

Dendritic Cells, Antigen Presentation, T Lymphocyte Activation

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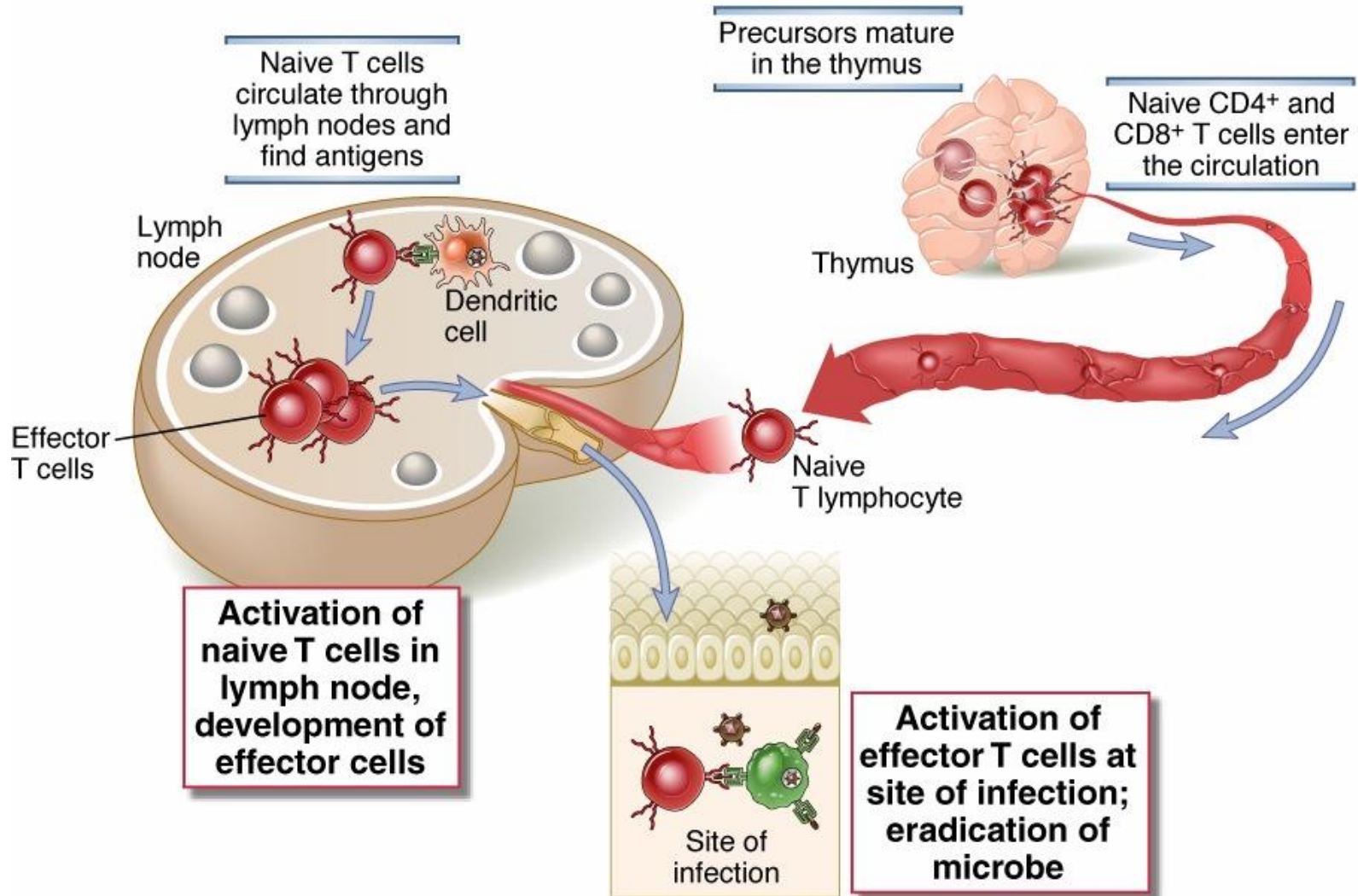
FOCiS



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

The challenge of finding antigens

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 - Specificity and diversity of antigen receptors: the immune system recognizes and distinguishes between 10^6 - 10^9 antigens
- **These few lymphocytes must be able to locate microbes that enter and reside anywhere in the body**
 - 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

The challenge of finding antigens

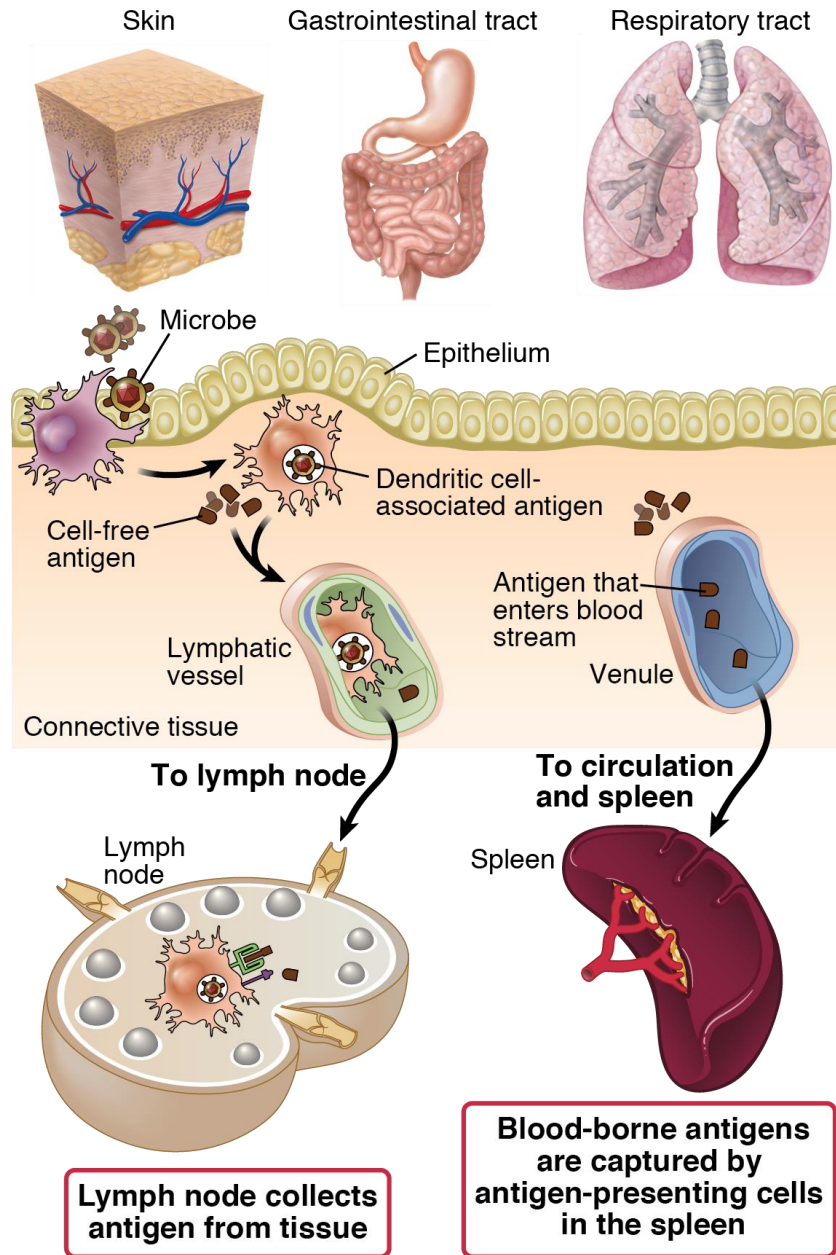
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 - The small number of lymphocytes specific for each antigen cannot patrol all epithelia (routes of microbe entry) or tissues where the antigen may be present
- **Therefore, antigens and lymphocytes have to be brought together**
 - **The function of peripheral (secondary) lymphoid organs**

Capture of antigens

Sites of antigen entry

Sites of initial antigen capture

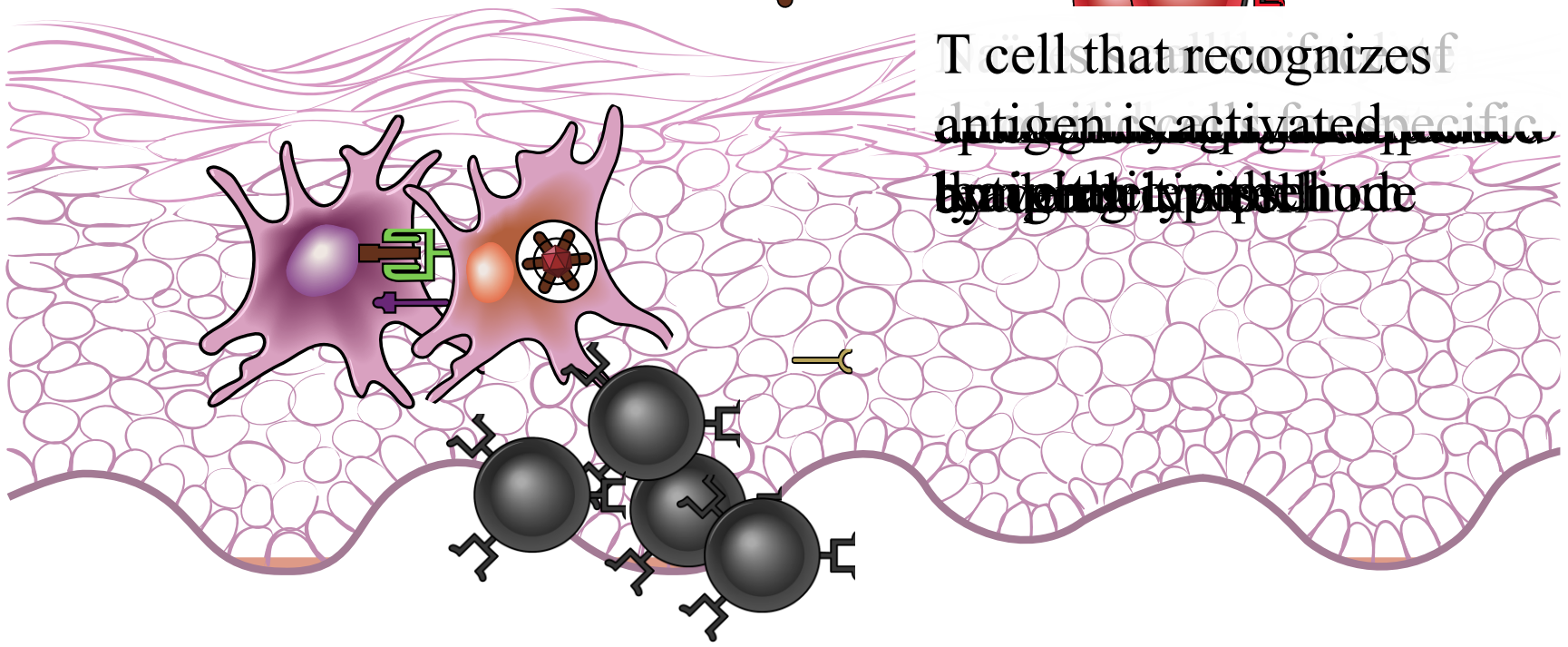
Sites of antigen collection and capture



Lymph node collects antigen from tissue

Blood-borne antigens are captured by antigen-presenting cells in the spleen

Capture and presentation of antigens by dendritic cells



T cell that recognizes antigen is activated by dendritic cell

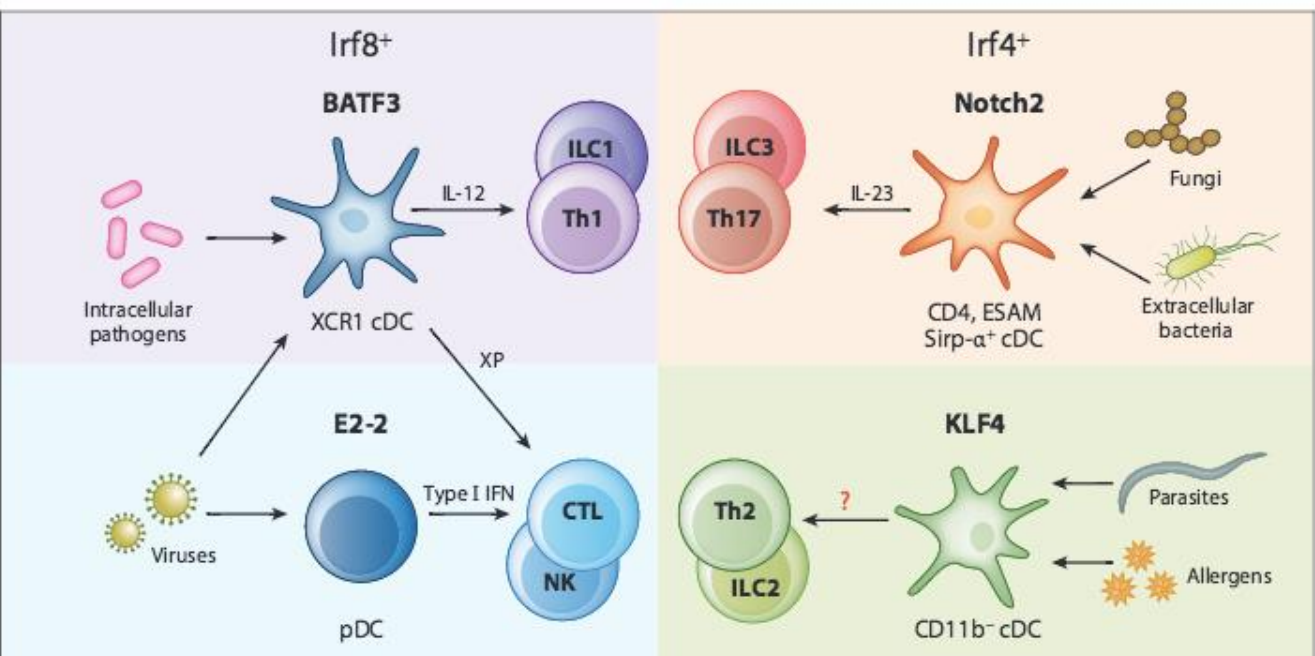
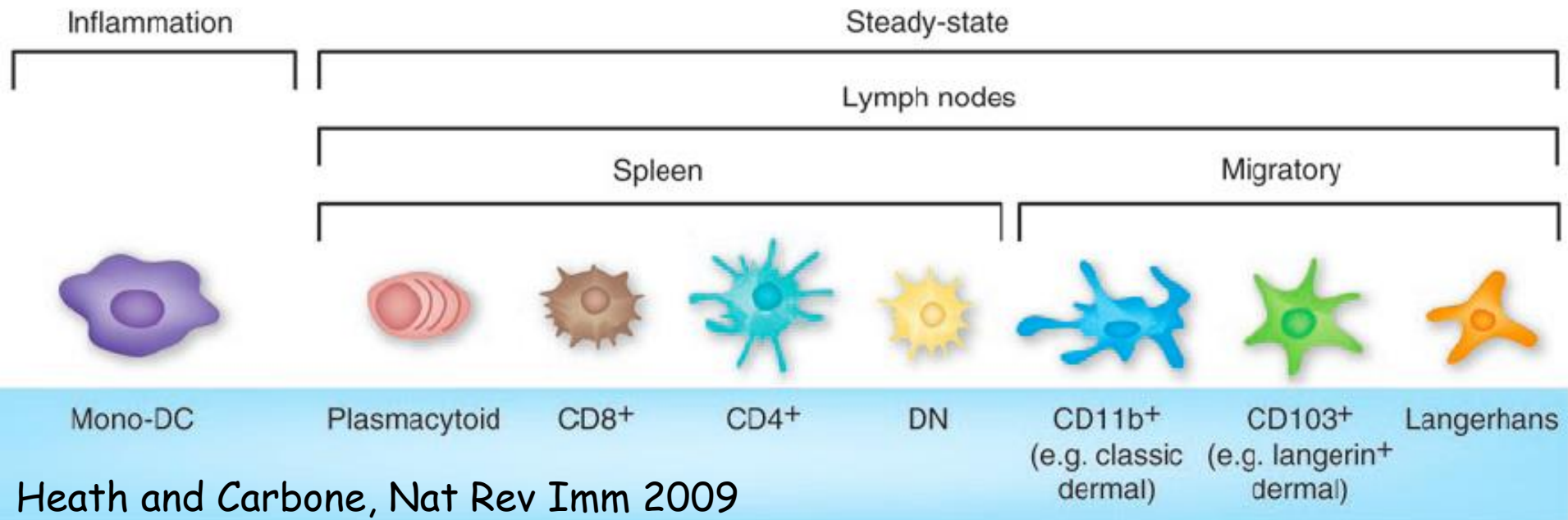
Why are dendritic cells the most efficient APCs for initiating immune responses?

- **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
- Many subsets have been described; significance unclear

Dendritic cell subsets



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

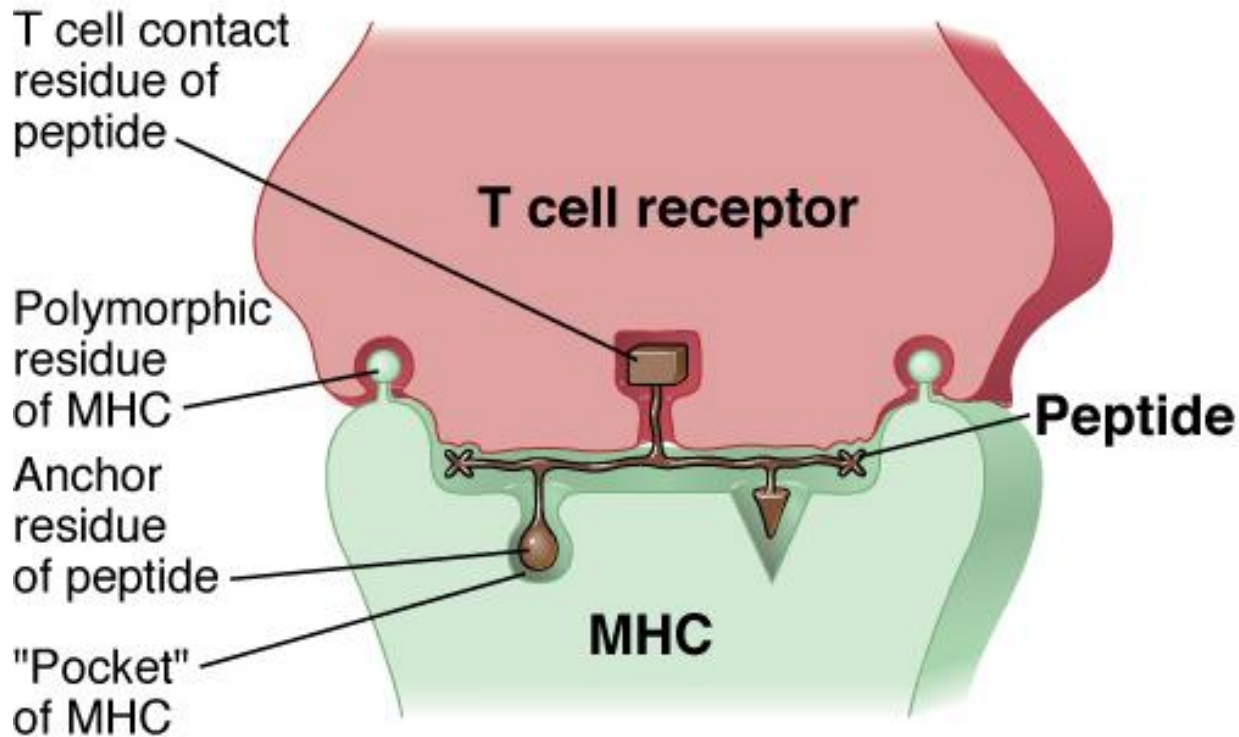
What do T cells see?

- 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?

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
- 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

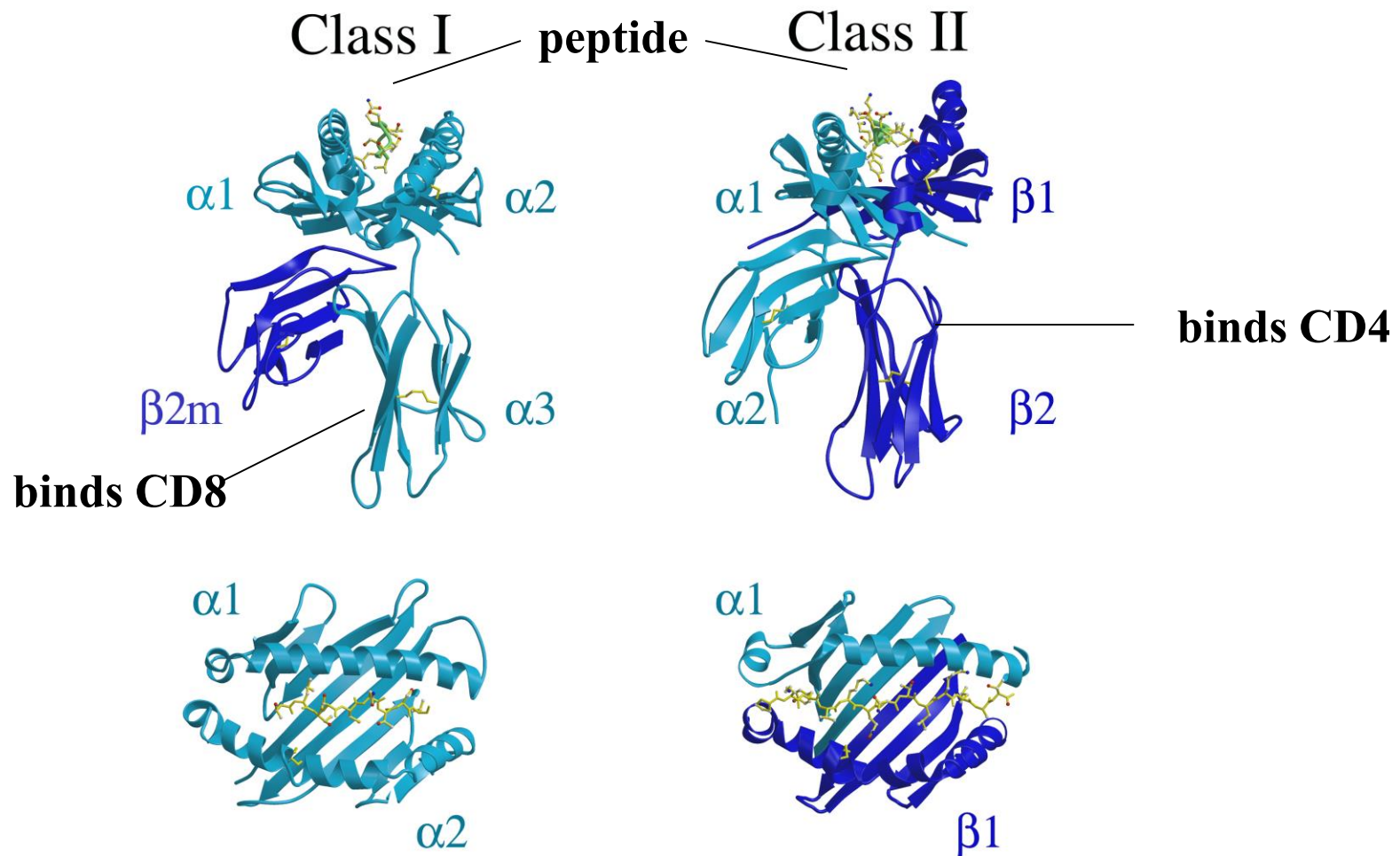
A model of T cell recognition of peptide displayed by an MHC molecule



Human MHC = HLA

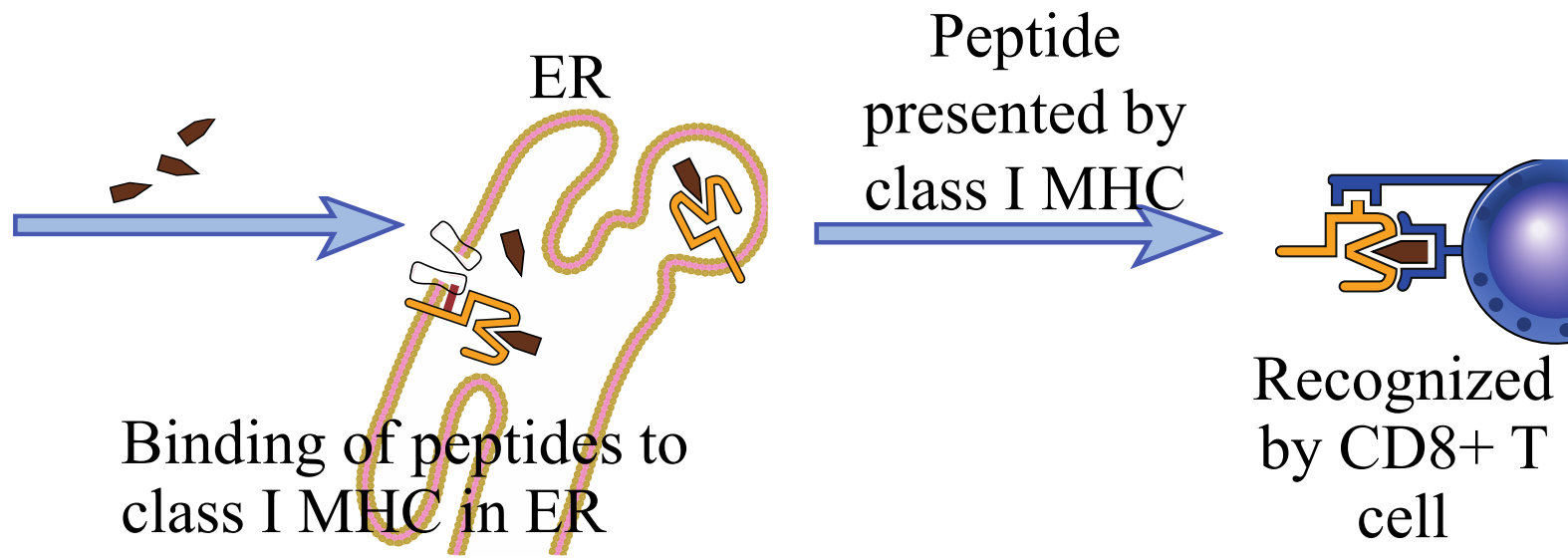
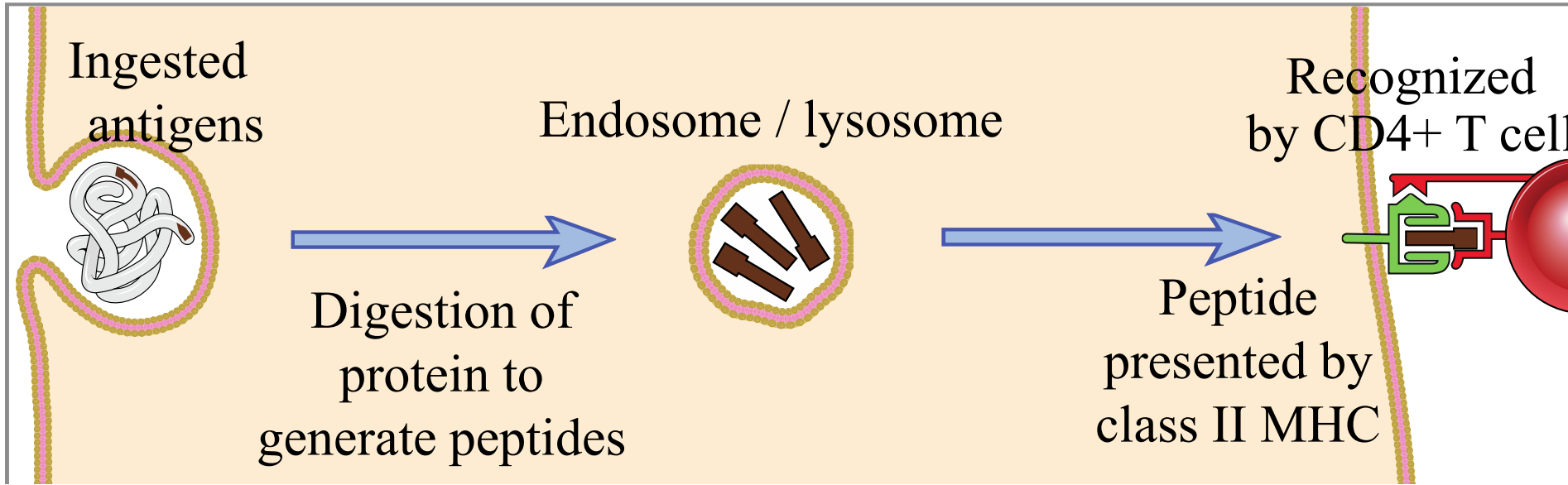
Because MHC molecules are on cells and can display only peptides, T lymphocytes can recognize only cell-associated protein antigens

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.

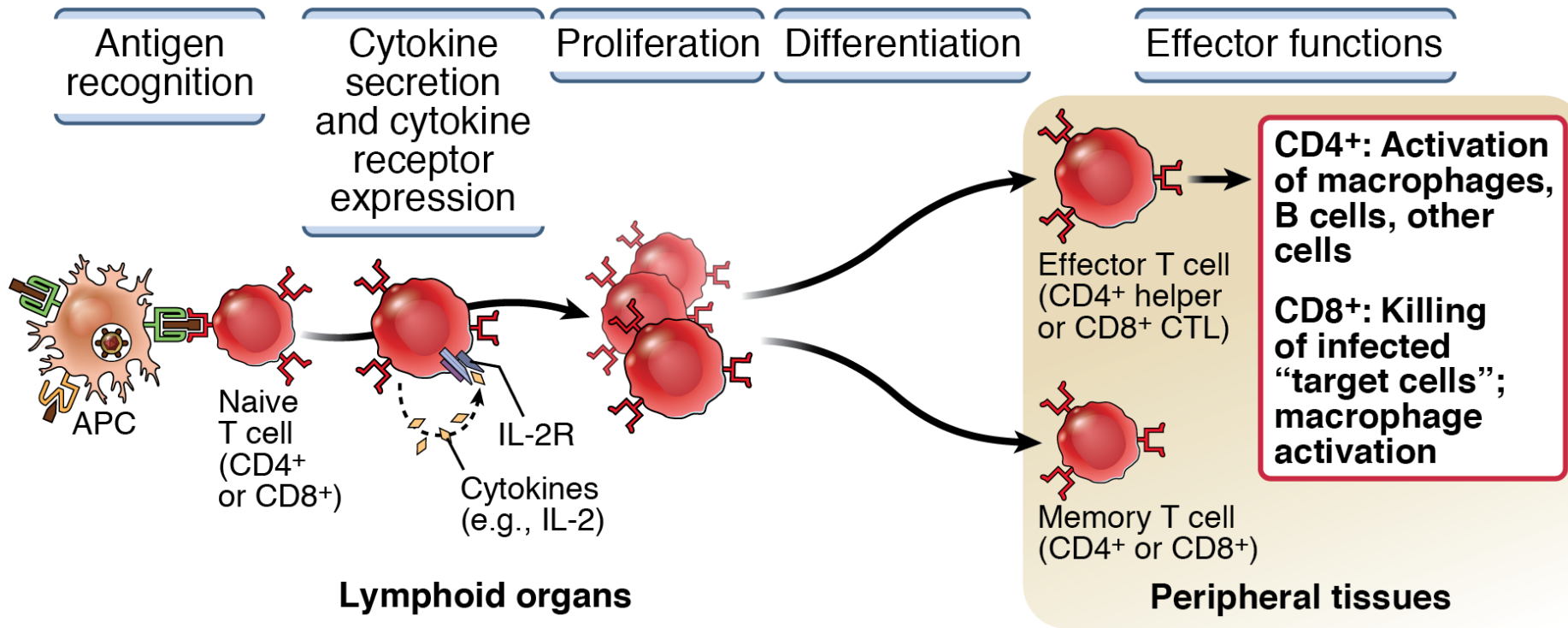
Pathways of antigen processing



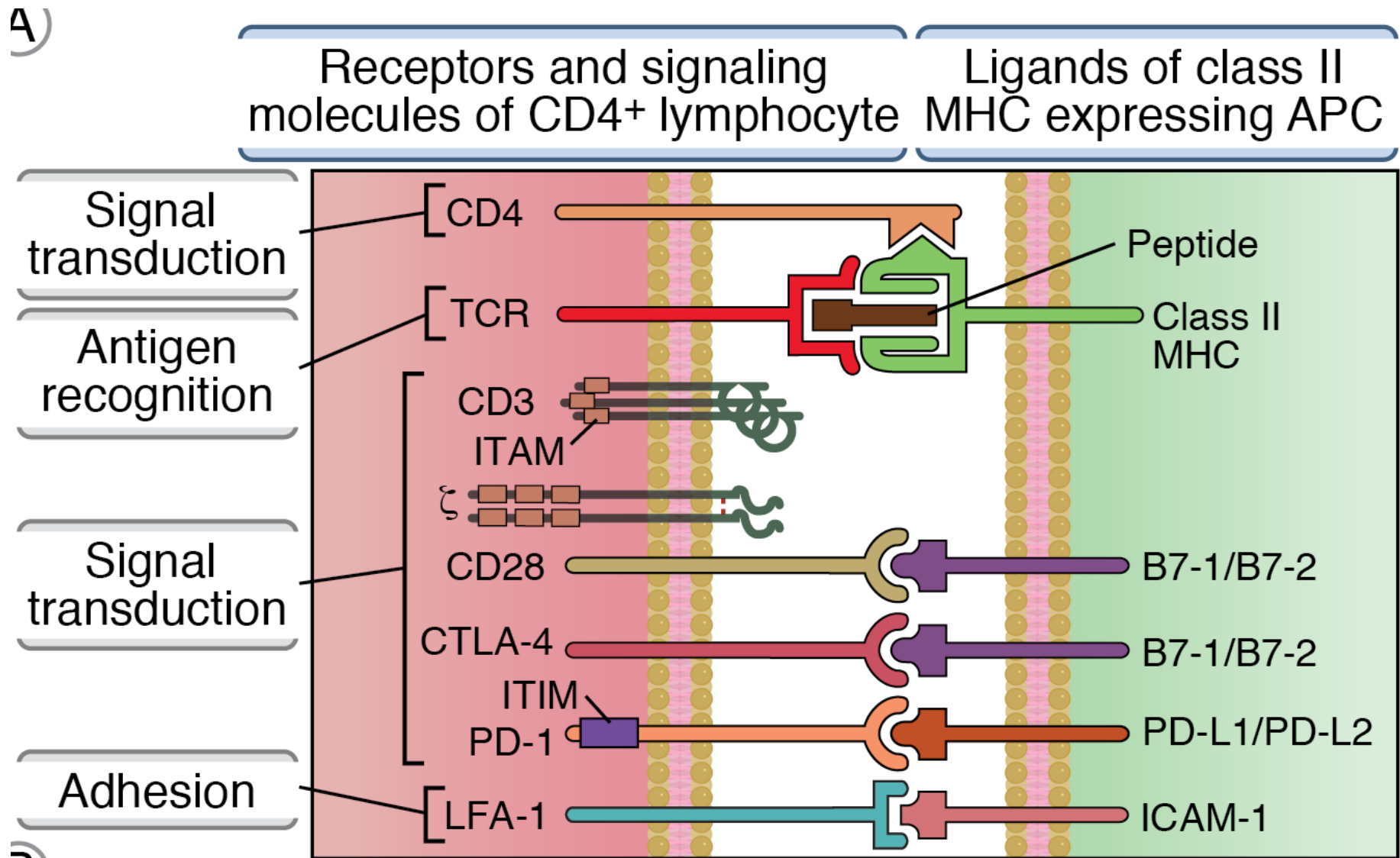
Functions of antigen-presenting cells

- 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

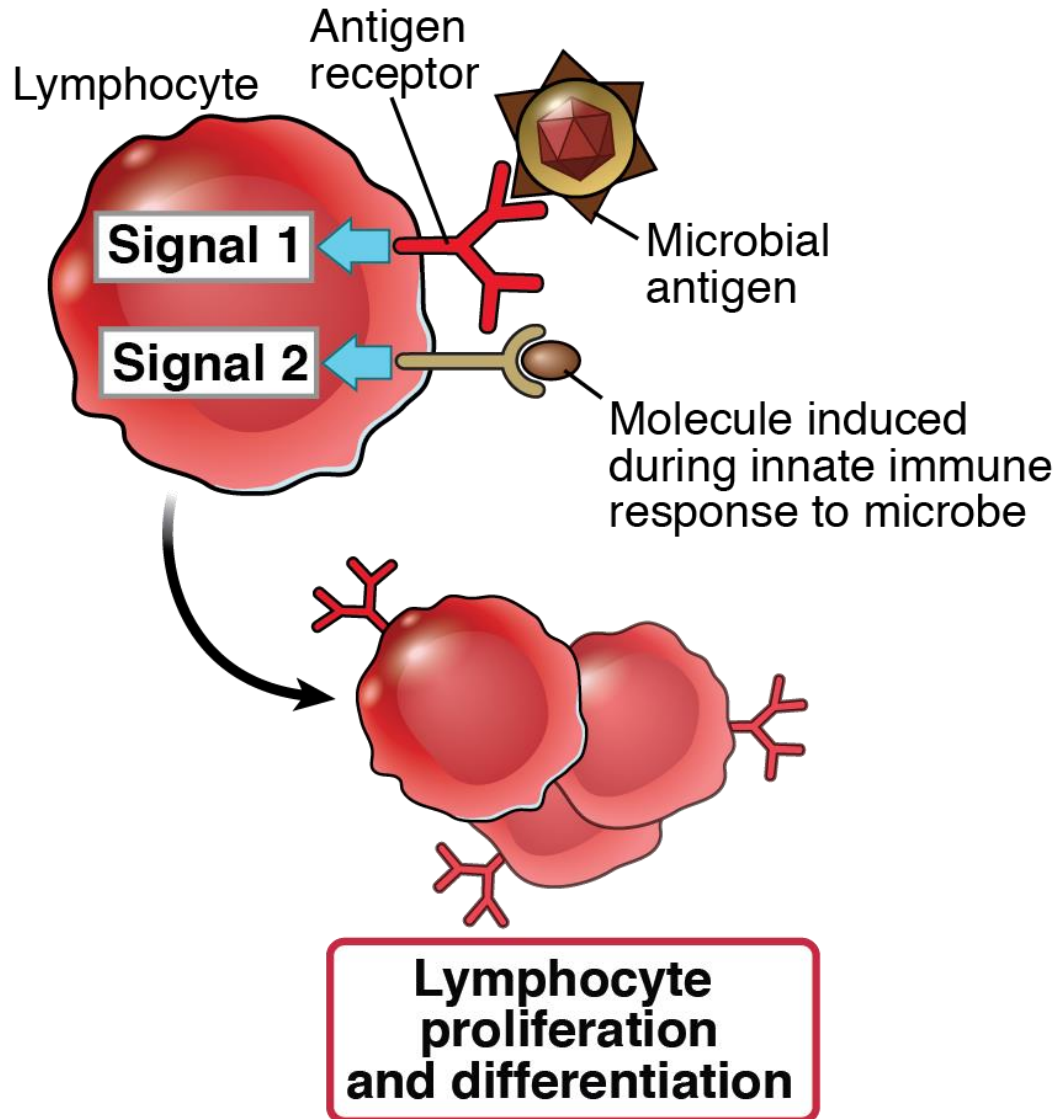
Steps in the activation of T lymphocytes



Molecules involved in T cell activation



The two-signal requirement for lymphocyte activation



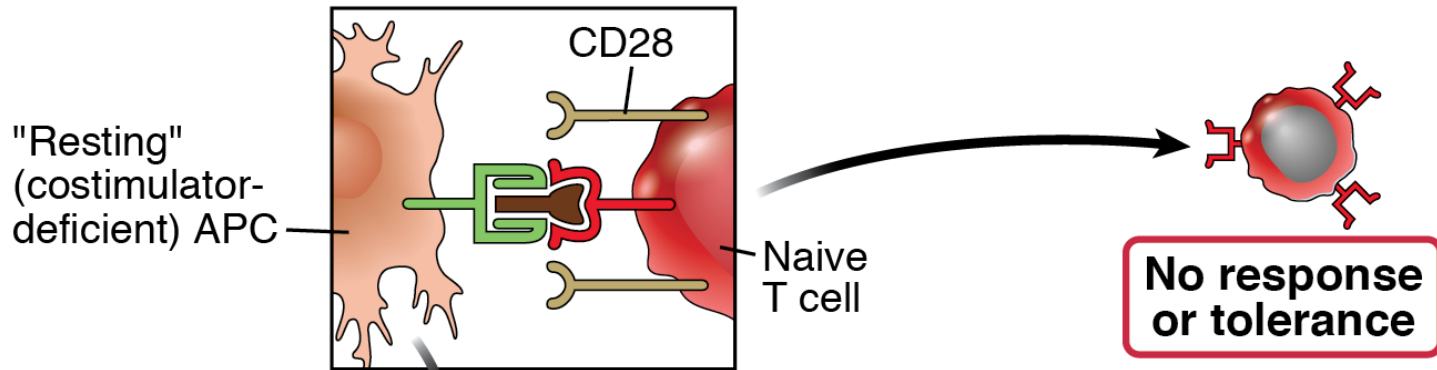
Second signals for T cells: "costimulators" induced on APCs by microbial products, during early innate response

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

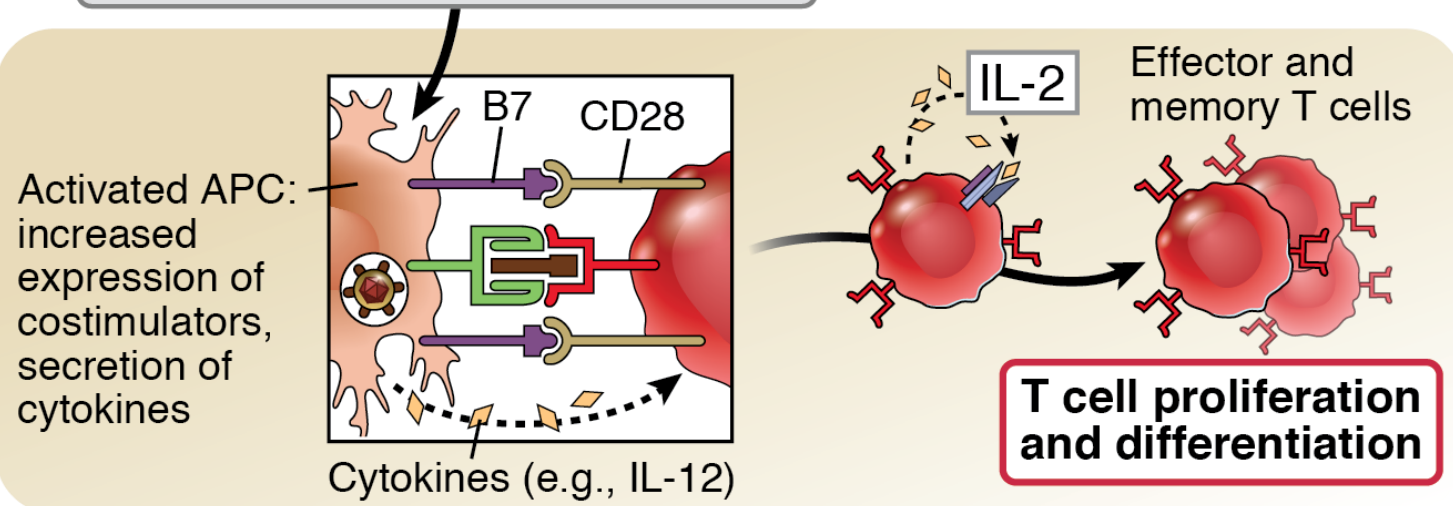
Role of costimulation in T cell activation

Antigen recognition

T cell response



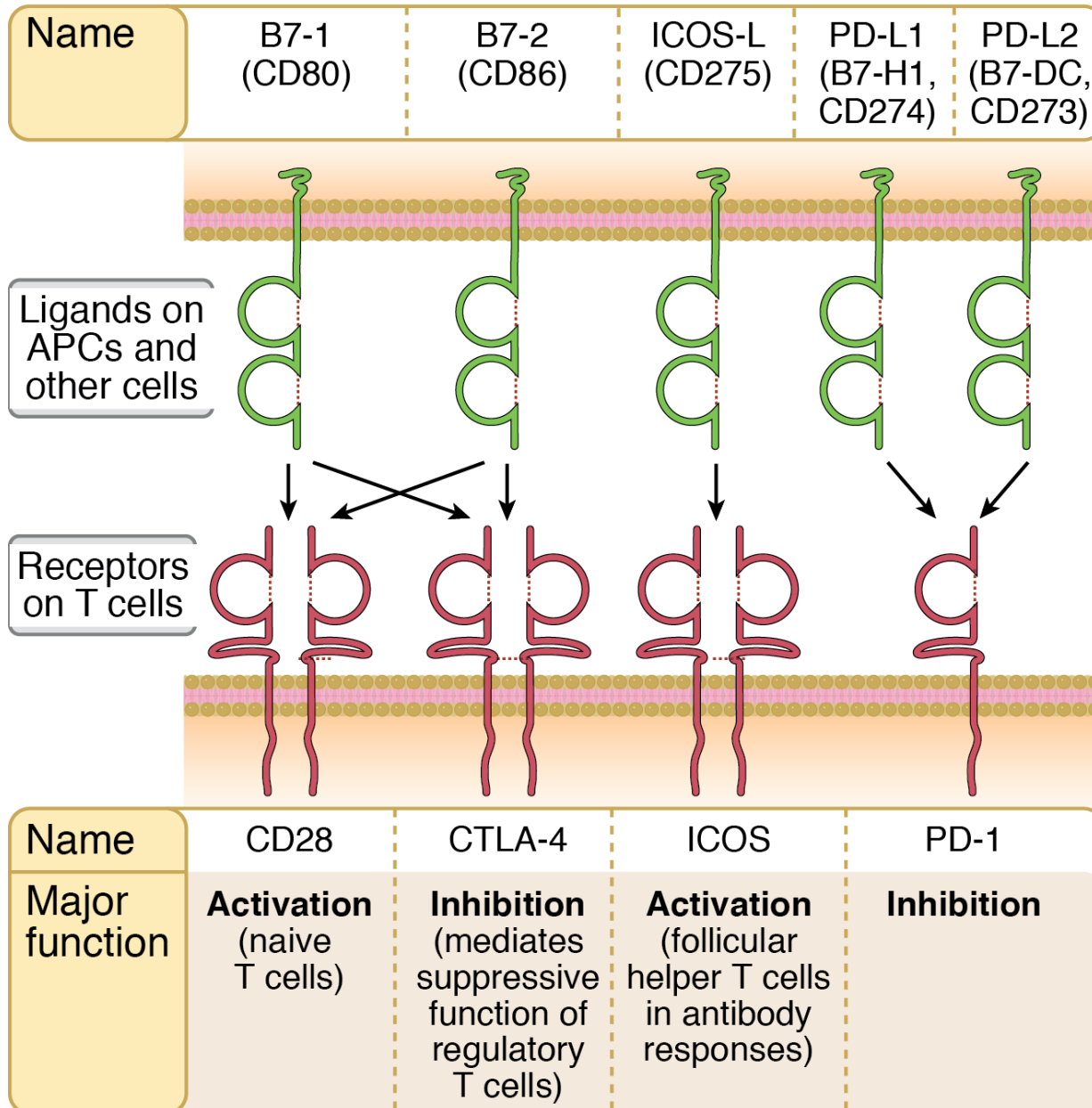
Activation of APCs by microbes, innate immune response



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
- 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

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

Inhibitory receptors

Activating receptors
(costimulators)

