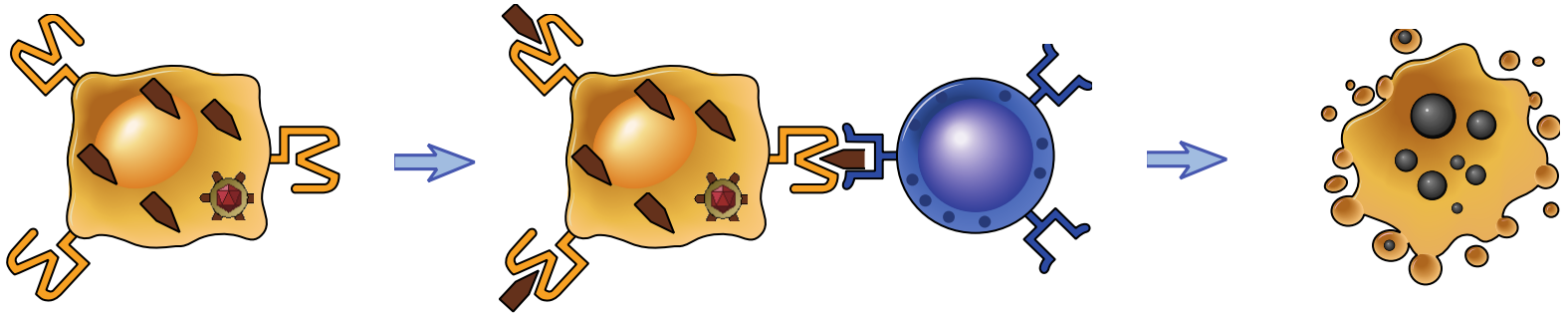
B cell recognizes antigen and ingests it

Antigen is presented by class II MHC

Antigen is recognized by CD4+ T cell

CD4+ T cells secrete cytokines that activate B cells to differentiate into antibody secreting plasma cells

Functional importance of class I MHC-associated antigen presentation



Viral antigen is produced inside virus-infected cell

Viral antigen is presented by class I MHC

Antigen is recognized by CD8+ cytotoxic (killer) T cell

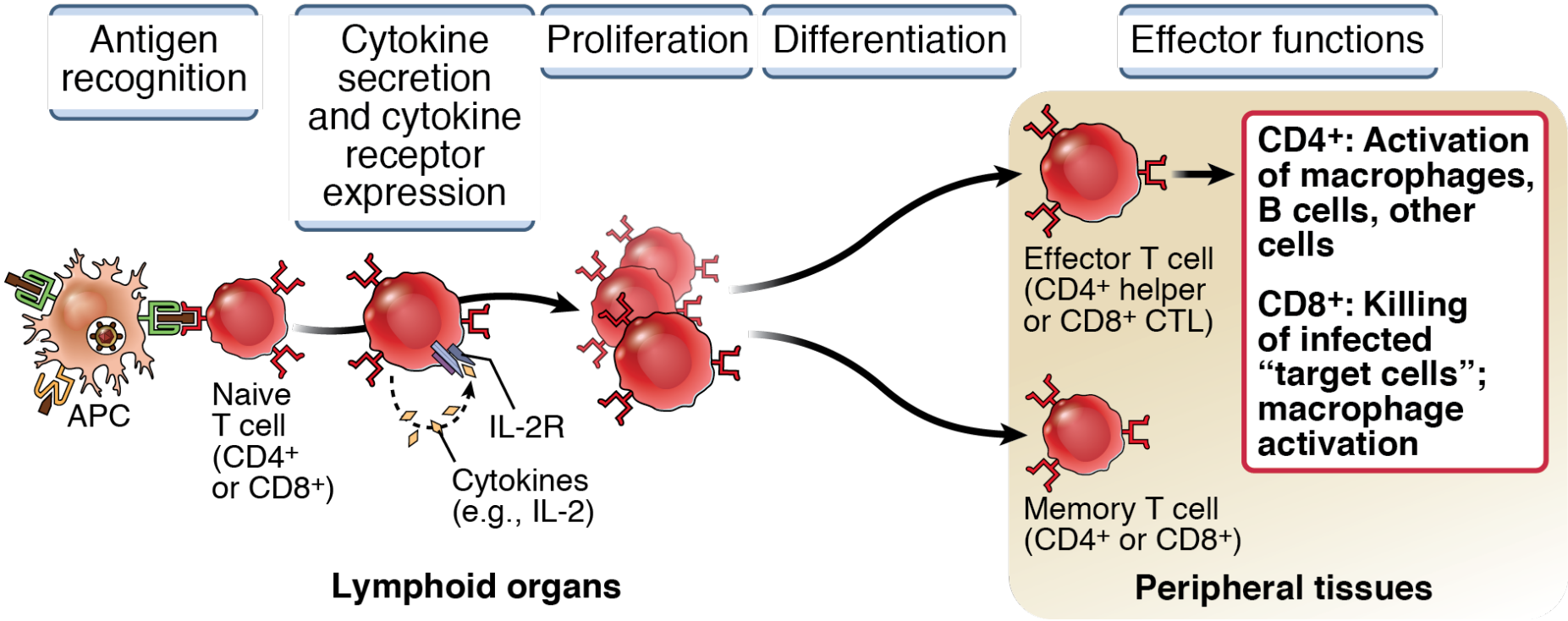
Infected cell is killed, eliminating the infection

Functions of antigen-presenting cells

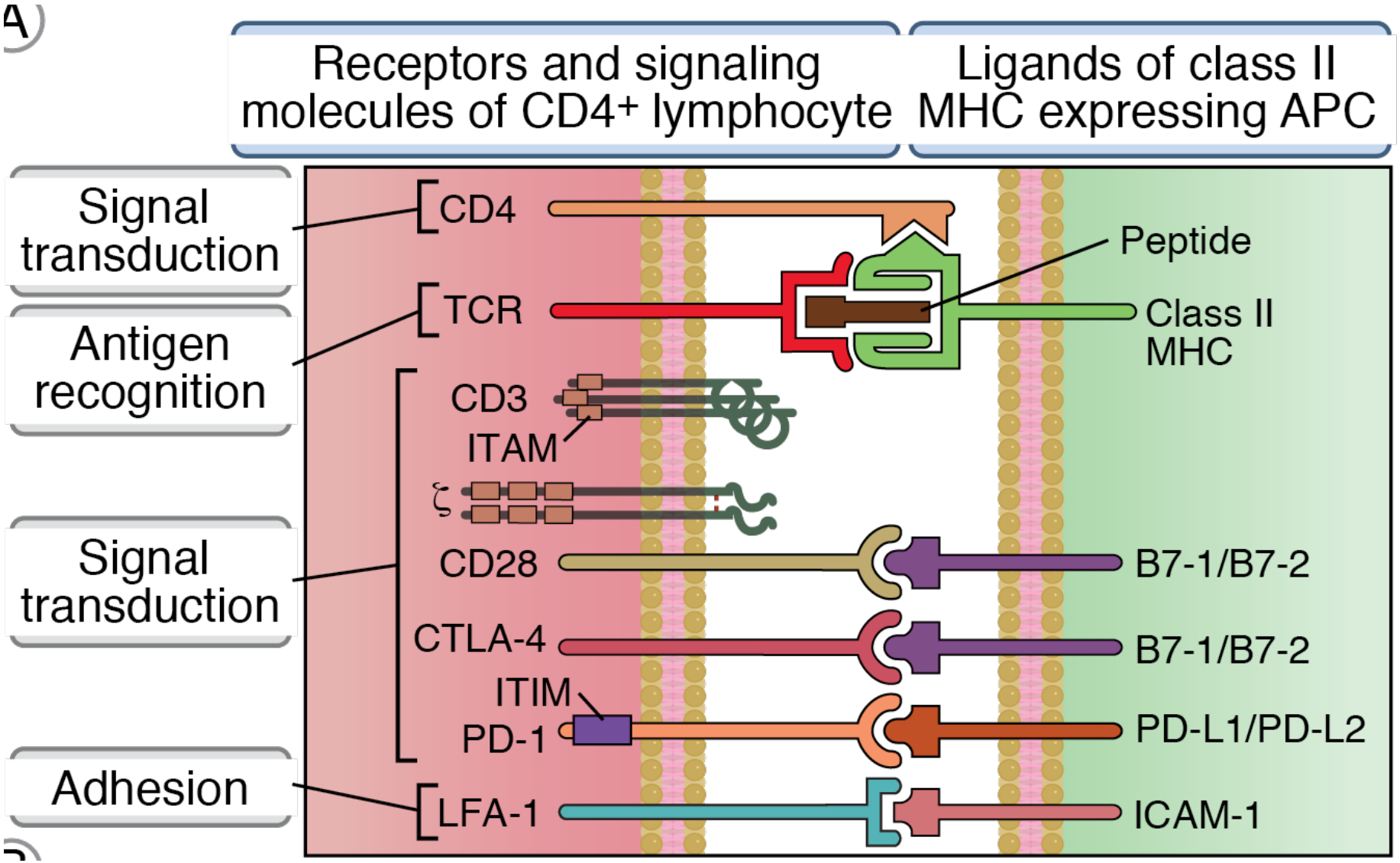
- Capture antigens and take them to the "correct" place
  - Antigens are concentrated in peripheral lymphoid organs, through which naïve lymphocytes circulate
- Display antigens in a form that can be recognized by specific lymphocytes
  - For T cells: MHC-associated peptides (cytosolic peptides to class I, vesicular peptides to class II)
  - For B cells: native antigens
- Provide "second signals" for T cell activation
  - Critical for initiation of responses

Take home messages

Steps in the activation of T lymphocytes



Molecules involved in T cell activation



Therapeutic targeting of molecules involved in T cell responses

- **CD3:** signaling molecule attached to the TCR on all T cells; anti-CD3 MAb to deplete T cells (transplants)
- **Integrins** (LFA-1, VLA-4, others): adhesion to APCs, endothelium; anti-integrin MAb's to block leukocyte migration
- **"Costimulators":** CD28, others; costimulatory blockade

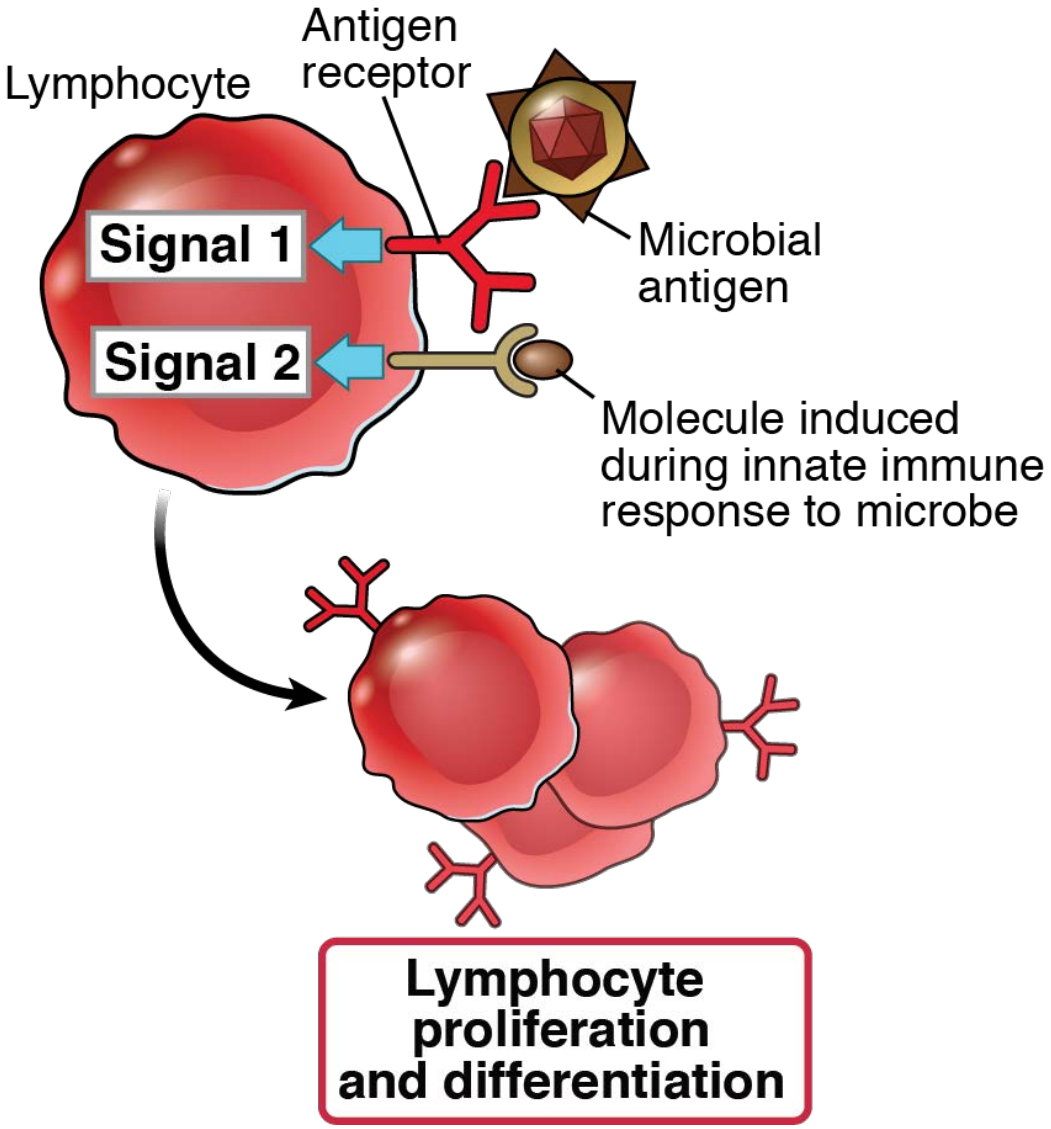
Principal signaling pathways in T cell activation

- Membrane signal (TCR complex, other receptors) --> biochemical intermediates --> transcription factors

- Calcium -- calcineurin --> NFAT
- Ras/MAP-kinase --> AP-1
- PKC -- CARMA/BCL-10 --> NFκB
- PI3-kinase -- Akt --> NFκB

- Cytokines --> Jak-Stat

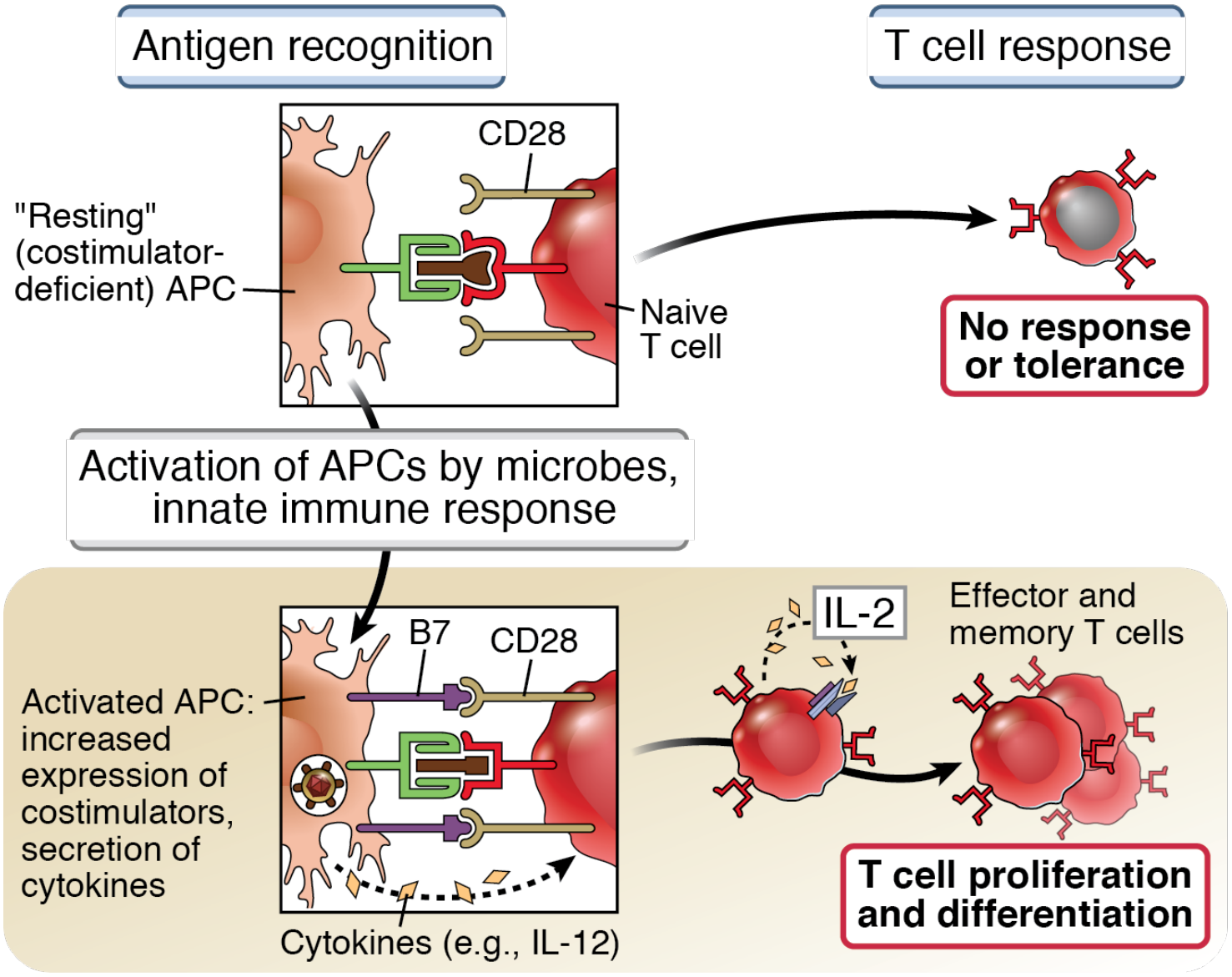
The two-signal requirement for lymphocyte activation



Second signals for T cells: "costimulators" induced on APCs by microbial products, during early innate response

Second signals for B cells: products of complement activation recognized by B cell complement receptors

Role of costimulation in T cell activation

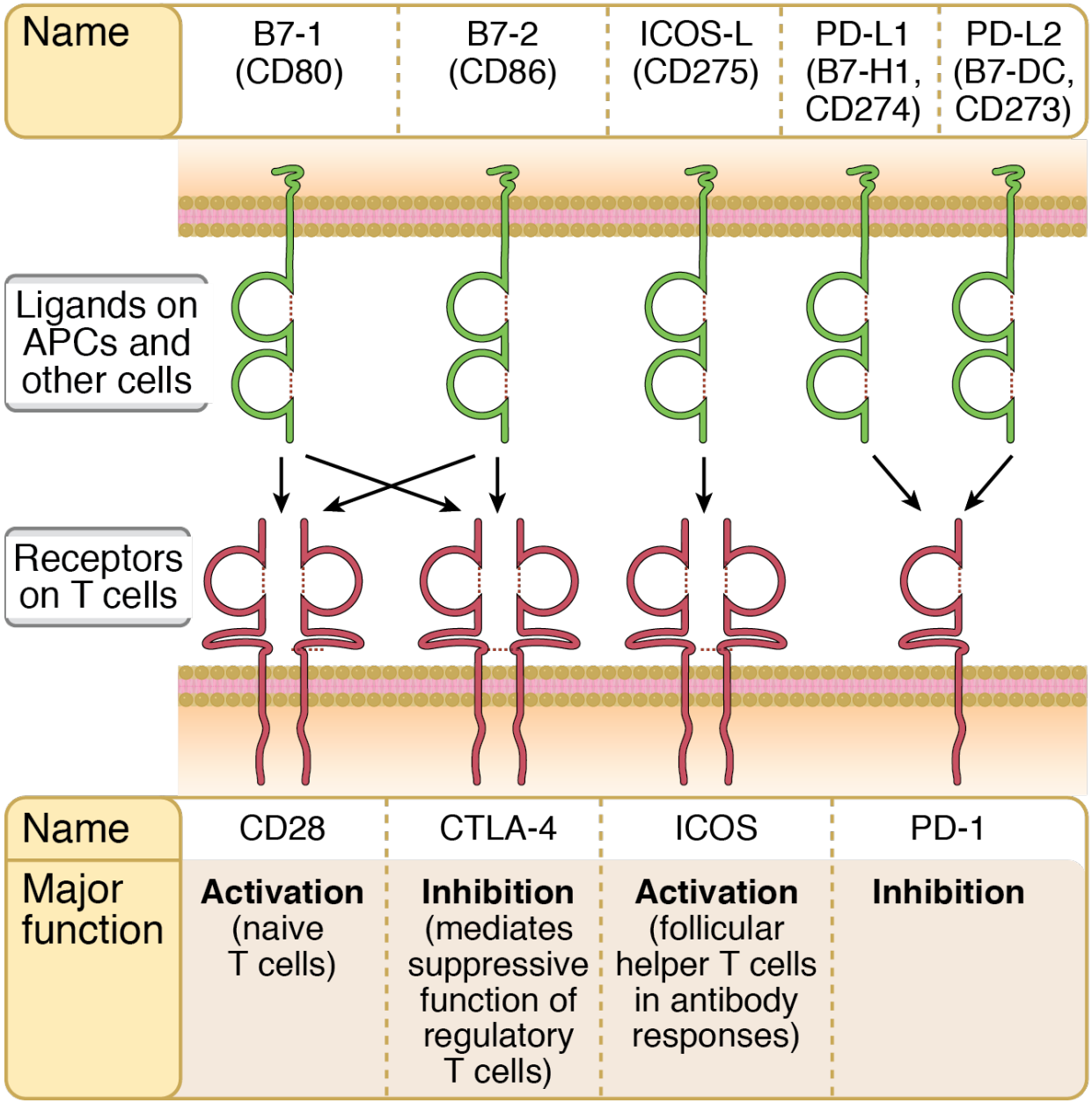


Costimulation

- Required for initiating T cell responses (activation of naïve T cells)
- Ensures that T cells respond to microbes (the inducers of costimulators) and not to harmless antigens
  - Source of costimulation during responses to tumors, transplants?
- Targets for therapeutic blockade of T cell responses

Take home messages

The B7:CD28 families



Major functions of selected CD28-B7 family members

Activation

- CD28-B7: initiation of immune responses
- ICOS-ICOS-L: T cell help in germinal center reactions (antibody responses)

Inhibition

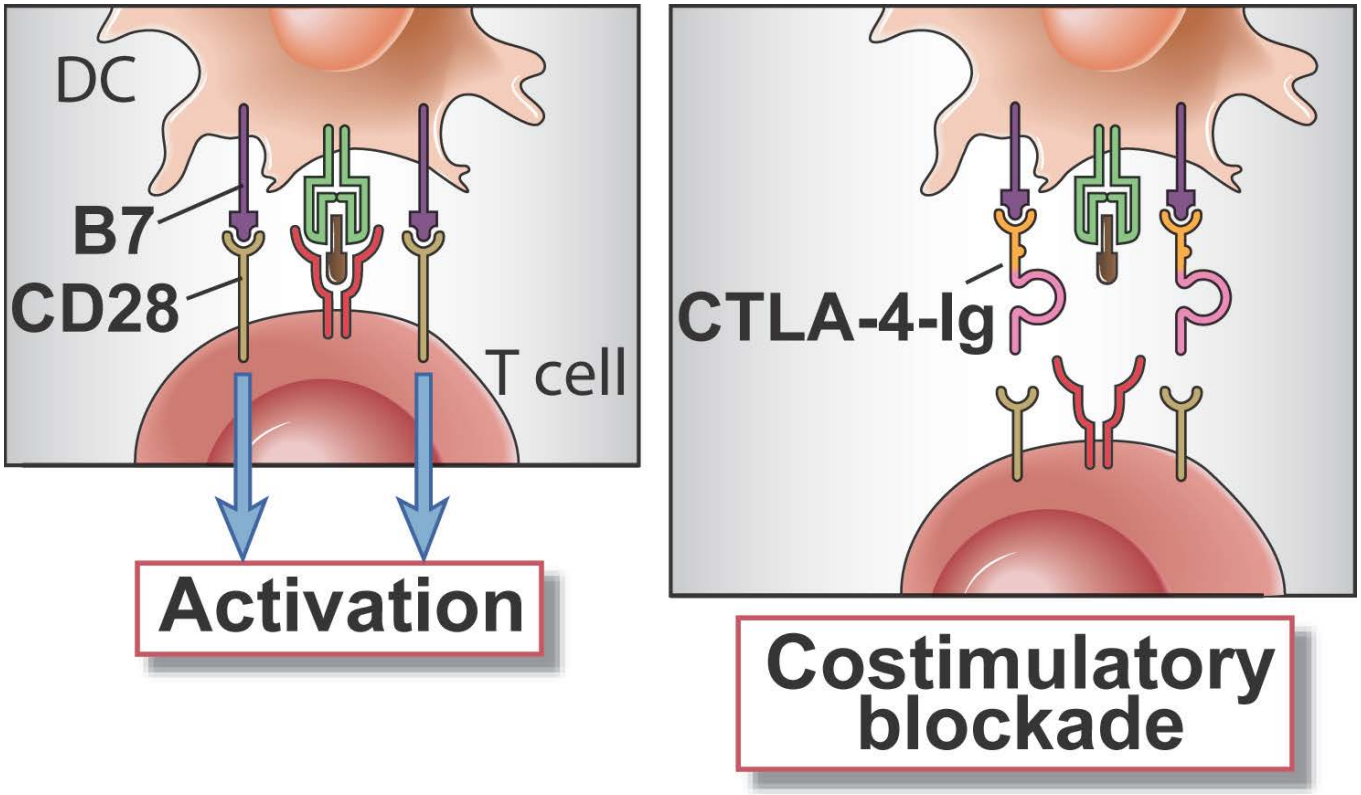
- CTLA-4-B7: inhibits early T cell responses in lymphoid organs
- PD-1:PD-L1,2: inhibits effector T cell responses in peripheral tissues

Complexities and unknowns of B7:CD28 costimulation

- Different T cell populations vary in their dependence on B7:CD28:
  - Naïve > activated > memory
  - CD4 > CD8
  - Regulatory T cells (controllers of immune responses) are also B7-dependent

- Redundancy of B7-1 and B7-2?
- Does B7 signal backwards into APCs?

Therapeutics based on the B7:CD28 family
1. Costimulatory blockade



CTLA-4.Ig inhibits T cell activation in diseases caused by T cell responses

Costimulatory blockade therapy

- B7-antagonist (CTLA-4.Ig, Abatacept) approved for RA, kidney allograft rejection (high-affinity version, Belatacept)

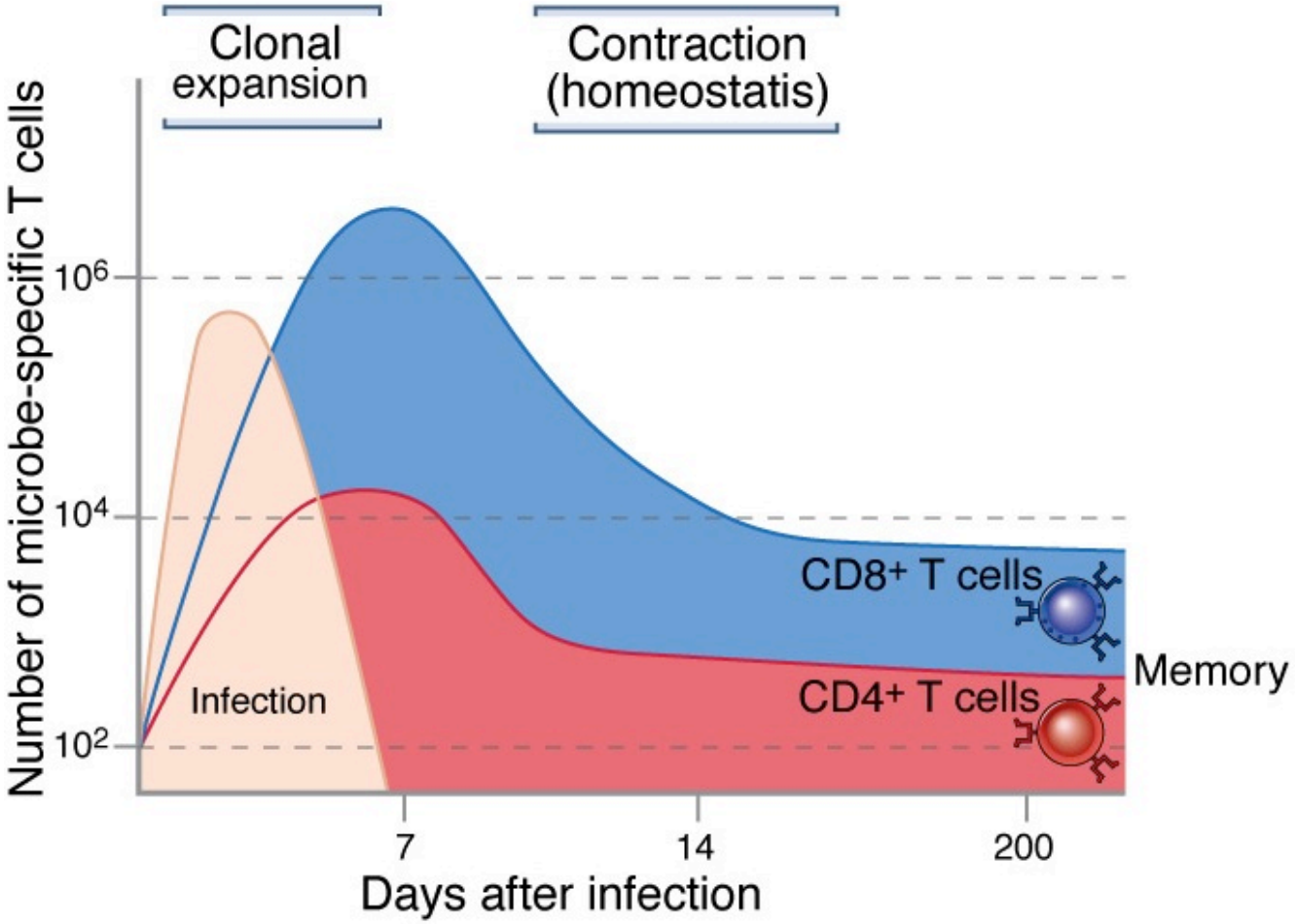
- If memory cells are relatively costimulation-independent, why does this treatment work in established autoimmune diseases?
  - We do not know the relative contribution of long-lived memory cells vs continuous recruitment of naïve cells into the autoimmune reaction?

Costimulators other than B7:CD28

- Many proteins of the TNF-receptor family are expressed on T cells and implicated in T-cell activation and control
  - Functions often demonstrated in complex experimental systems or in vitro
  - Roles in disease (human or animal models) not definitely established

- Possible therapeutic targets?

T cell expansion and contraction (decline)



Many aspects of T cell responses and functions are mediated by cytokines: initial activation -- IL-2; maintenance of memory cells -- IL-7; effector functions -- various

Clonal expansion of T cells

- **Stimulated mainly by autocrine IL-2**
  - Antigen recognition → secretion of IL-2 and expression of high-affinity IL-2 receptors → preferential expansion of antigen-specific cells

- **CD8+ T cells may expand >50,000-fold within a week after an acute viral infection**
  - Up to 10% of all CD8+ T cells in the blood may be specific for a pathogen
  - Minimal expansion of "bystander" cells (not specific for the virus)
  - CD8+ cells expand much more than do CD4+ cells