Antigen Presenting Cells, Antigen Presentation, T Lymphocyte Activation

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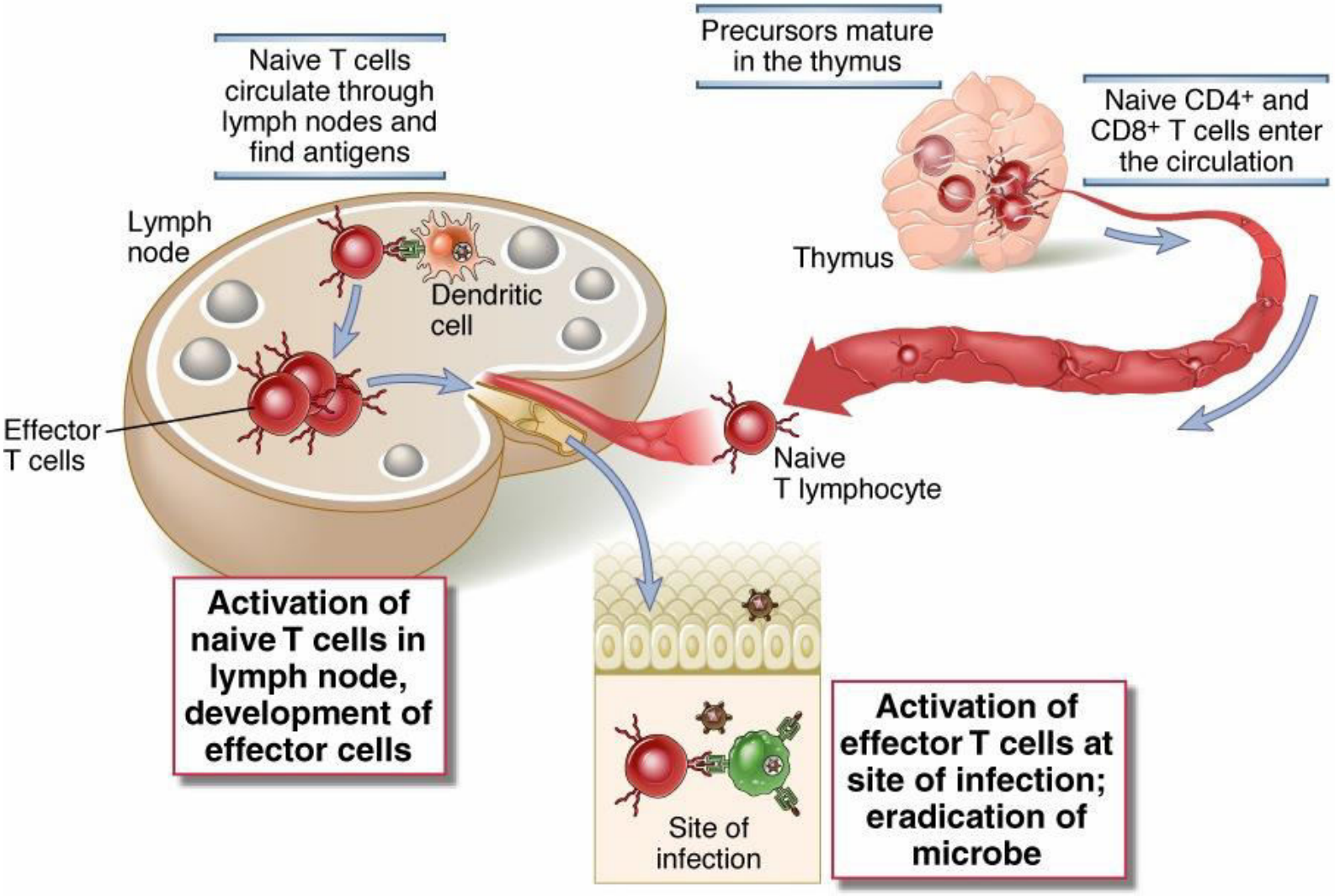
FOCiS

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



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: T and B lymphocytes recognize 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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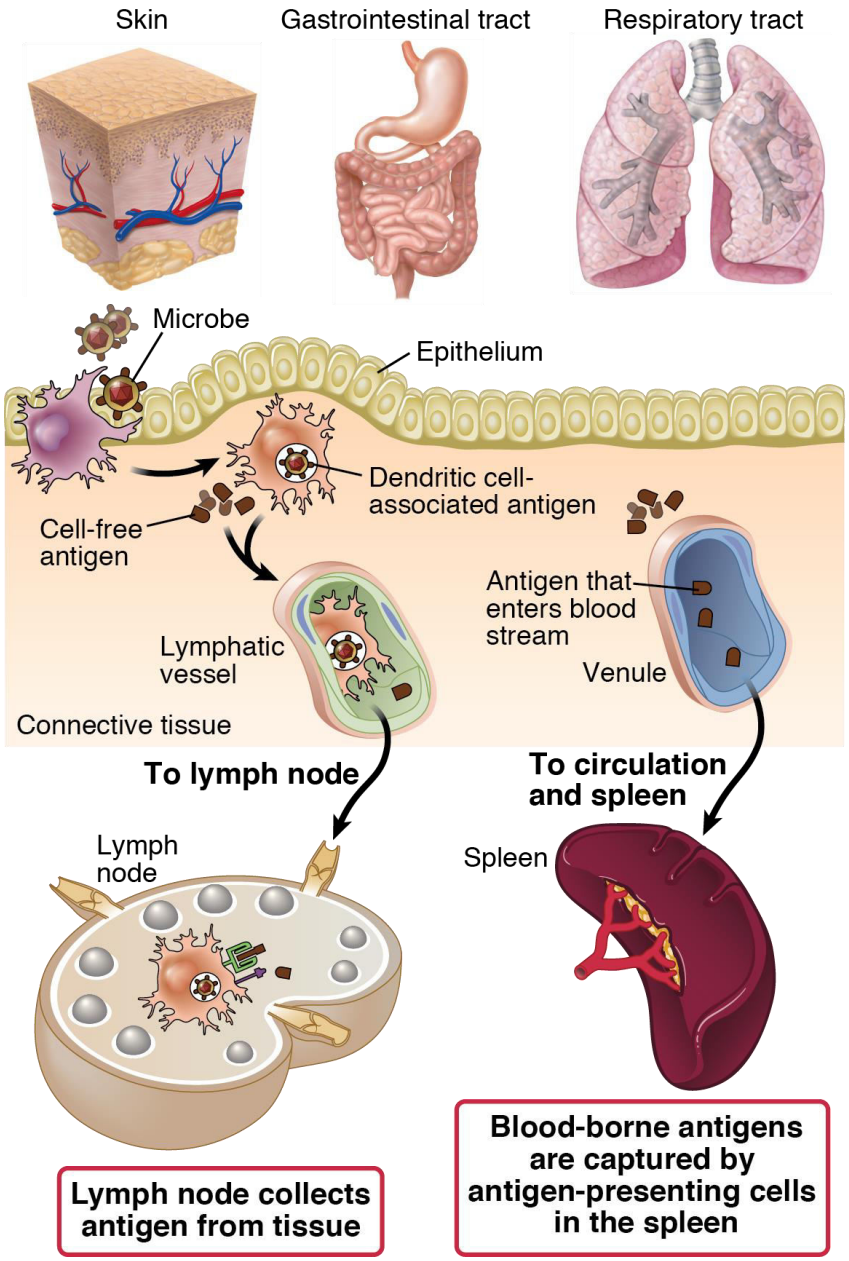
- **Therefore, antigens and lymphocytes have to be brought together**
  - **The function of peripheral (secondary) lymphoid organs**

Capture of antigens

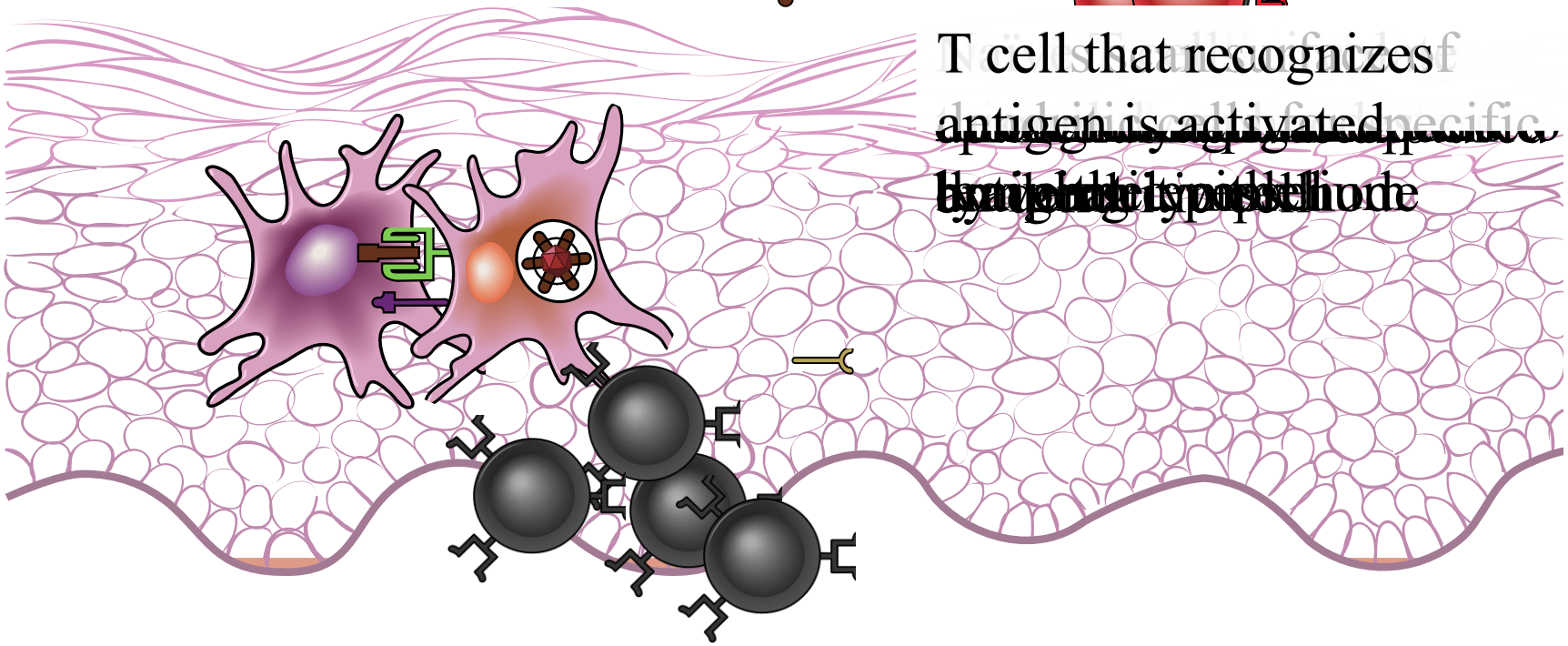
Sites of antigen entry

Sites of initial antigen capture

Sites of antigen collection and capture



Capture and presentation of antigens by dendritic cells



T cell that recognizes antigen is activated

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

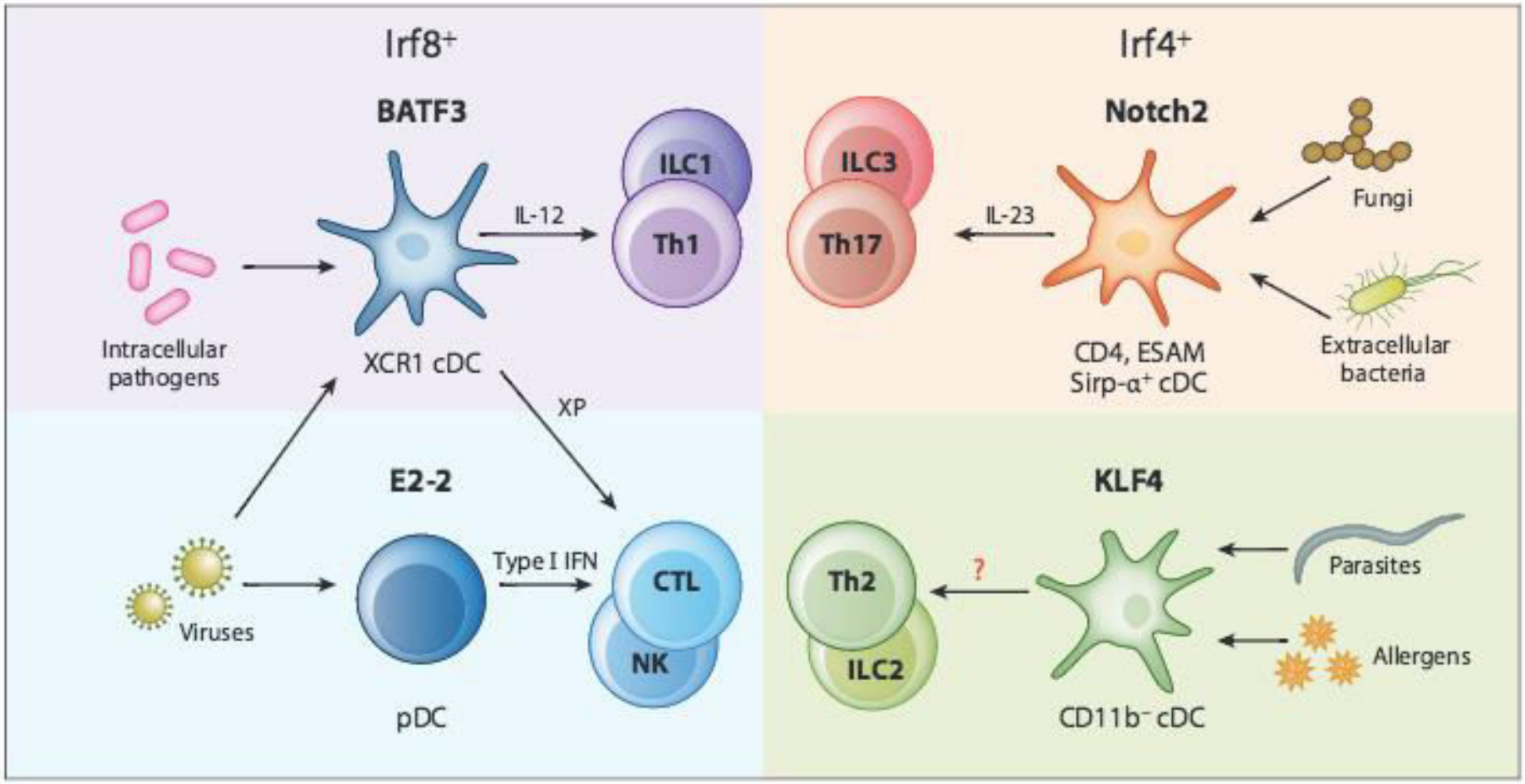
- **Location:** at sites of microbe entry (epithelia), tissues
- **Receptors for capturing and reacting to microbes:** Toll-like receptors, other receptors
- **Migration to T cell zones of lymphoid organs**
  - Role of CCR7
  - Co-localize with naïve T cells
- **Practical application:** dendritic cell-based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

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



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

What do T cells see?

- All functions of T cells are mediated by interactions with other cells
  - CD4+ helper T cells help B cells to make antibodies and "help" macrophages to destroy what they have eaten
  - CD8+ 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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- 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
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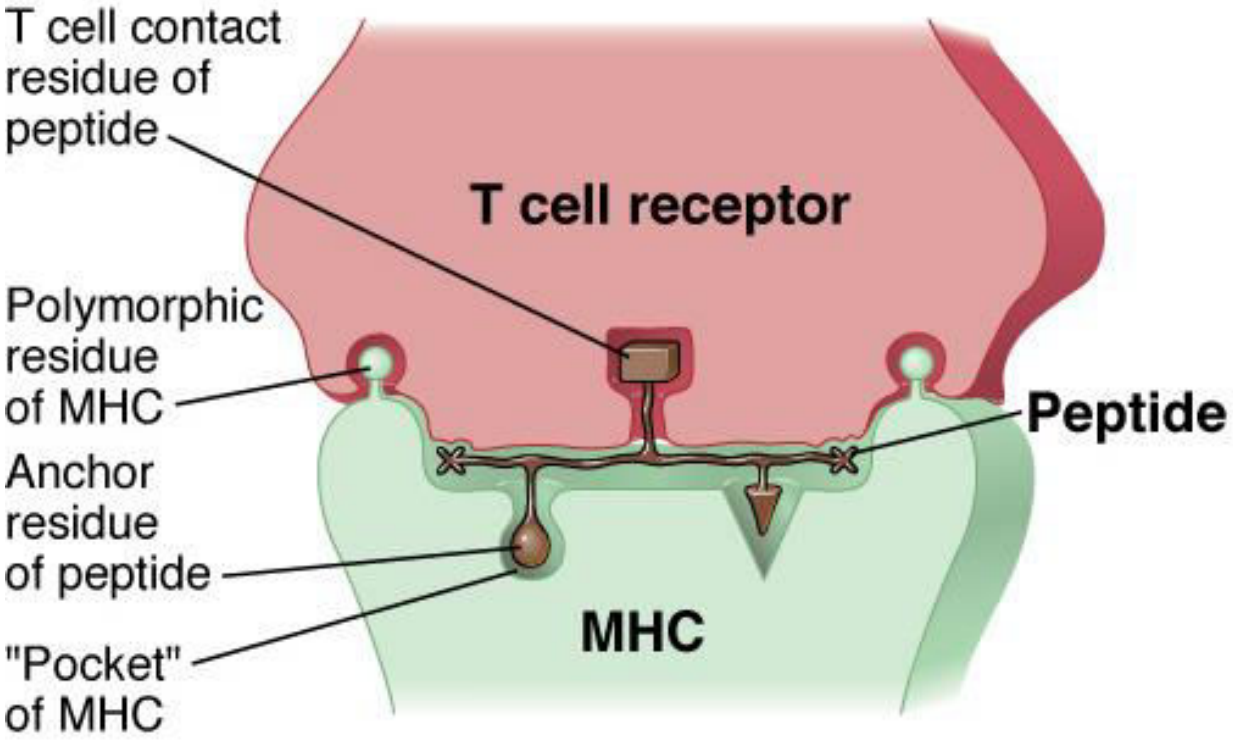
- To ensure cellular communications, T cells see antigens NOT in the circulation but only when displayed by molecules on the surface of other cells
  - These molecules are HLA (generic name: MHC) and the cells displaying the antigen are APCs

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

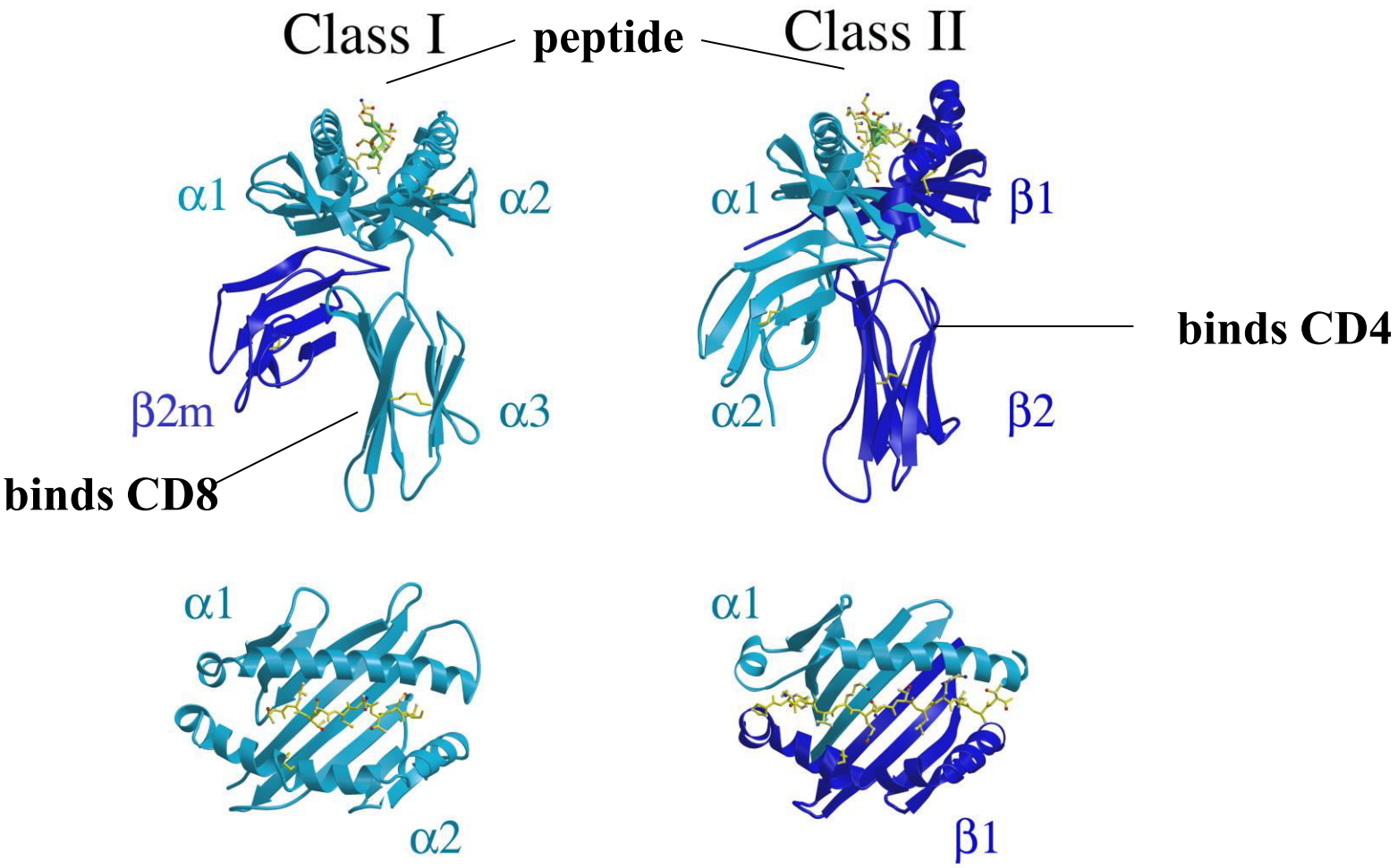


Abbas, Lichtman and Pillai. *Cellular and Molecular Immunology, 7th edition, 2011* © Elsevier

Human MHC = HLA

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

MHC 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.

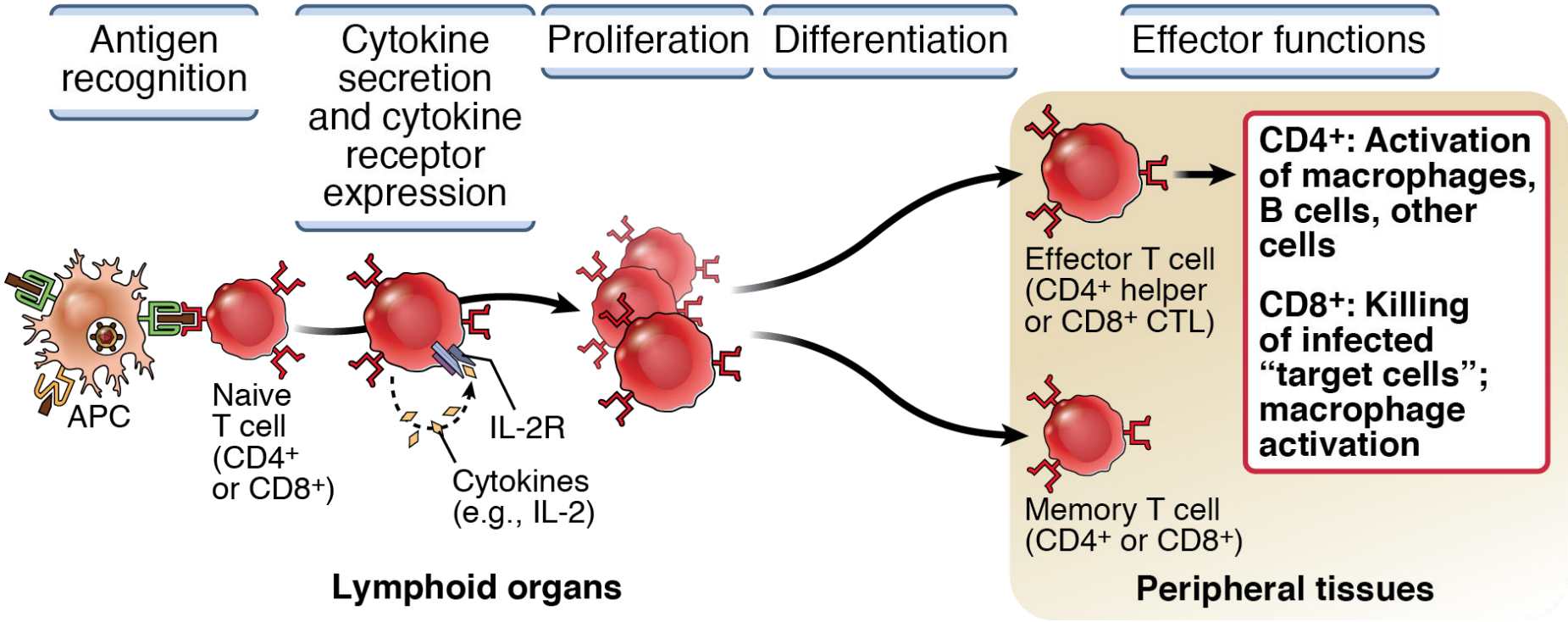
MHC polymorphism

- 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
- MHC polymorphism evolved to ensure recognition of any microbial peptide
- Polymorphism means unrelated individuals express different MHC molecules
  - Every person may recognize slightly different peptides

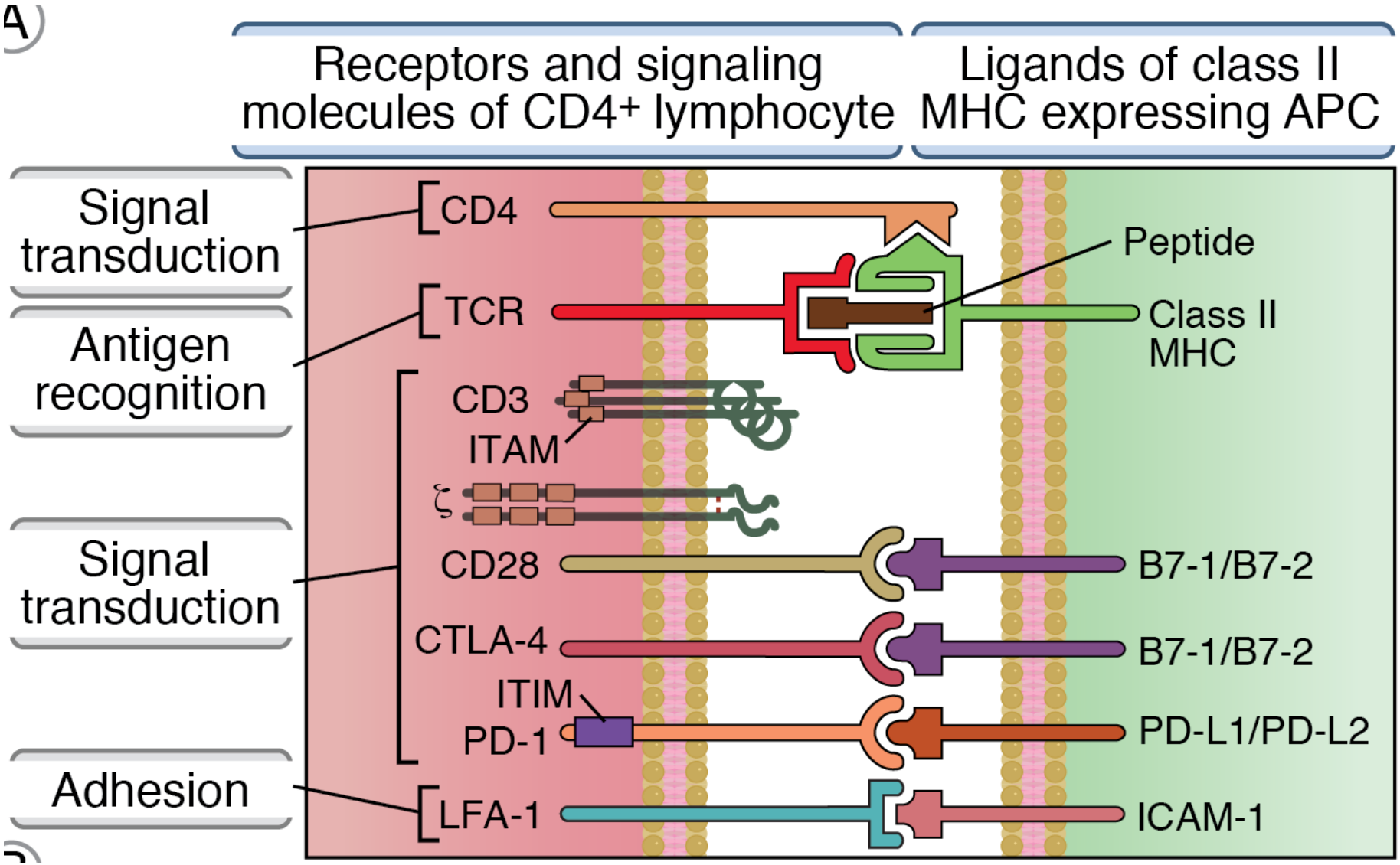
Functions of antigen-presenting cells

- 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

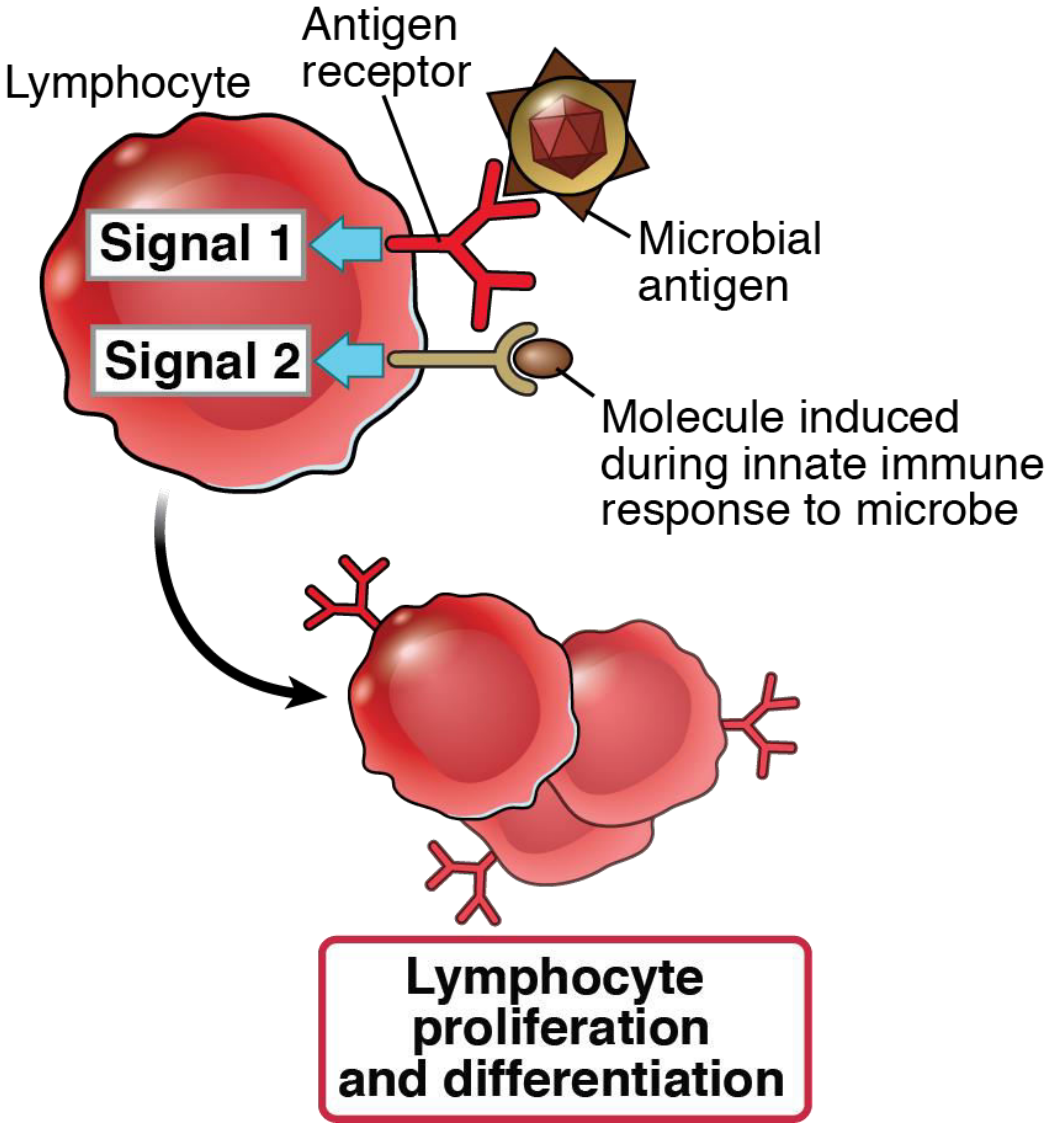
Steps in the activation of T lymphocytes



Molecules involved in T cell activation



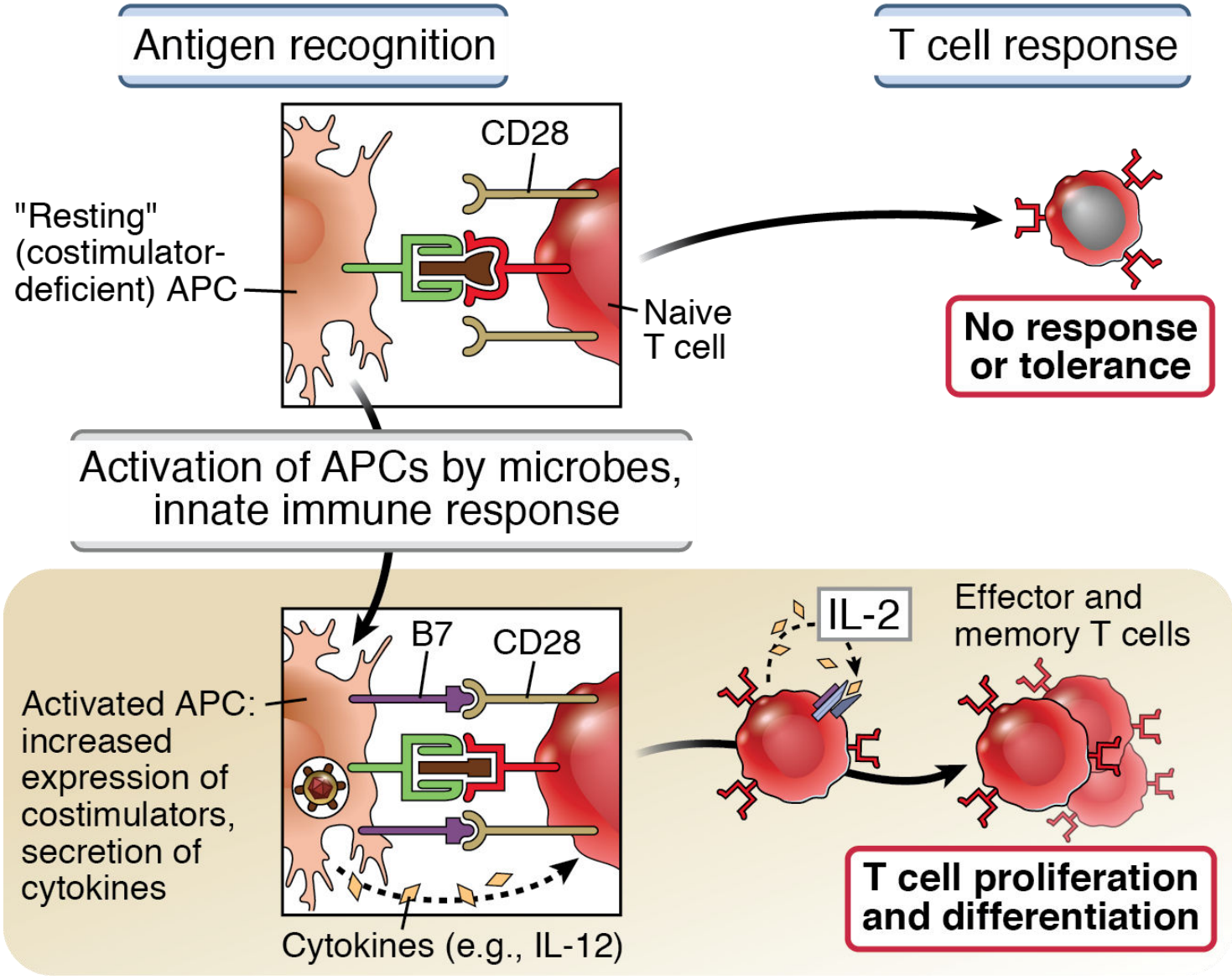
The two-signal requirement for lymphocyte activation



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

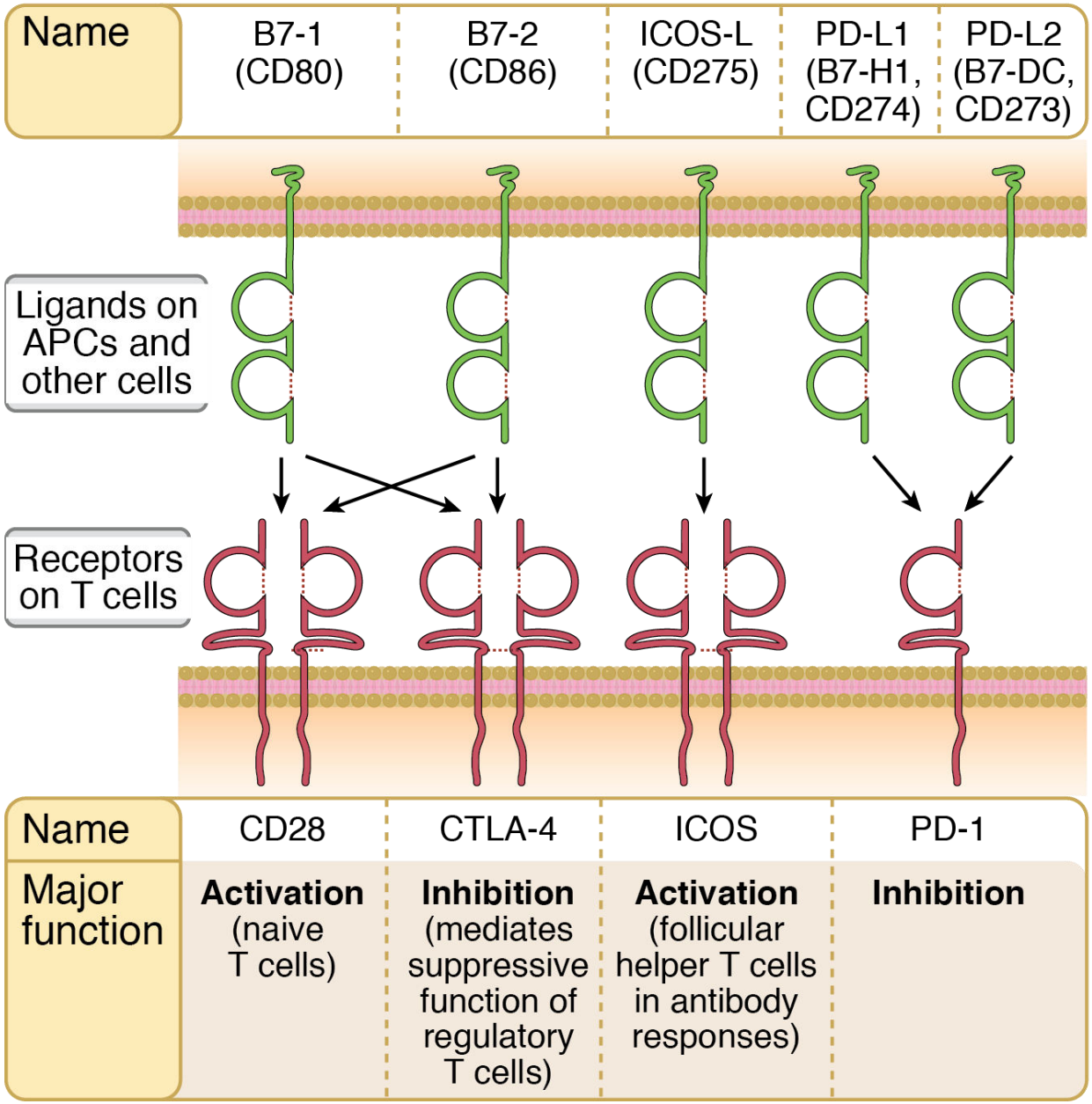
Role of costimulation in T cell activation



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

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

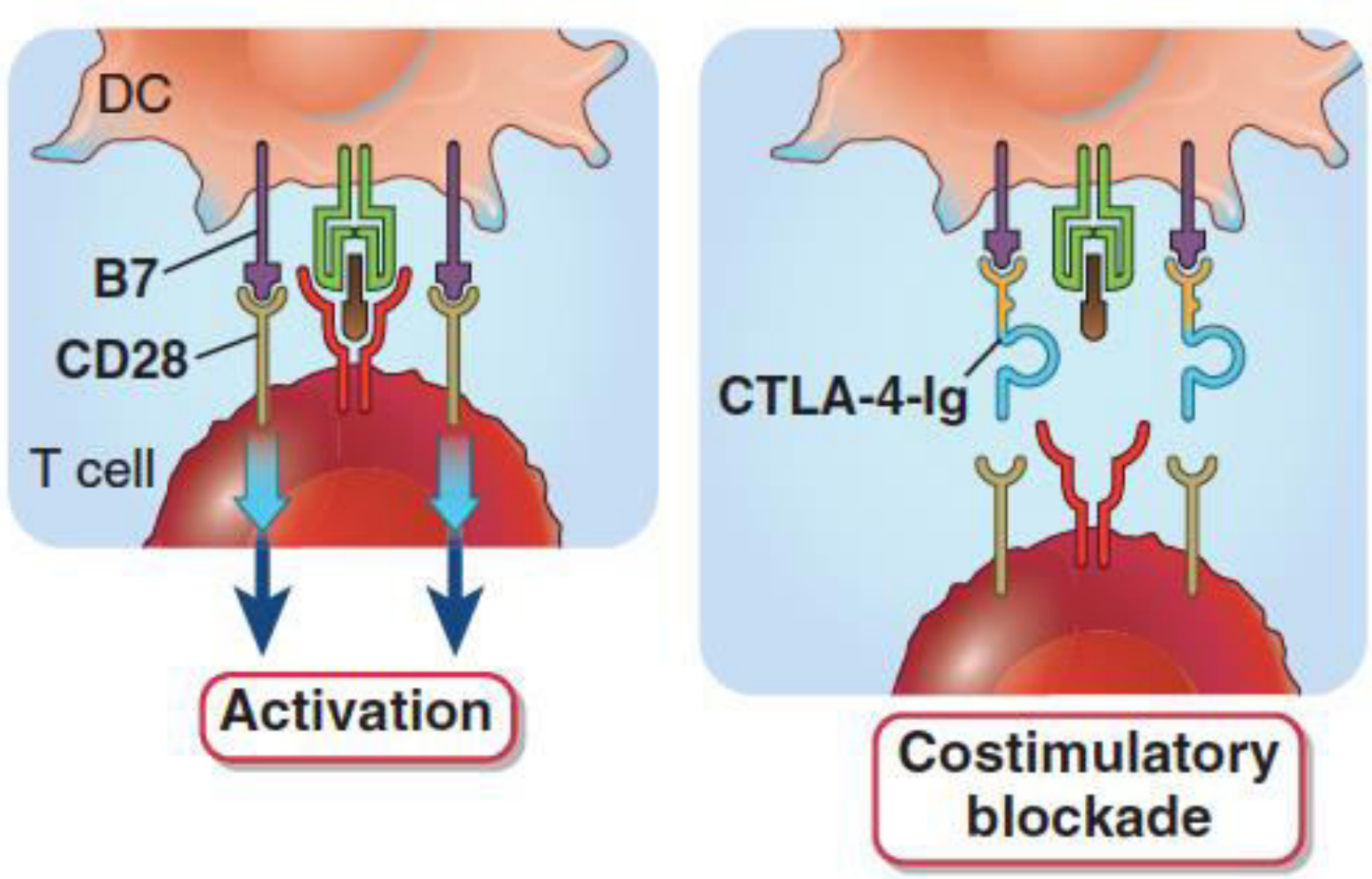
- CTLA-4-B7: inhibits early T cell responses in lymphoid organs
- PD-1:PD-L1,2: inhibits effector T cell responses in peripheral tissues

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?

Costimulatory blockade



CTLA4-Ig (abatacept/belatacept) is approved for rheumatoid arthritis, graft rejection

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 activating and inhibitory receptors