Basic Immunology

Lecture 7^{th} - 8^{th}

Communication between cellular components of the immune system

Co-receptors and adhesion molecules.
Cytokines, chemokines and their receptors.
Microvesicles.

Mediators of cell-cell interactions

Cell-cell interactions play basic biological role in development and function of multicellular organisms. These interactions allow cells to communicate with each other. This ability to send and receive signals is essential for the further functions of the cells.

- **Direct interactions:** adhesion molecules
- **Microparticles:** microvesicles, microtubes
- **Soluble mediators perform indirect interactions:** cytokines, chemokines, interleukins, interferons, growth factors, tissue hormones, complement factors, etc.

Main fields of immunological „cross-talk”

-Haematopoiesis: adhesion between stromal cells of the bone marrow and the differentiating leukocytes

-Lymphocyte recirculation and recruitment: adhesion between endothelial cells and the circulating leukocytes, recruiting immune active cells into the inflammatory tissues

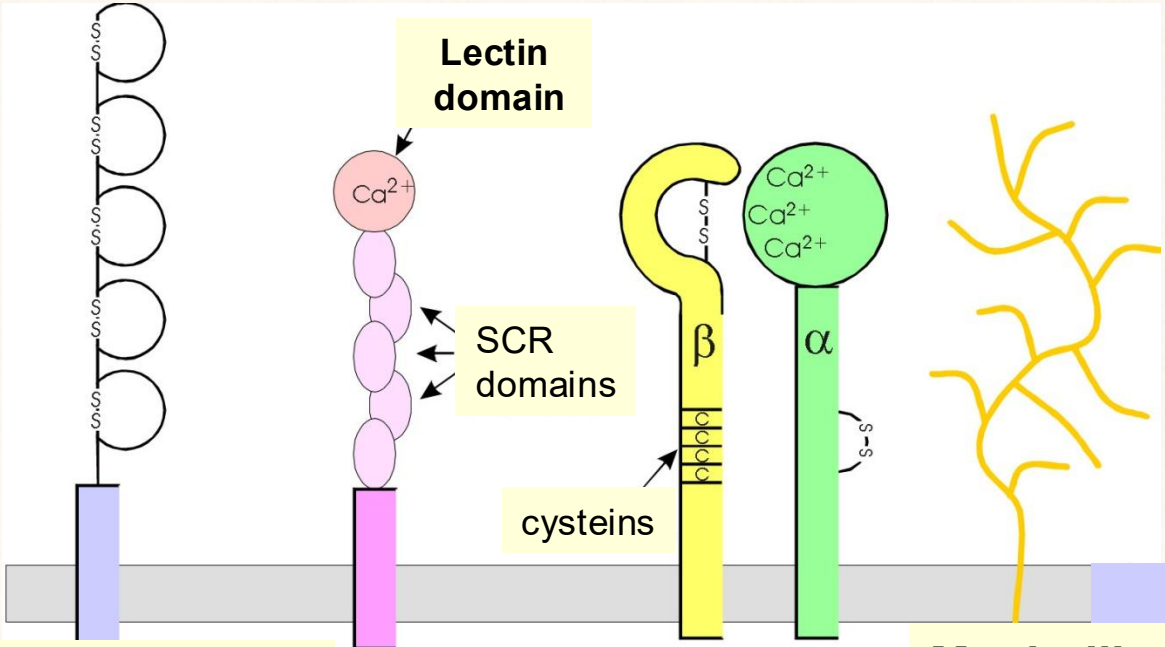
-Immune response: T cell and APC/B cell interactions during antigen presentation, activation and differentiation of immune cells, cytotoxic effector reactions

Adhesion molecules

Cell surface molecules whose function is to promote adhesive interactions with other cells or the extracellular matrix and initiate signal transduction.

Leukocytes express various types of adhesion molecules, such as **selectins, integrins**, and members of the **Ig superfamily**, and these molecules play crucial role in cell migration and cellular activation both in innate and adaptive immune response.

Families of adhesion molecules

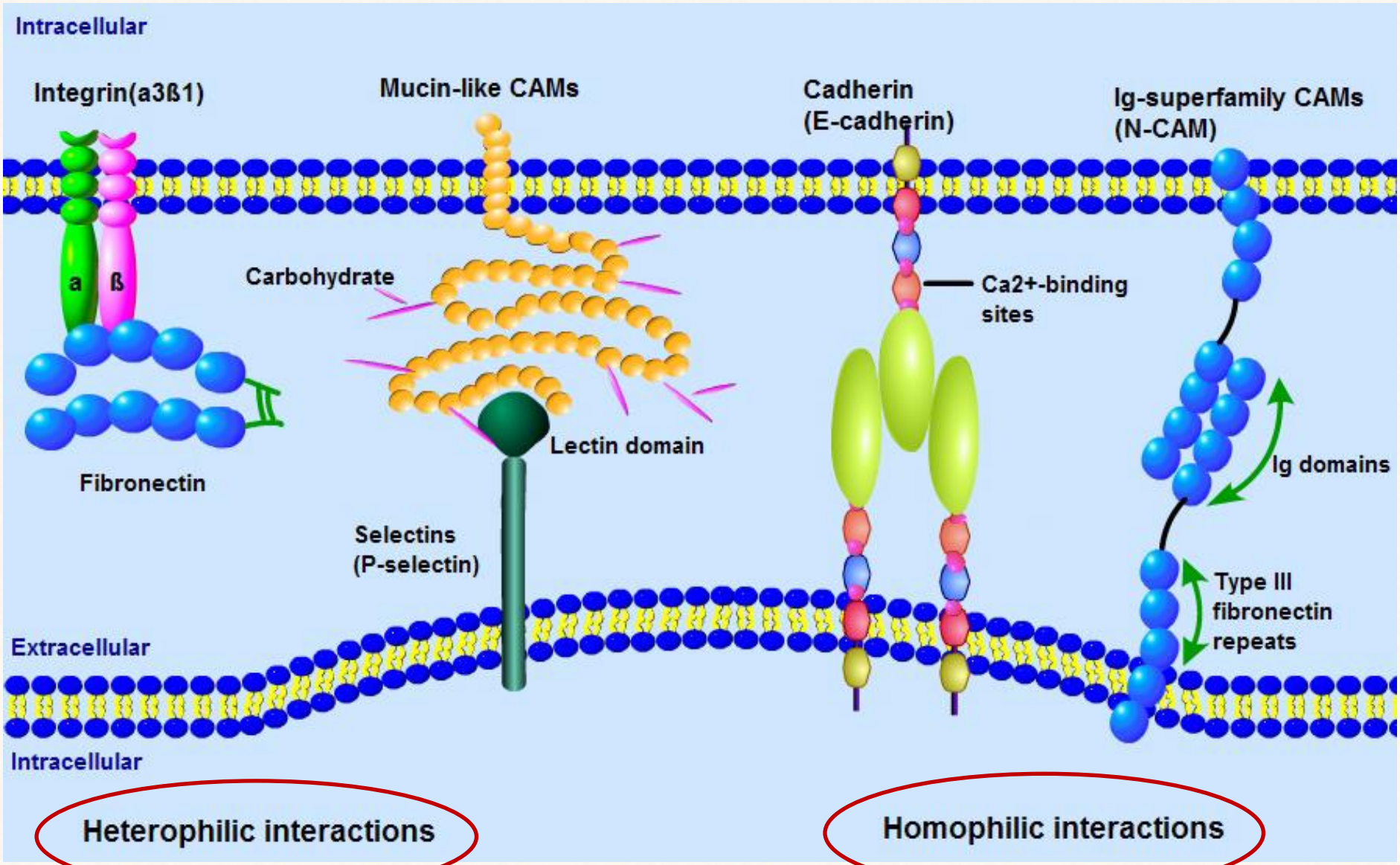


„other" accessory molecules

Ig-superfamily members	Selectins	Integrins	Mucin-like molecules
CD2	L selectin	VLA	„vascular addressins"
CD4	E selectin	LFA	
CD8	P selectin	Mac1	
B7			
CD28			
CTLA 4			
ICAM			

CD45
CD44
CD40, CD40L
CD19/CD21/CD81
CD22

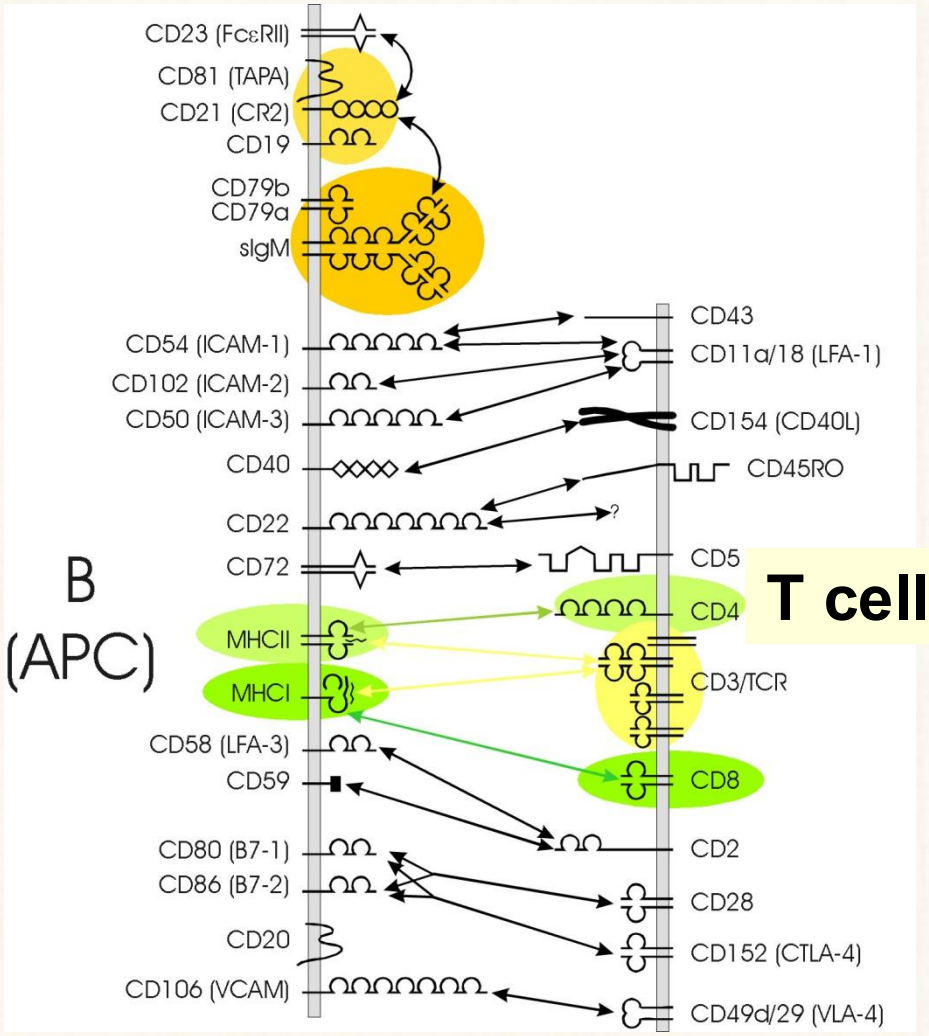
Types of cell adhesion molecules



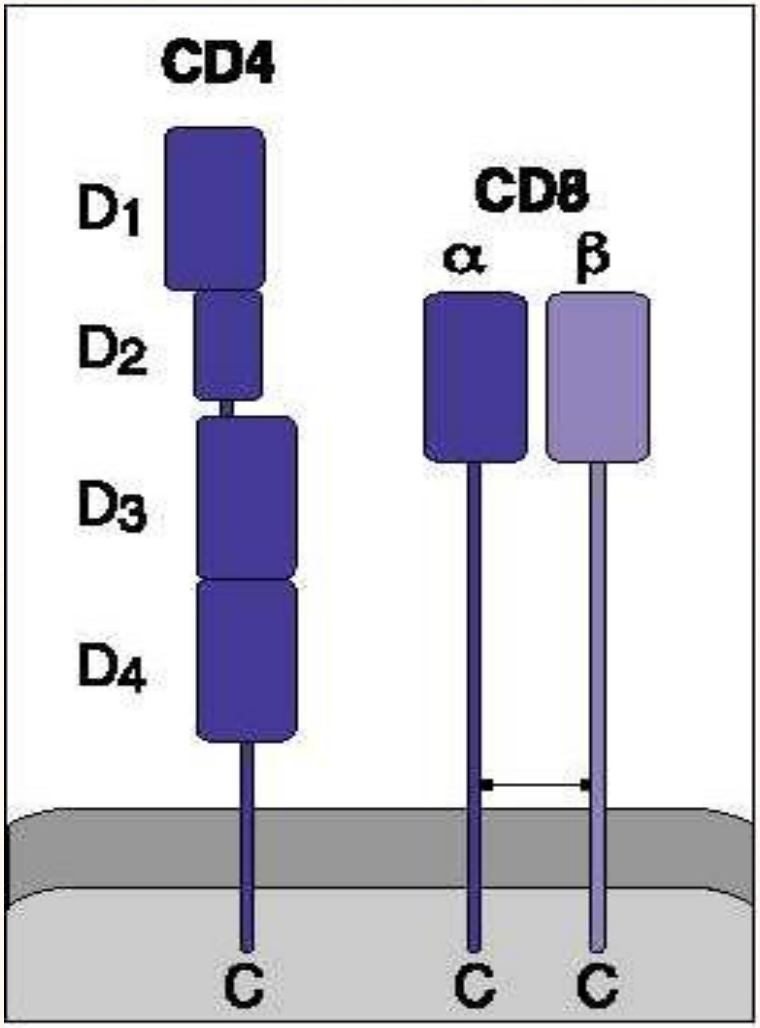
Family of accessory molecules, adhesion molecules, co-receptors

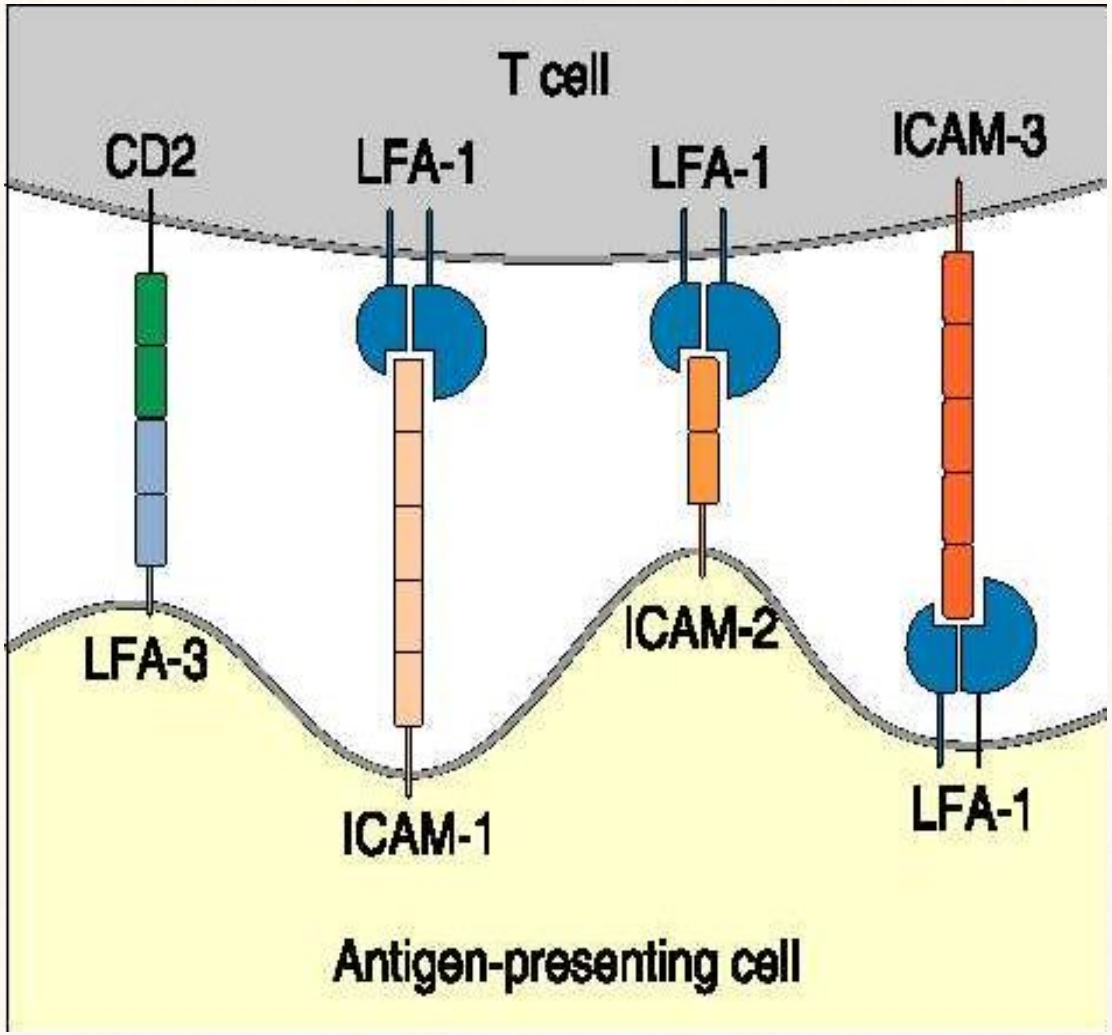
Common characteristics:

1. Molecules, responsible for the <u>direct interaction</u> of the immune cells
2. Their interaction is not antigen-specific
2. Low-affinity, reversible association
4. Increase the antigen-specific interaction
5. *Co-receptors:* - signaling function
6. *Co-stimulatory* molecules: help cell activation
7. Non-polymorphic, well conserved



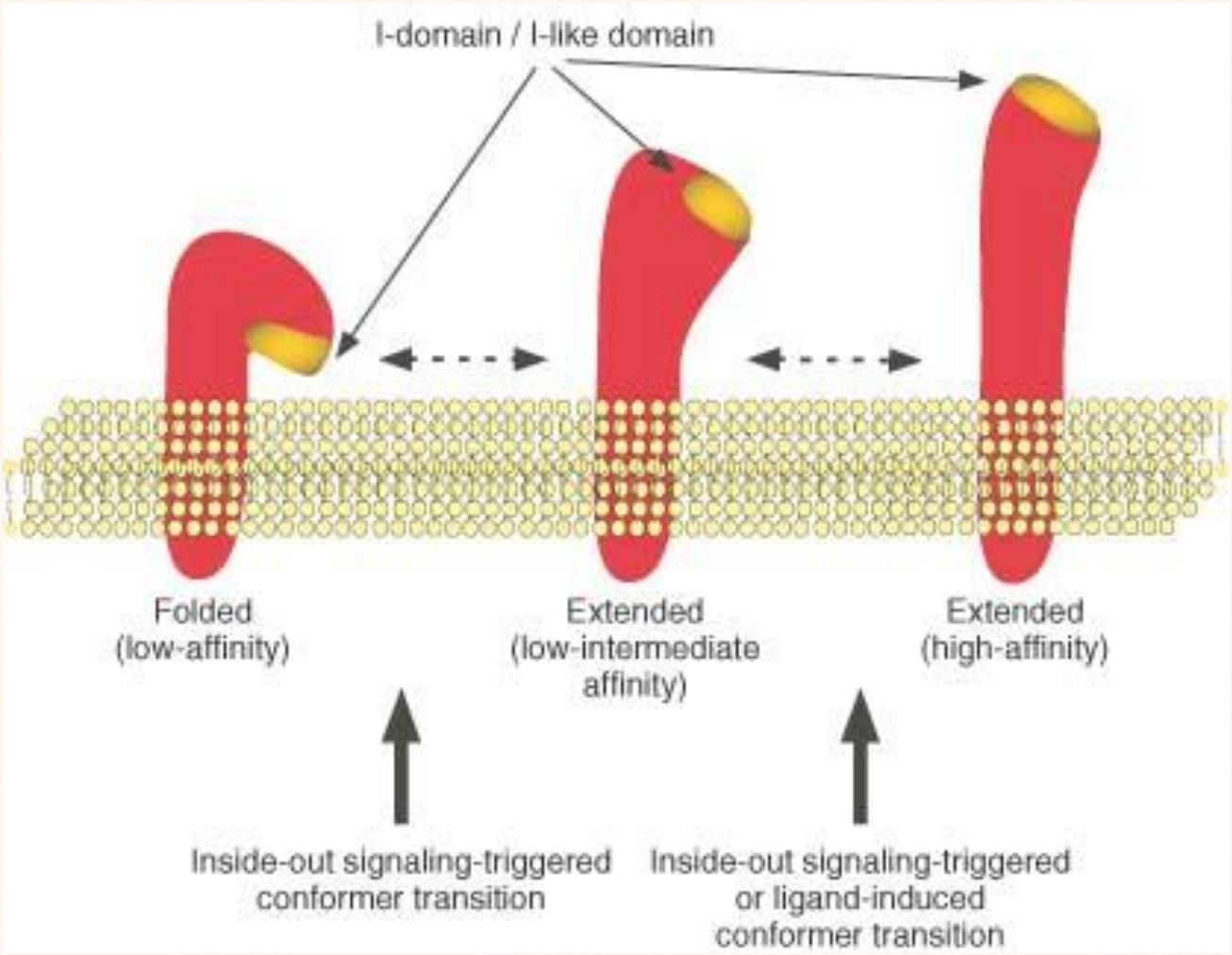
Accessory molecules on T cells



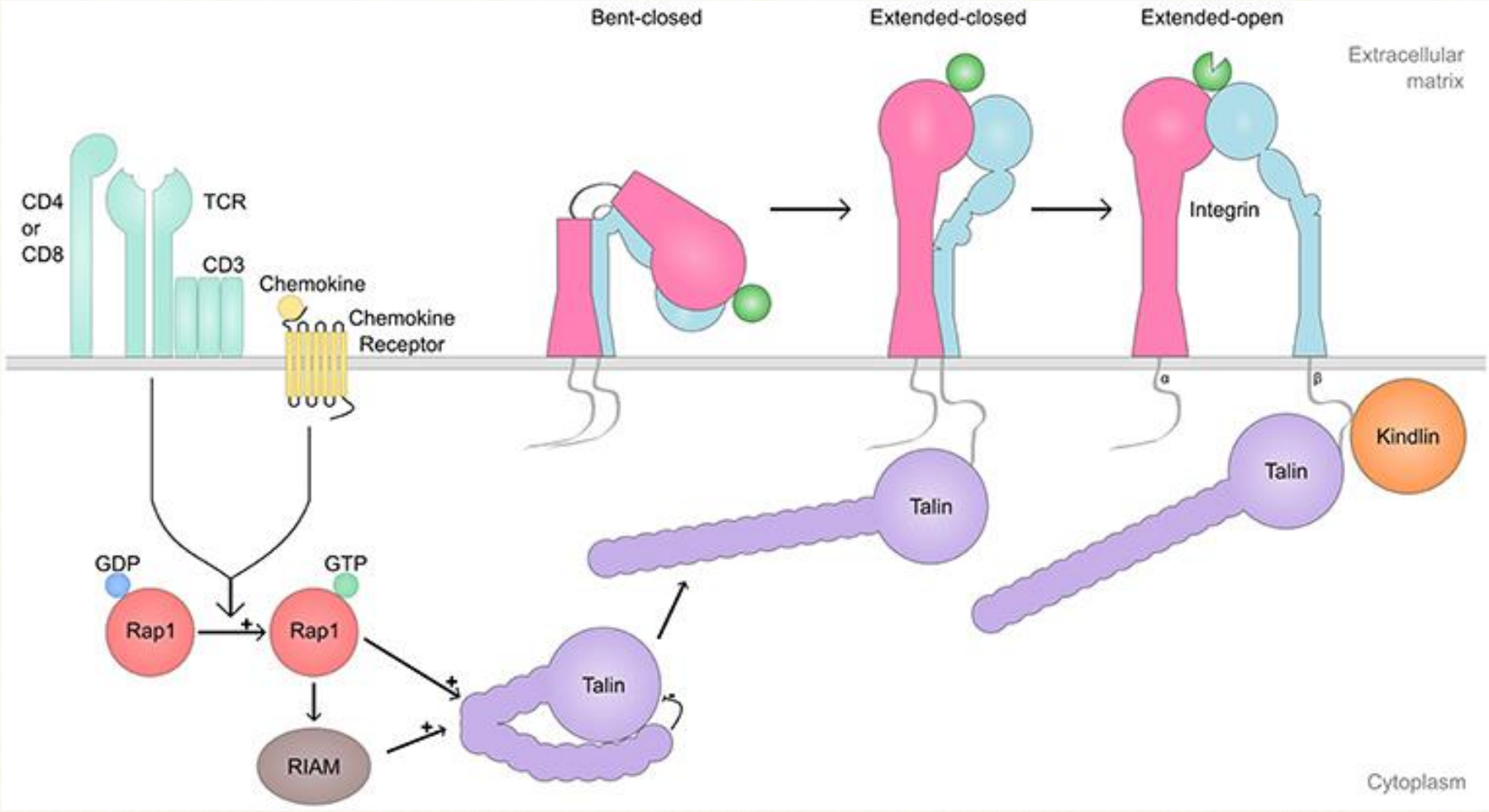


Activation of adheseion molecules

- **L**ymphocyte **F**unction-associated **A**ntigen
- **I**ntra**C**ellular **A**dhesion **M**olecule

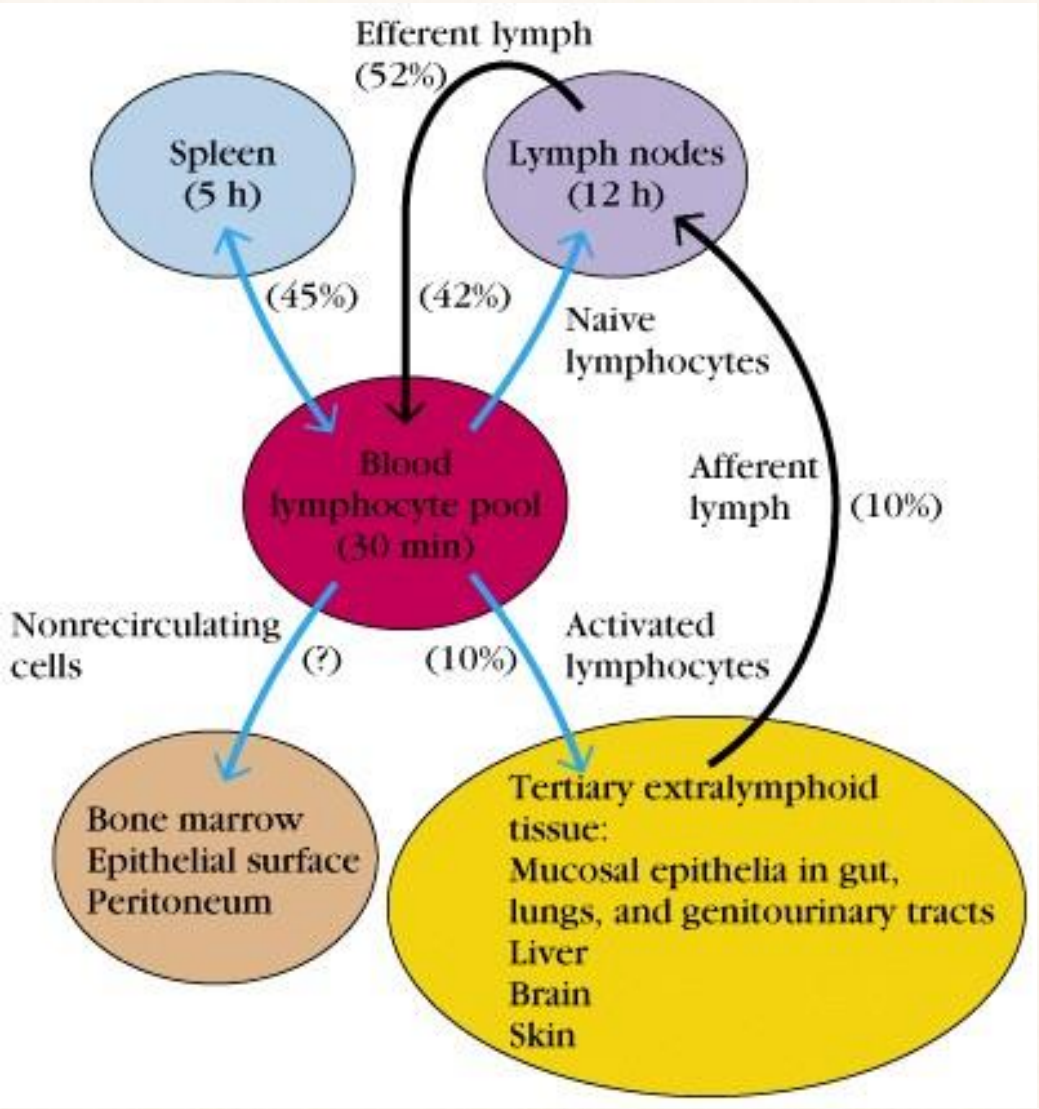


Integrin inside-out signaling



Cell signalling initiated by receptors such as chemokine receptors, T-cell receptor (TCR), Toll-like receptors (TLR) activate selectins and trigger activation of the ligand-binding domain.

Lymphocyte recirculation: continuous migration of cells from the blood flow and lymph to the lymphatic organs and to the inflammation **= HOMING**



Role:

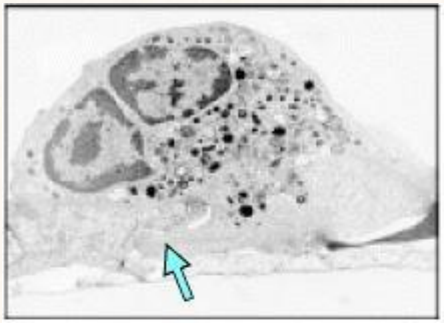
- Promotes the antigen capturing

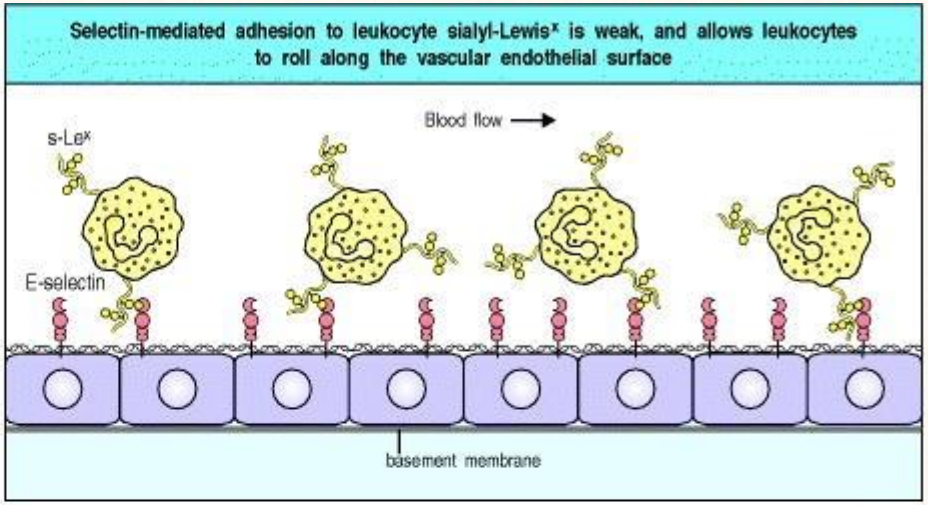
- Promotes the development of inflammatory reactions

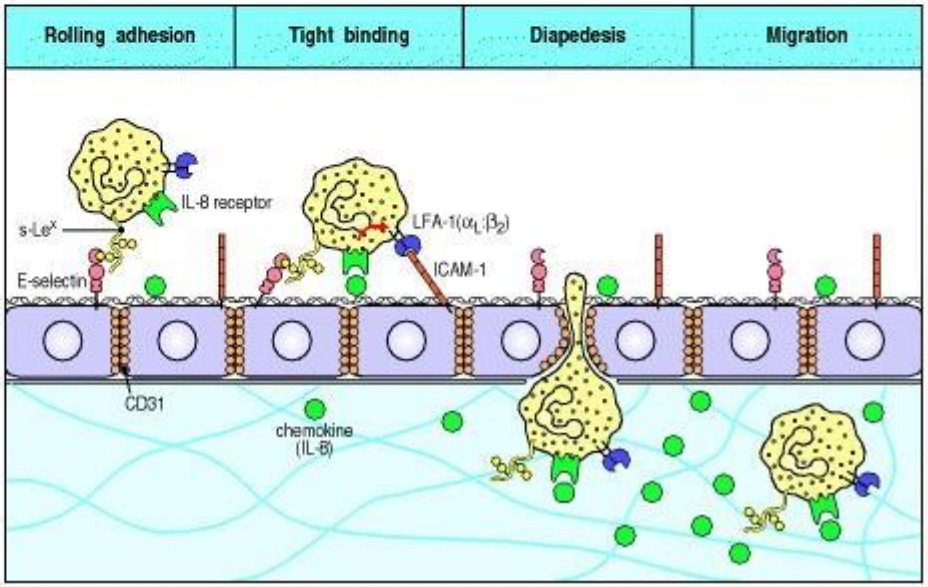
Mechanism:

-Extravasation: leucocyte adhesion to the endothel, and migration across the wall of the blood vessels to the tissue

1-2 total circle managed by all white blood cells pro day



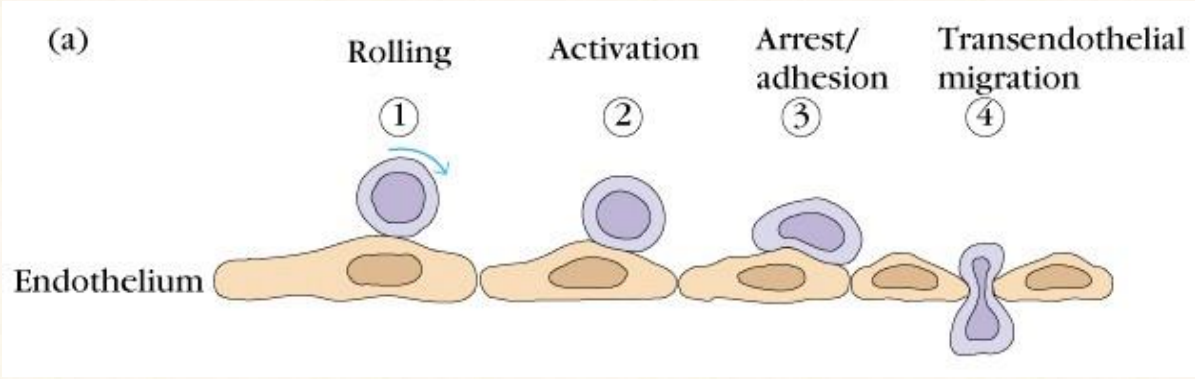


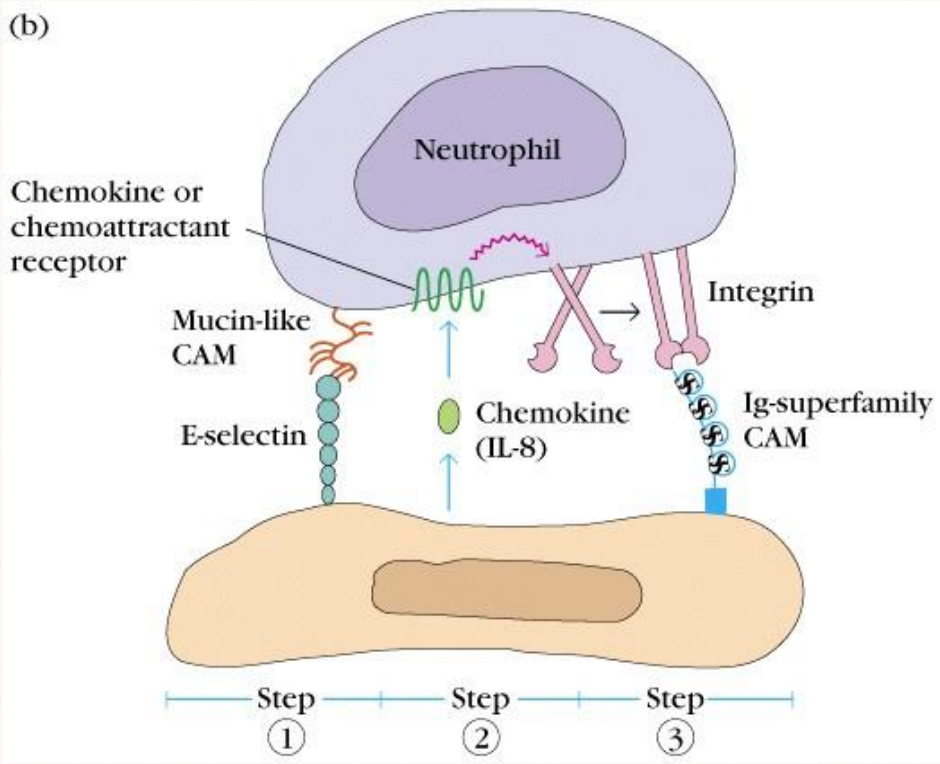


See more details in the Inflammation lecture (Lecture 4)

Neutrophils leave the blood and migrate to sites of infection in a multistep process mediated through adhesive interactions that are regulated by macrophage-derived cytokines and chemokines.

Migration of neutrophil granulocytes to the inflammed tissues throgh the endothel

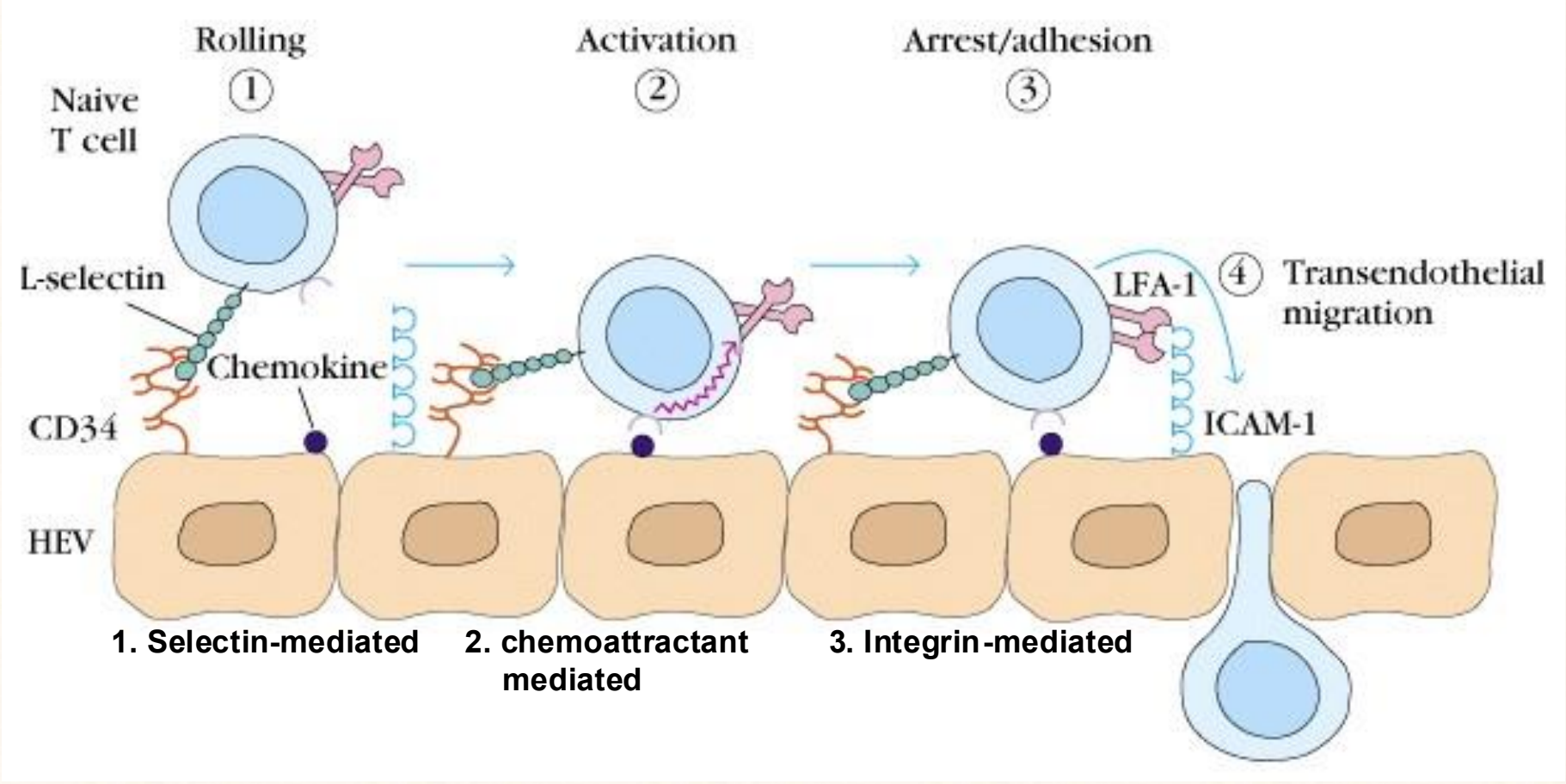




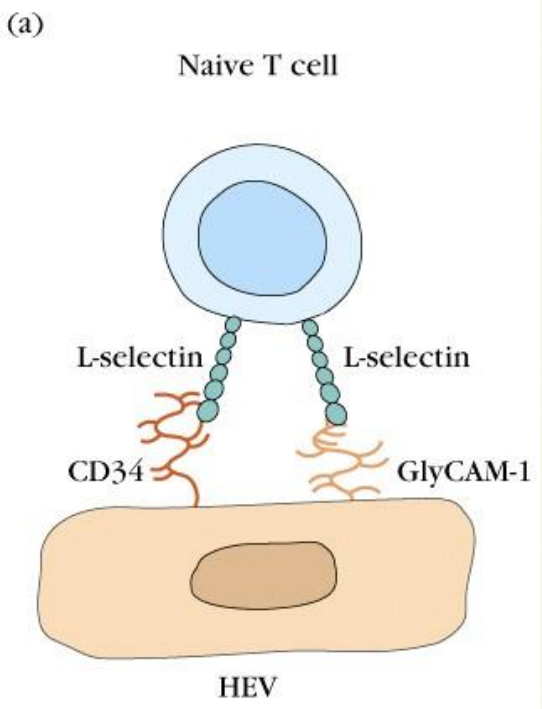
See more details in the Inflammation lecture (Lecture 4)

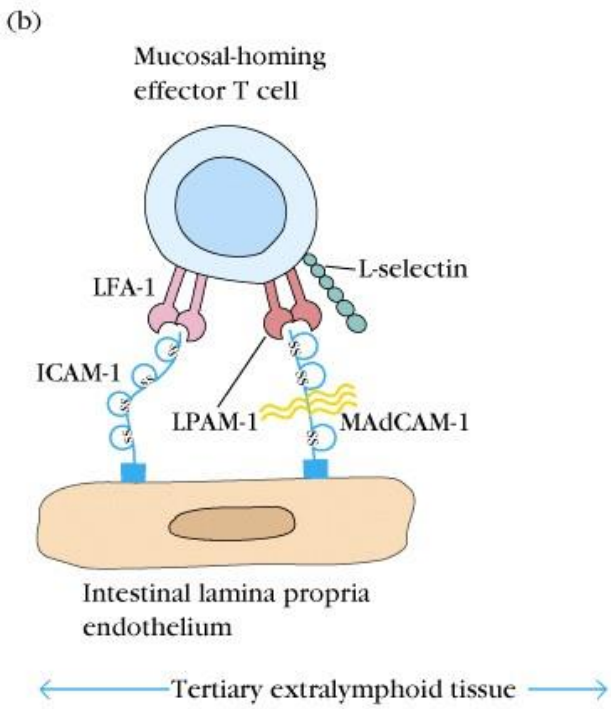
Naive lymphocytes migrating to the peripheral lymphatic tissues

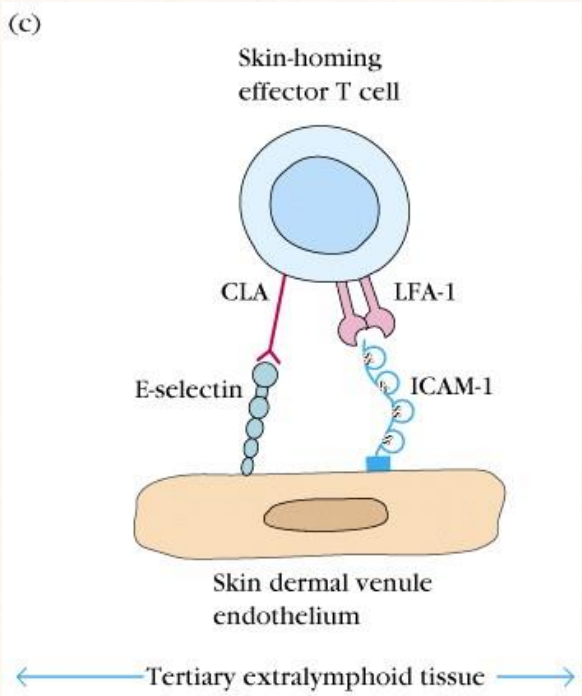
The role of the high endothelial venules (HEV), and the adhesion molecules



Different adhesion molecules determine the migration of naive and memory (effector) cells







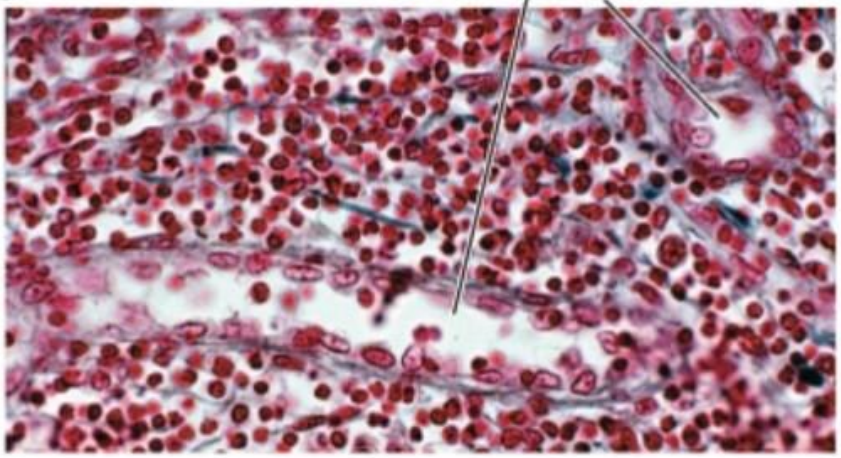
Peripheral lymphatic tissue

Inflammatory tissue

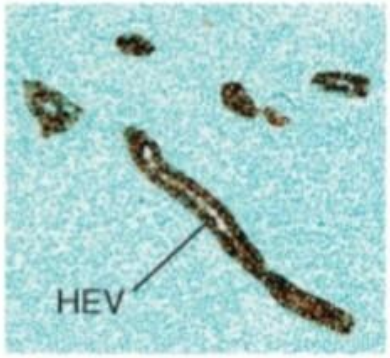
See more details in the lecture about T cell activation (Lecture 12)

High endothelial venules (HEV)

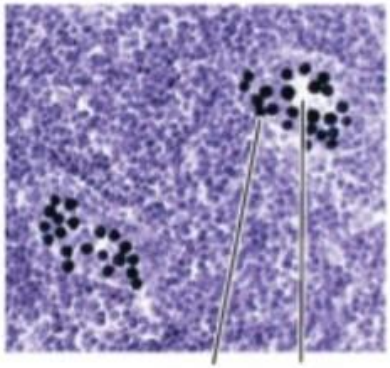
A HEVs in a lymph node



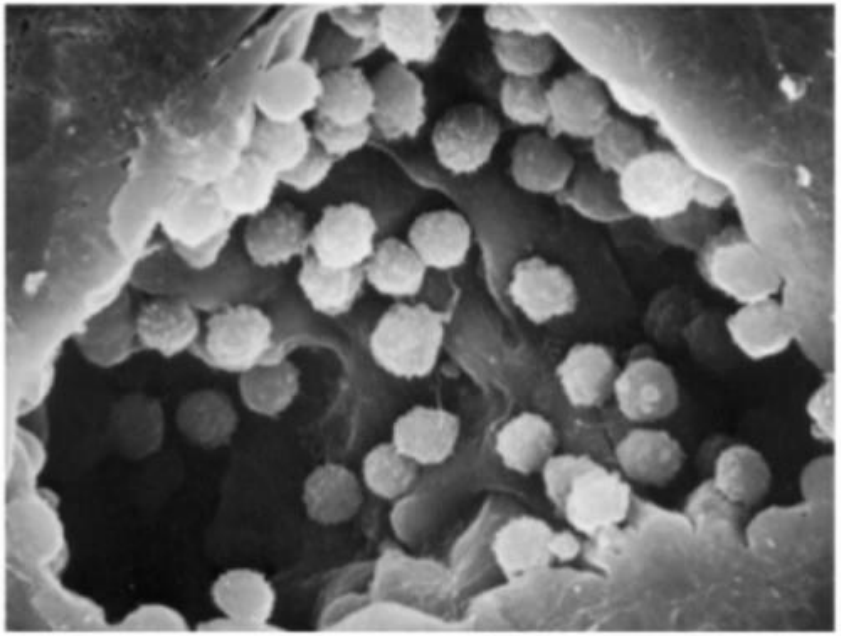
B L-selectin ligand on endothelial cells (IHC)



C T cells binding to HEV (frozen section assay)

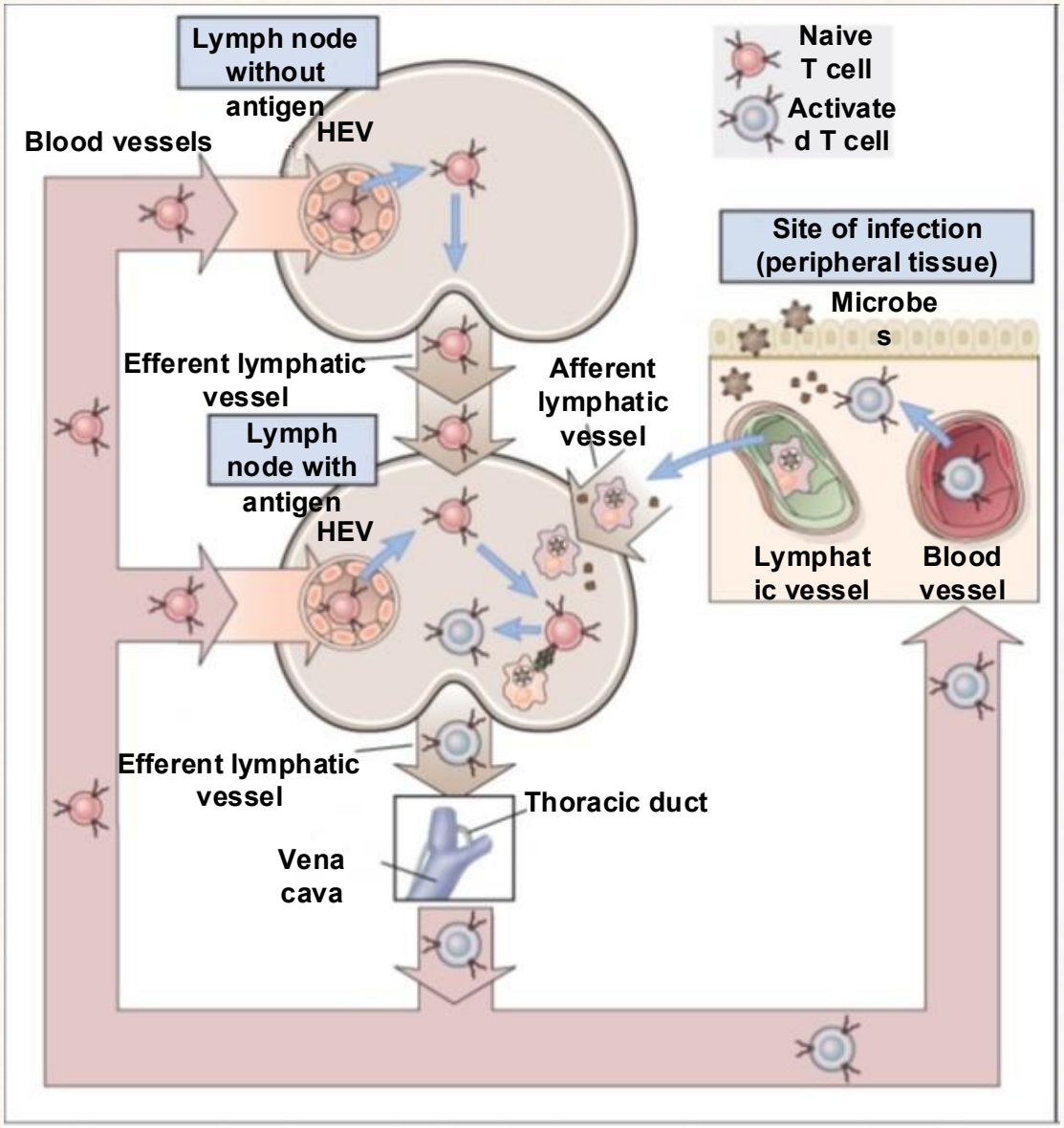


D T cells binding to the luminal surface of a HEV (electron microscopy image)



- Lymphocytes use HEVs to enter lymphoid organs. (through L-selectin, see later)
- Found in all secondary lymphoid organs (e.g. lymph nodes, tonsils, Peyer's patches), **EXCEPT THE SPLEEN**[10.]

Filtration of lymph by nodes 1.



1. Infection on the periphery
2. The same antigen may enter the **lymphatic vessels** in different forms:
   - **Native bound antigen** (e.g. living bacteria)
   - **Native soluble form** (e.g. proteins derived from dead bacteria)
   - **Processed form: dendritic cells** phagocytose the antigen and **present it** as a peptide to **helper T cells** (see later)
3. Lymphocytes enter lymph nodes either through **afferent lymph vessels** or **HEV**s and meet with the antigens (see

Ig-superfamily member CD2

CD2

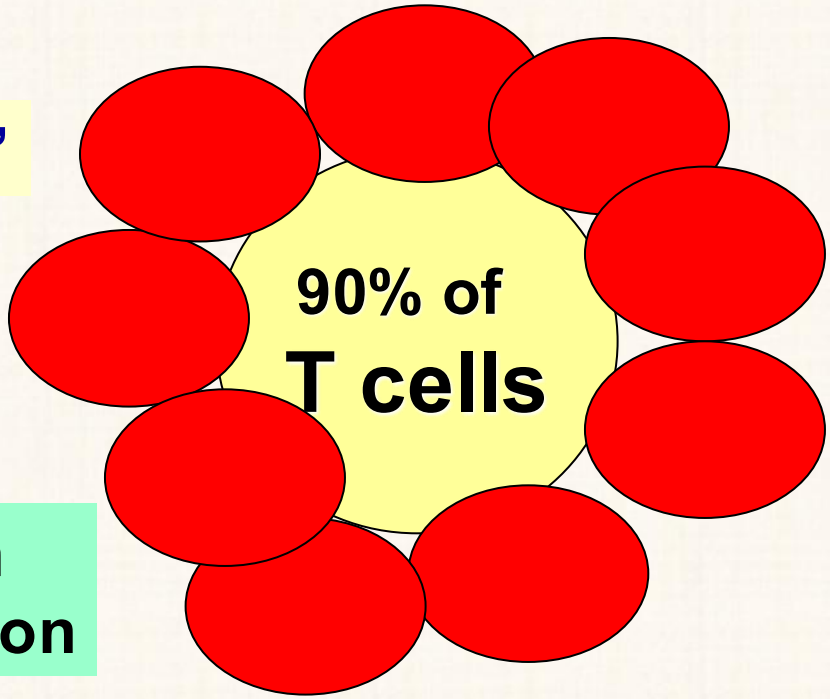
„sheep red-blood cell receptor”

Binds to CD58

(LFA3) expressed

on APCs

„T cell rosette”



Adhesion
Cell activation

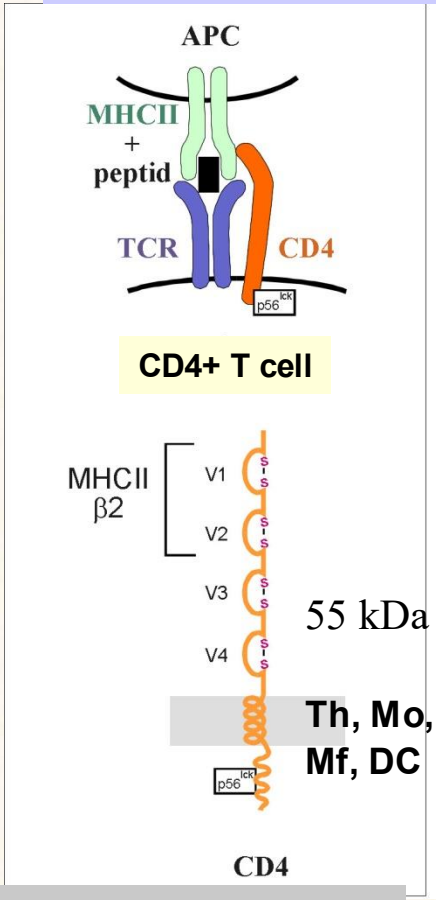
T cell activation, CTL- and NK-mediated lysis

Ig Superfamily members CD4 and CD8:

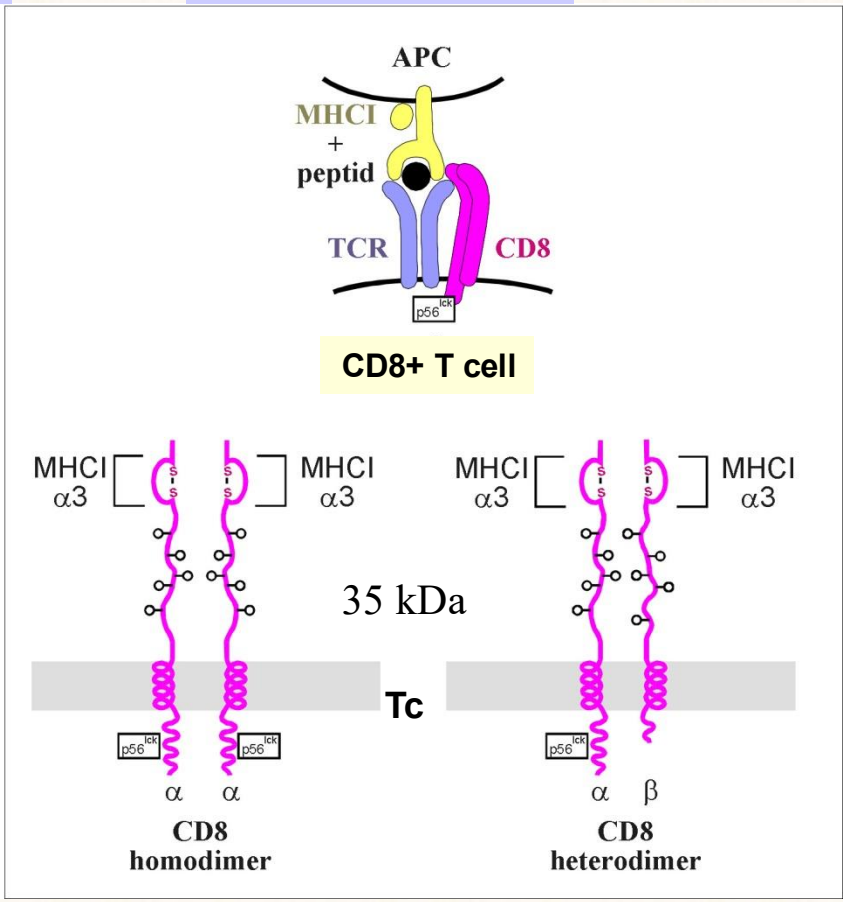
extracellular domain: binding to MHC constant domain

intracellular domain: signal transduction, binding kinases

CD4 - MHCII



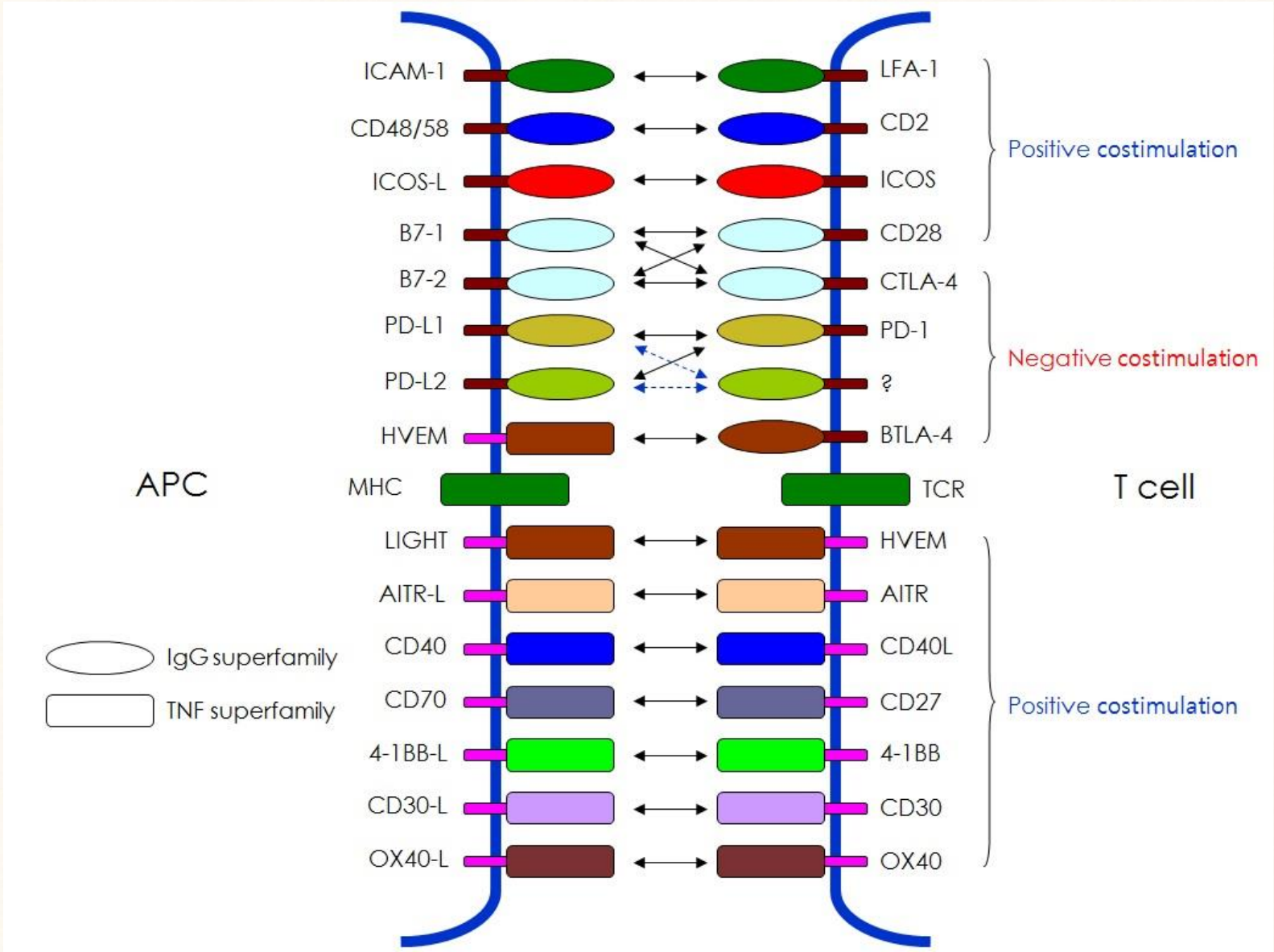
CD8 - MHCI



CD4 expressed in T cells and macrophages - HIV-receptor as well

See more details in the lecture about MHC and ag presentation (Lecture 5-6)

Co-stimulatory molecules in APCs and T cells

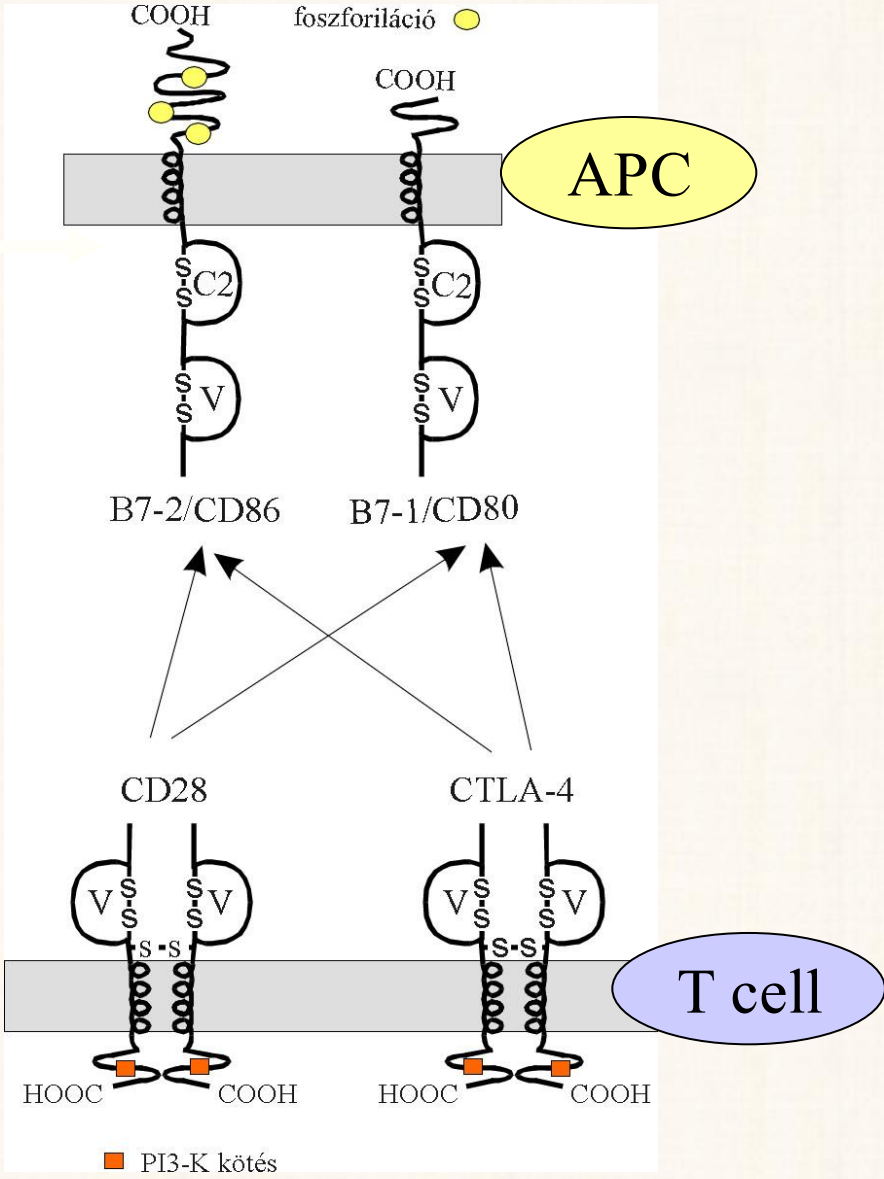


B7 (CD80, CD86), CD28 and CTLA-4 molecules

CD28 and CTLA-4 of T cells bind to the **B7-1** (CD80), **B7-2** (CD86) molecules of the APC

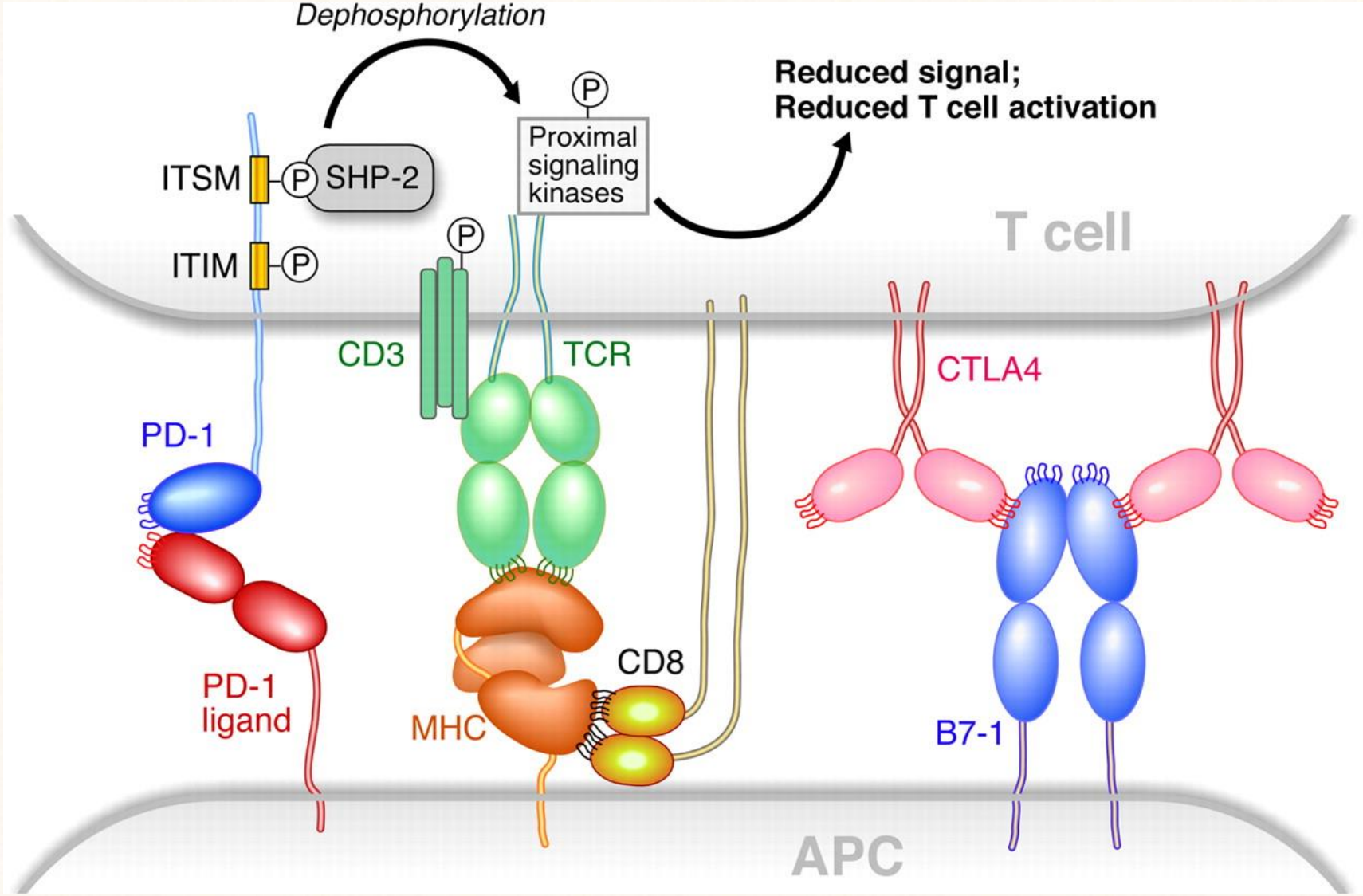
CD28: - co-stimulatory molecule in T cell activation
- Increases IL-2 and IL-2R expression,
- Induces T cell proliferation

CTLA-4 (CD152): - expressed in a later phase of the T cell activation
- inhibitory function

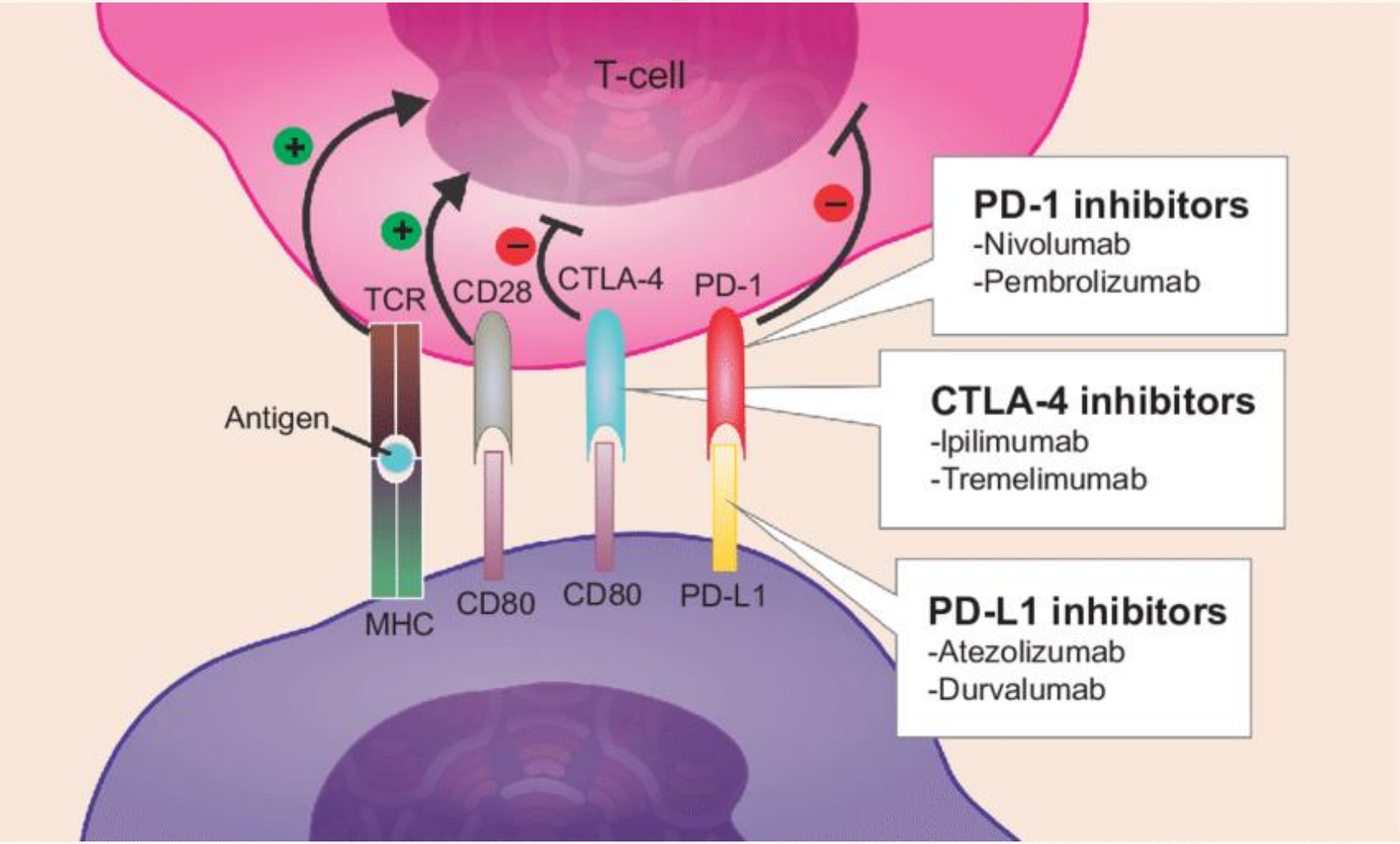


CTLA: **Cytolytic T lymphocyte associated Antigen**

Co-stimulatory molecules with blocking effects on T cells and APCs



Immune checkpoint inhibitors



James P. Allison, PhD **Tasuku Honjo**, MD, PhD

2018 Nobel Prize: use of immune checkpoint inhibitors to treat cancer.

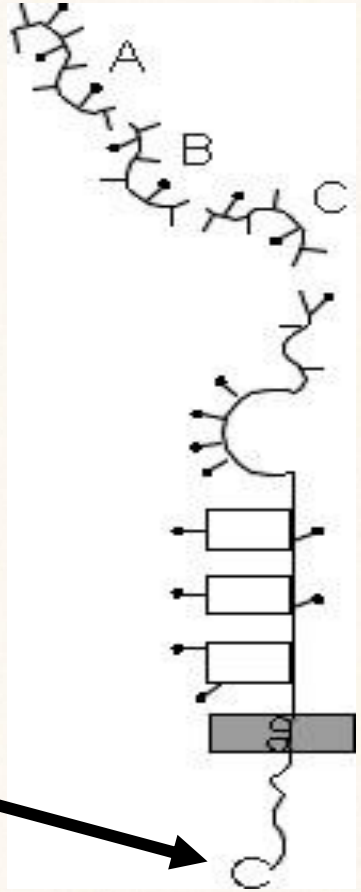
See more details in the Tumor immunology lecture (Lecture 28)

„OTHER” accessory molecules

CD45

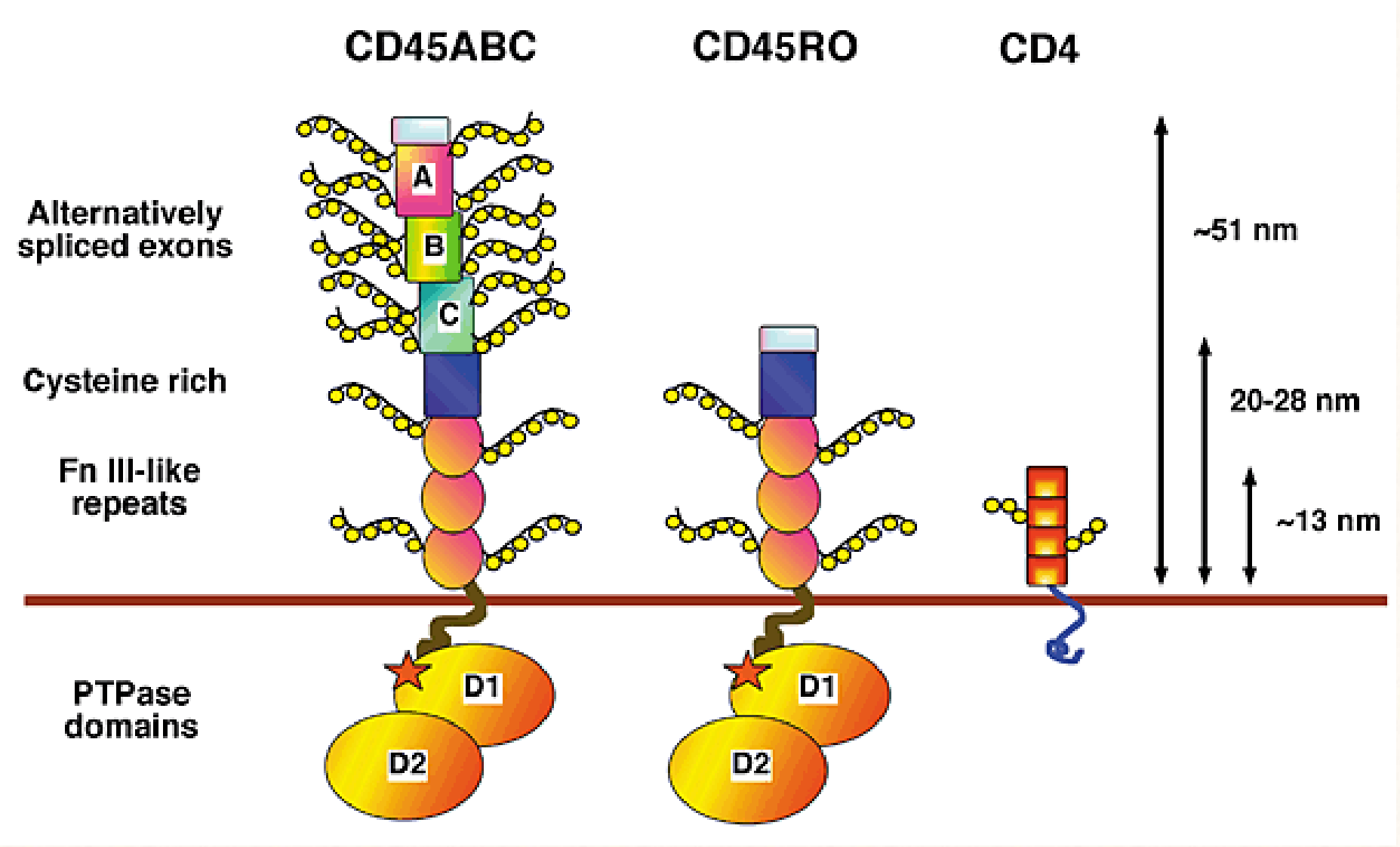
Expressed on every leukocyte
“pan-leukocyte marker”
- Highly glycosylated,
- More isoforms (180, 190, 200, 205, 220 kDa)
- alternate splicing

Plays important role in cell activation and in regulation of signal transduction
- ***protein-tyrosine-phosphatase domain: dephosphorylation***



CD45

CD45 isoforms



Cell-cell communication with cytokines

Basic characteristics of cytokies

- Low molecular weight (10-40 kDa), and genetically well conserved glycoproteins
- Isolated cells secrete them, due to gene activation
- They mediate cell-cell interaction:

  - sending information

  - general regulation of biological homeostasis including immune response
- Mechanism of action:

  - produced after transient gene activation

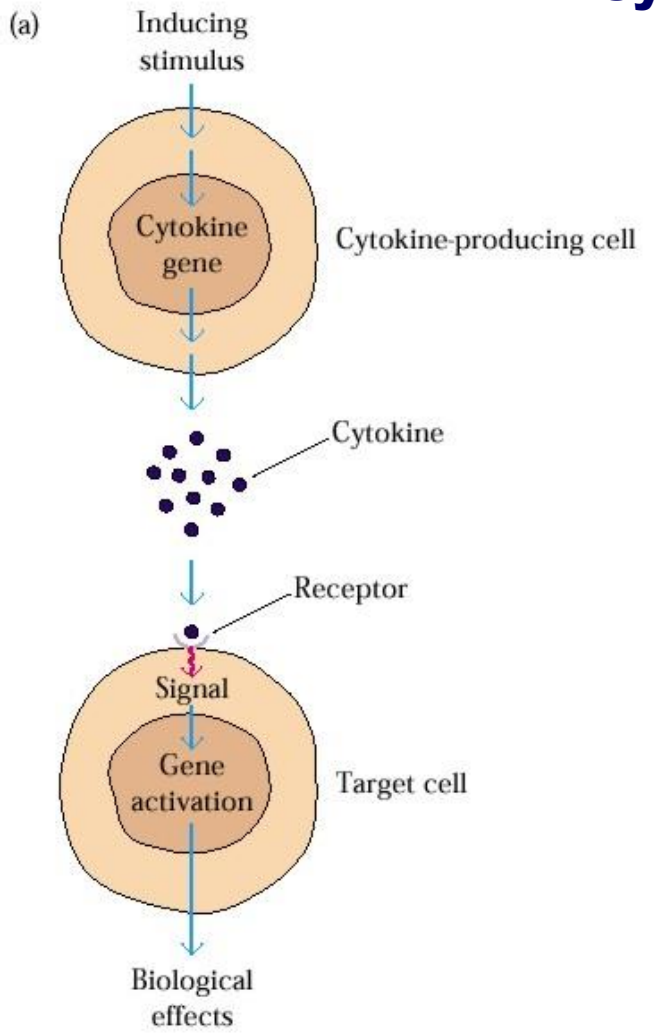
  - act through receptors triggering signal-transduction

  - high affinity

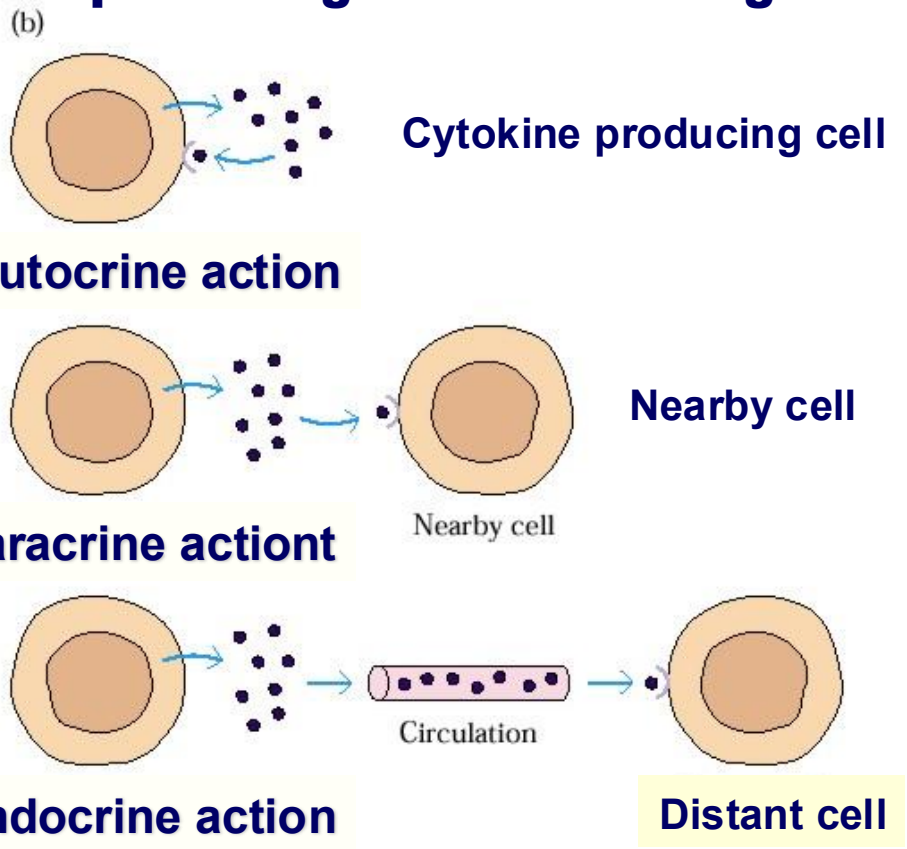
  - picomolar concentration

  - they act mostly locally

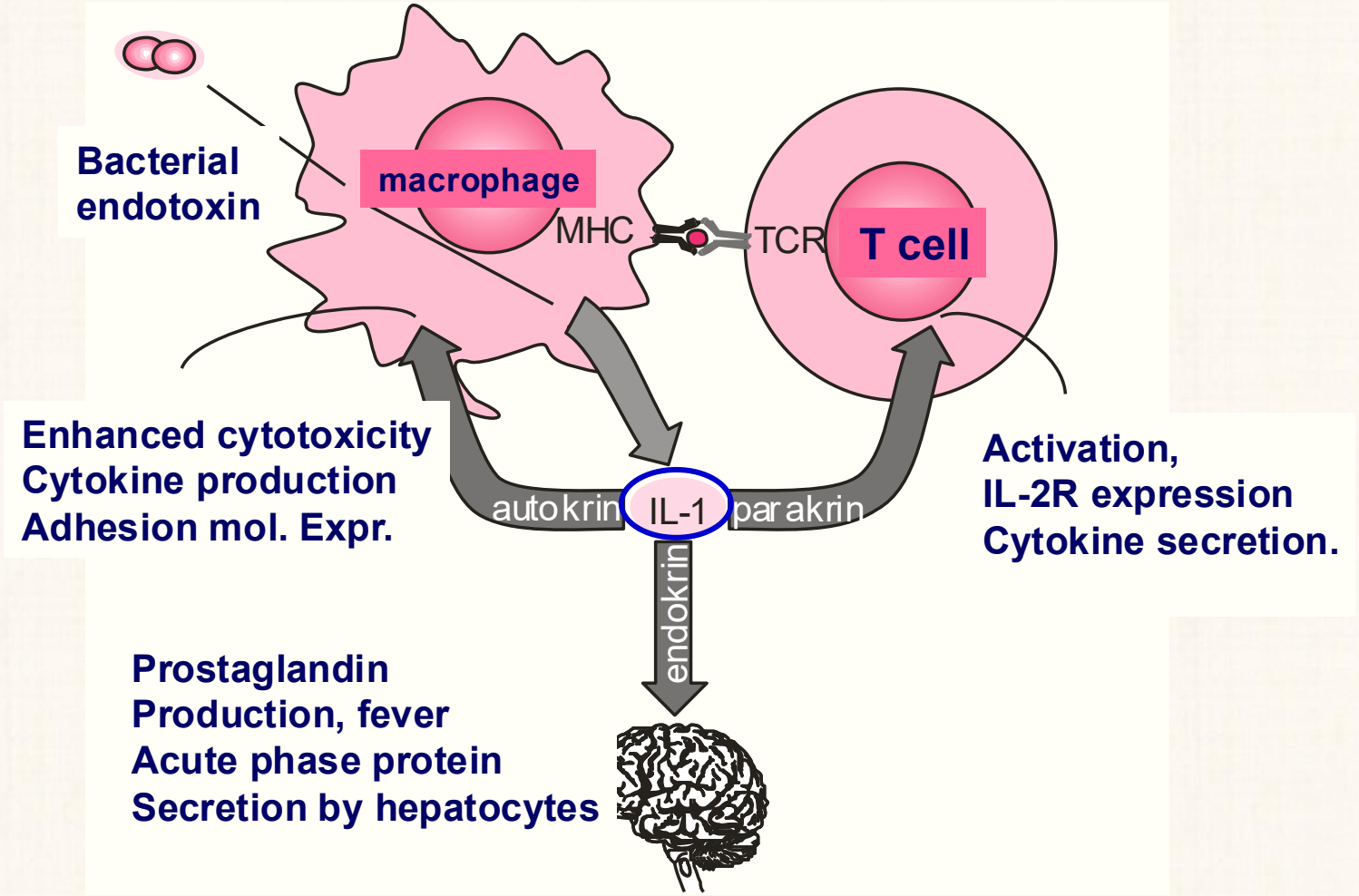
Mechanism of cytokine action I.



Cytokine producing cell **Target cell:**



Autocrine, paracrine and endocrine action of IL-1



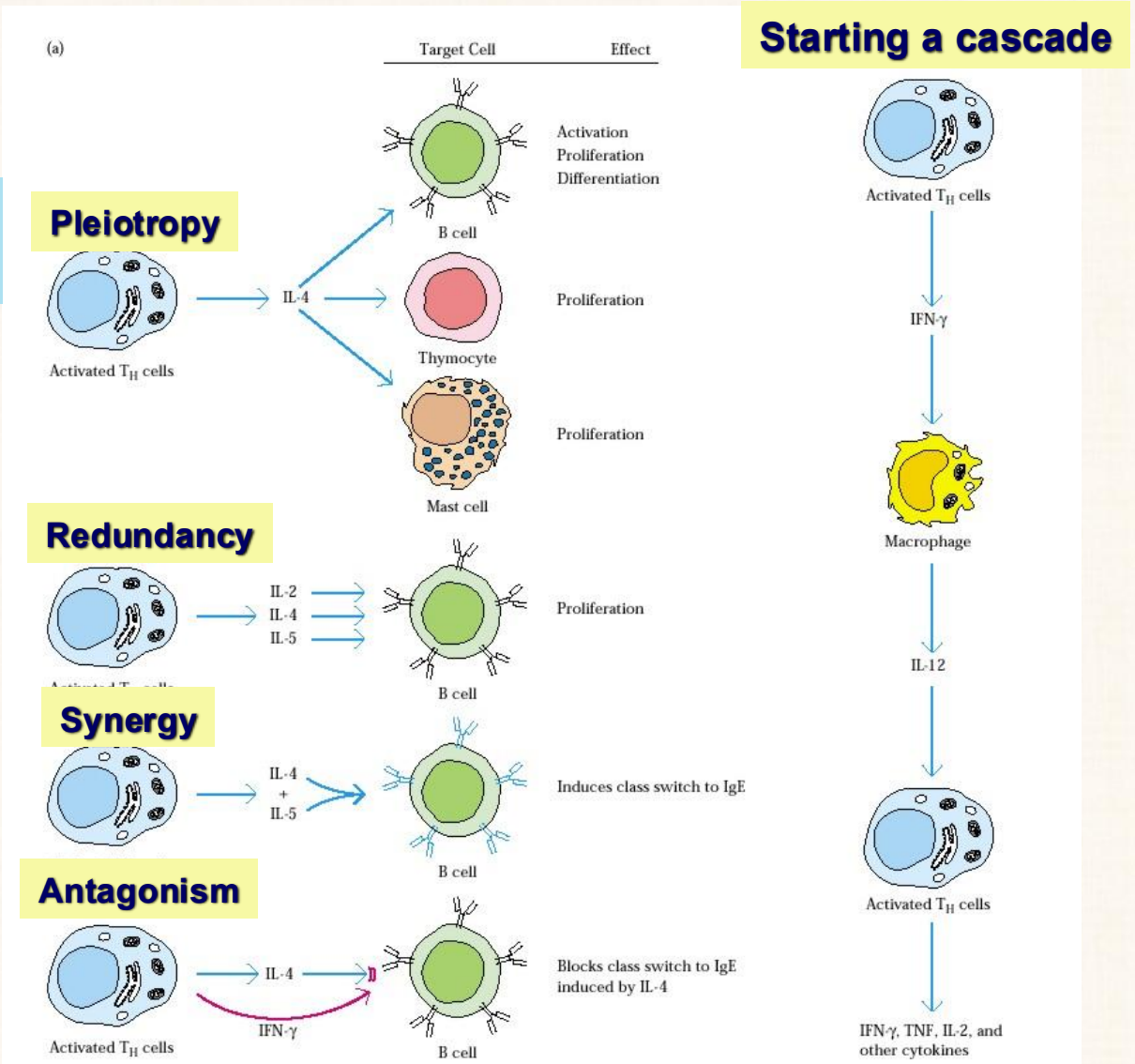
Mechanism of cytokine action II.

A cytokine induces different effects on different target cells

The action of more cytokine on the target cell is similar

The effect of two cytokines is stronger than their additive effects

One cytokine inhibits the effects of another cytokine

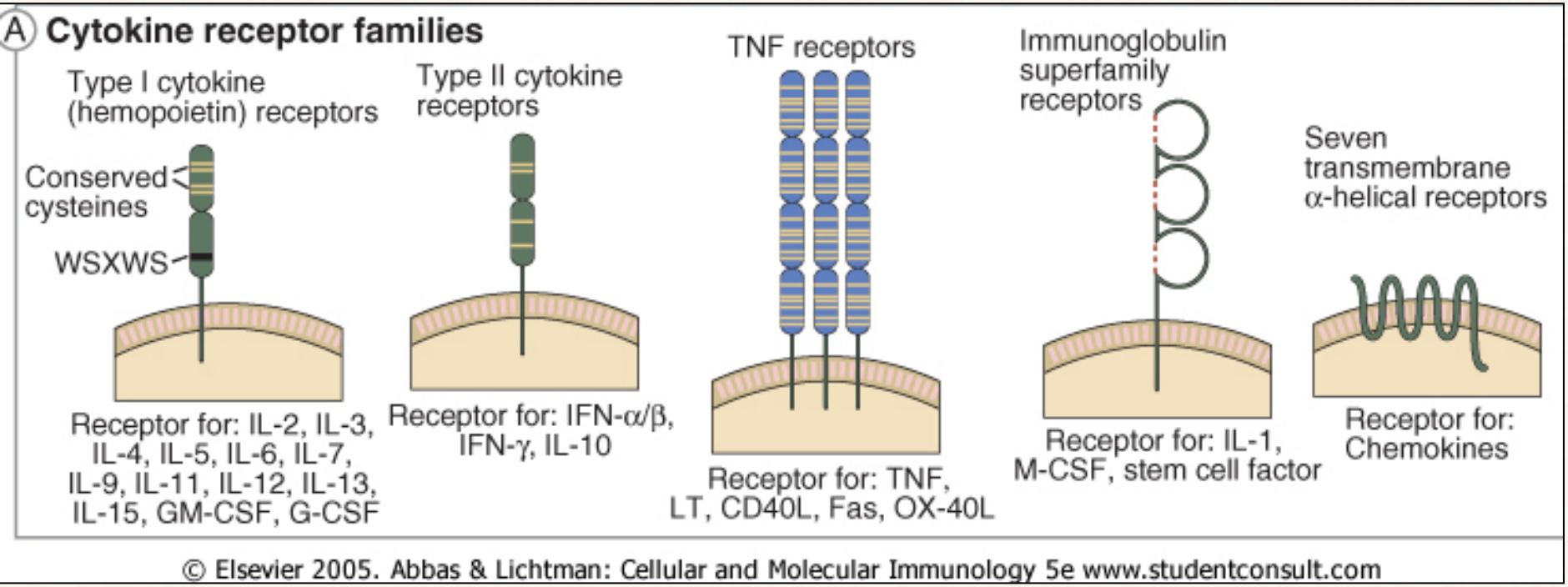


Functional groups of cytokines

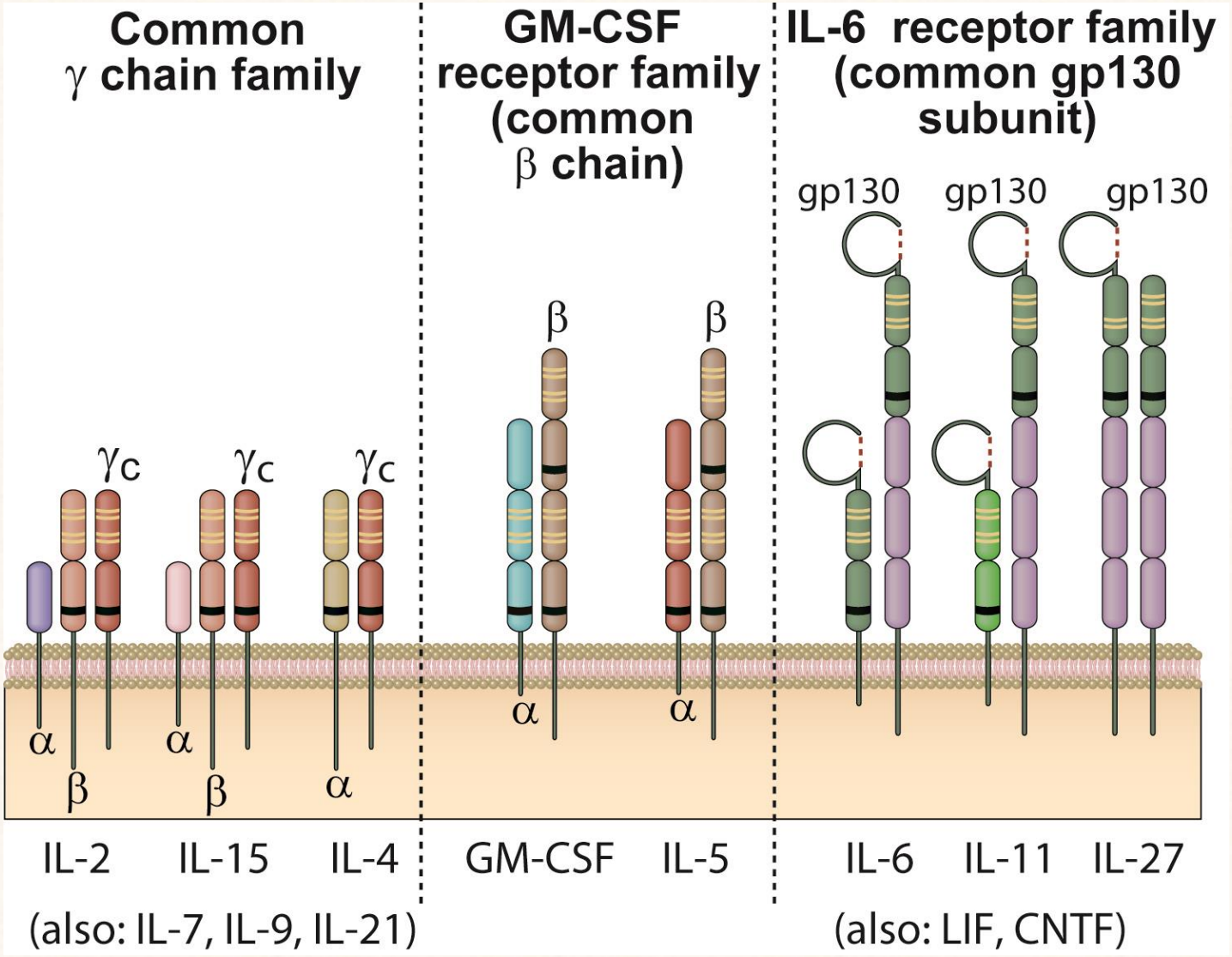
I. Regulators of natural immunity and inflammation	**IFNα, IFNβ, TNFα, TNFβ (LT), IL-1α, IL-1β, IL-6, IL-12,** **MIF, chemokines**
II. Regulators of lymphocyte activation and differentiation	**IL-2, IL-4, IL-5, IL-6, IL-13, IL-15, INFγ,** **IL-10 and TGFβ**
III. Regulators of haematopoiesis	**IL-3, IL-7, GM-CSF, SCF**

Cytokine receptors

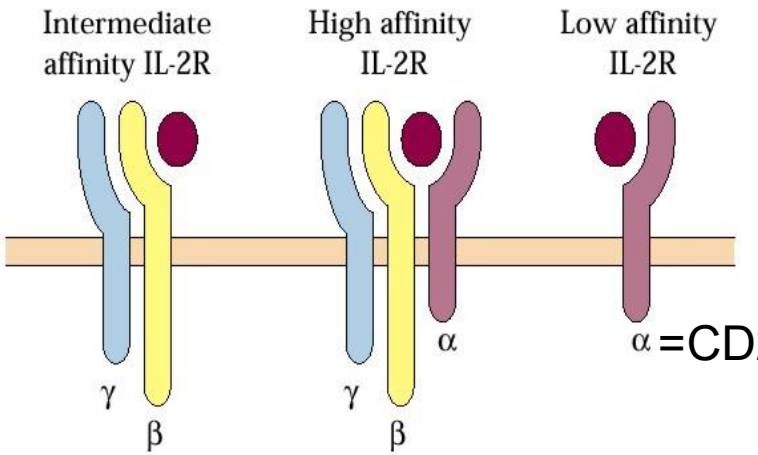
Cytokine receptors



Multichain cytokine receptors



IL-2 receptor chains:



Subunit composition:	IL-2Rβ IL-2Rγ	IL-2Rα IL-2Rβ IL-2Rγ	IL-2Rα
Affinity constant (K_a):	$10^7 M$	$10^{11} M$	$10^8 M$
Dissociation constant (K_d):	$10^{-9} M$	$10^{-11} M$	$10^{-8} M$
Cells expressed by:	NK cells Resting T cells (low numbers)	Activated CD4+ and CD8+ T cells Activated B cells (low numbers)	

See more details in the lecture about T cell activation (Lecture 12)

Cytokine Induction of JAK-STAT Signaling

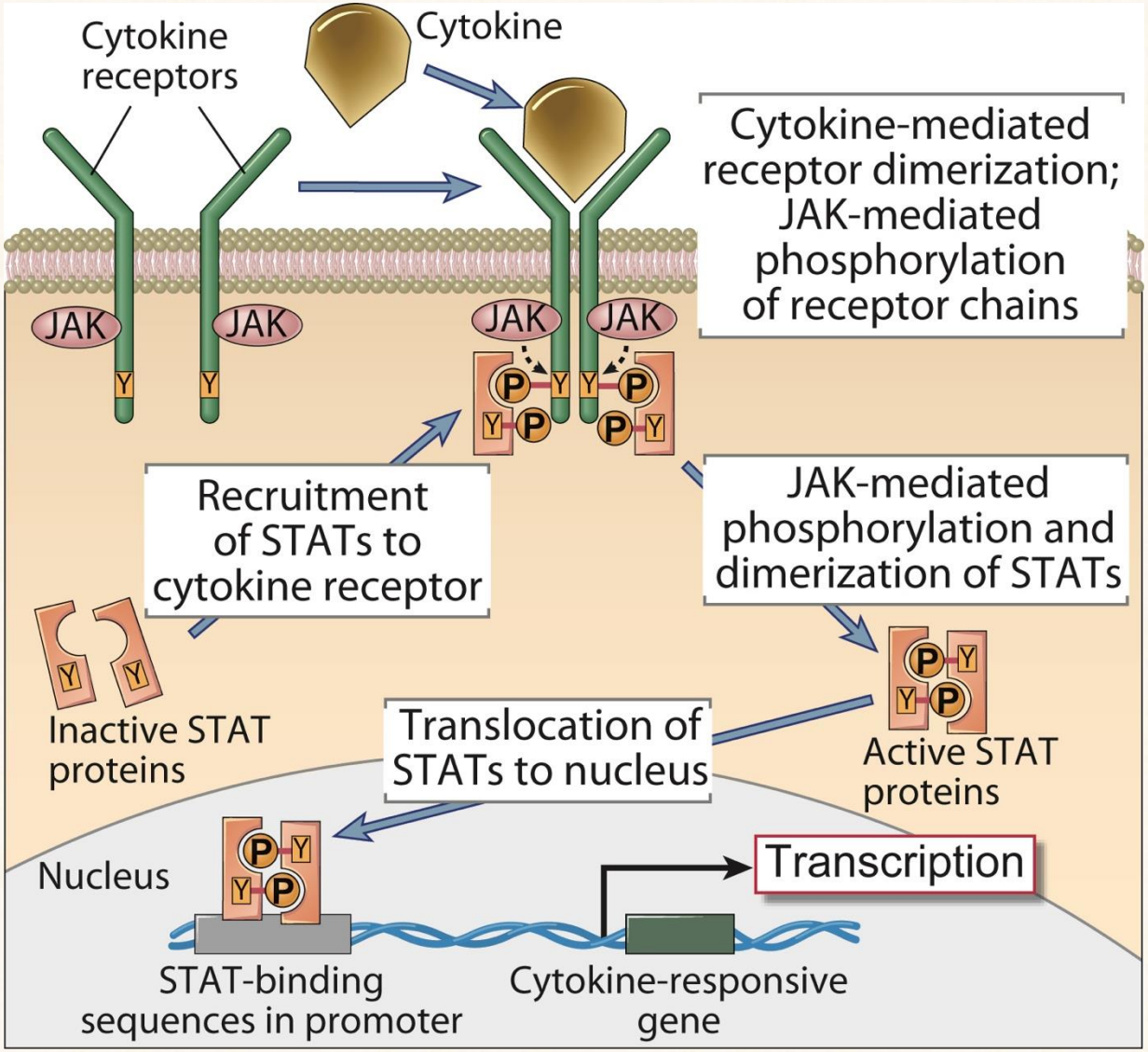
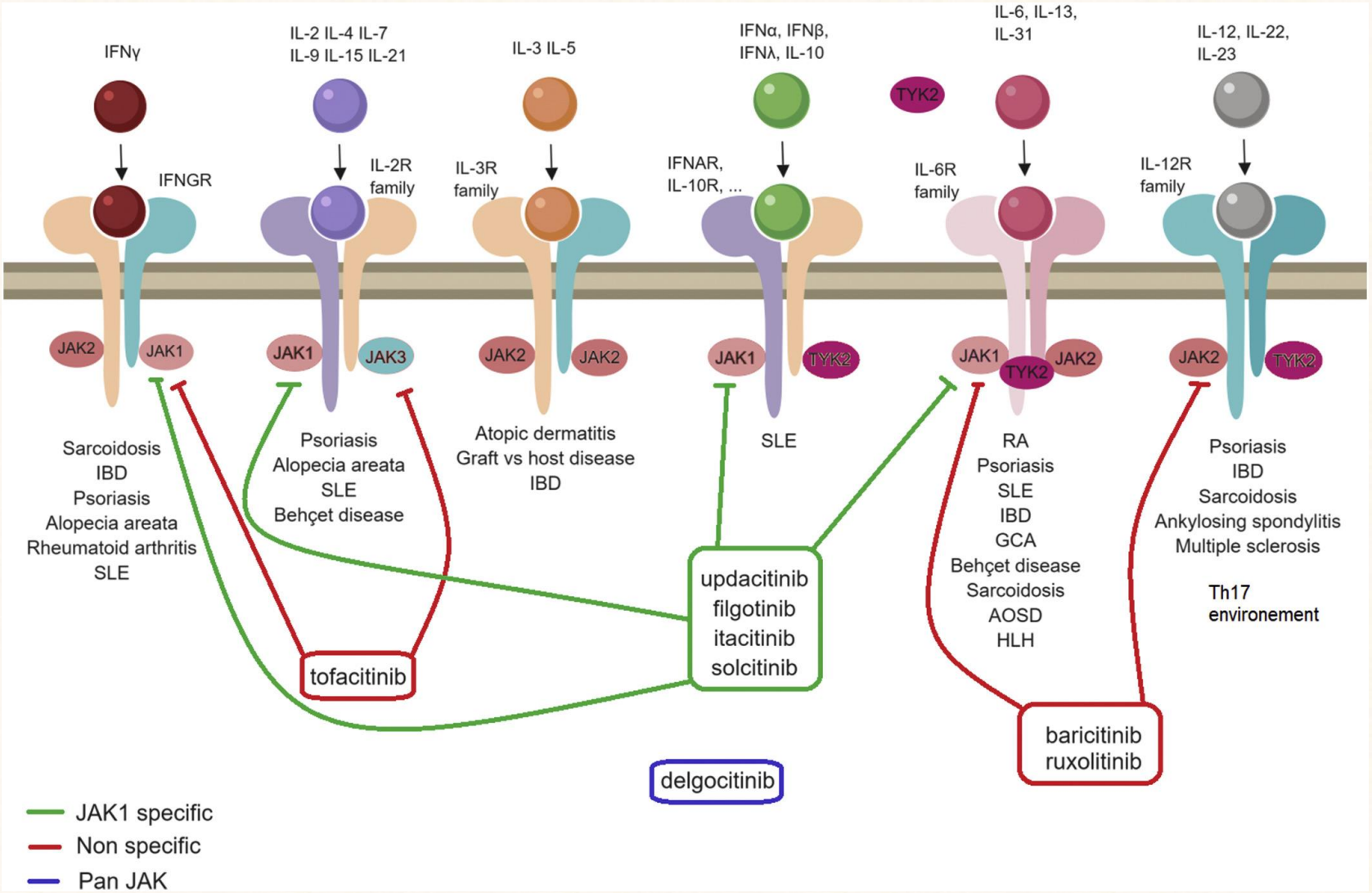


Fig. 7-25

JAK inhibitors



JAK inhibitors are such kinase inhibitors which are used to inhibit the cytokine signaling pathways in bone marrow hemopoetic diseases (eg. Polycythaemia vera) or inflammatory/autoimmune conditions.

TNF Receptor Signaling

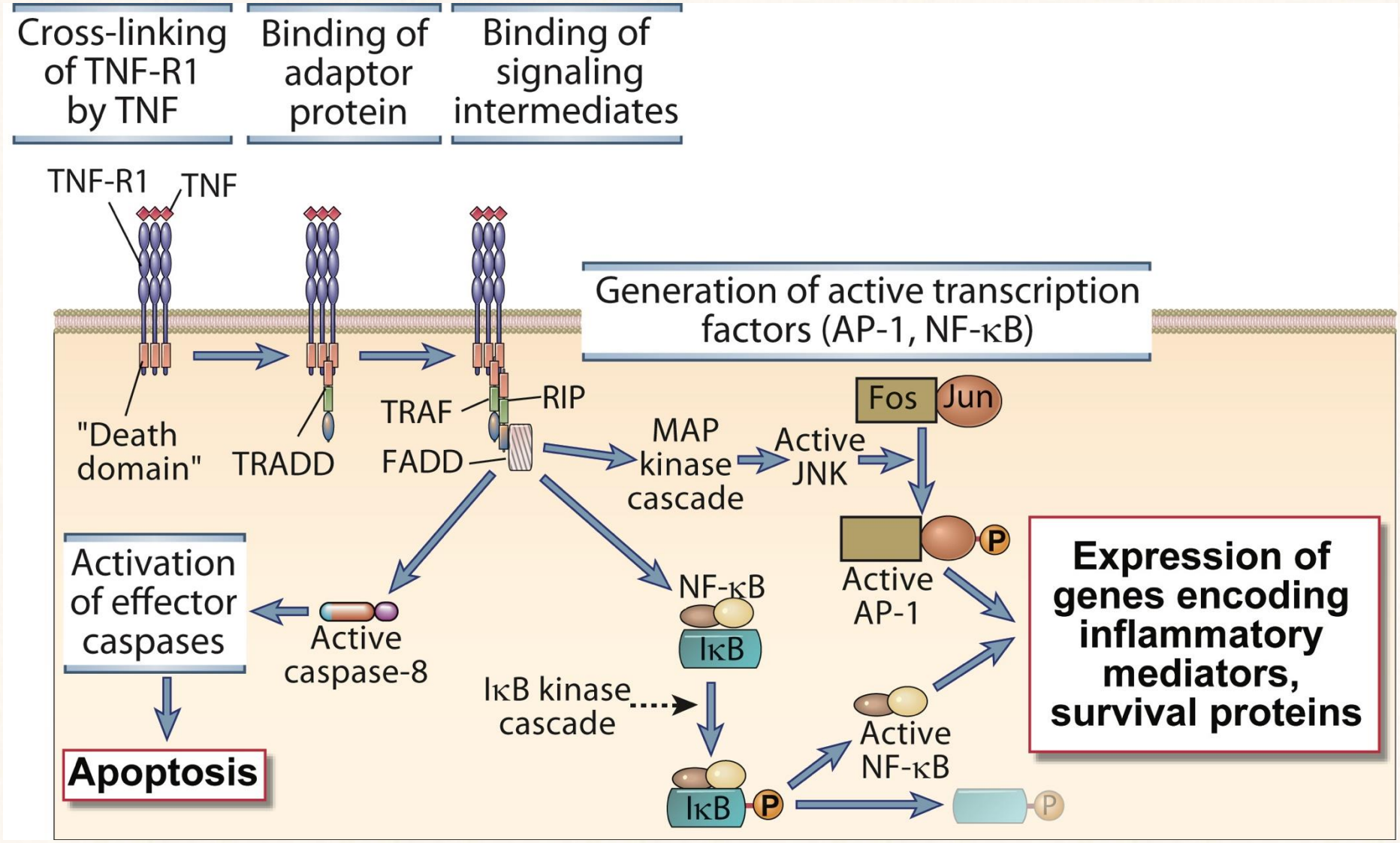
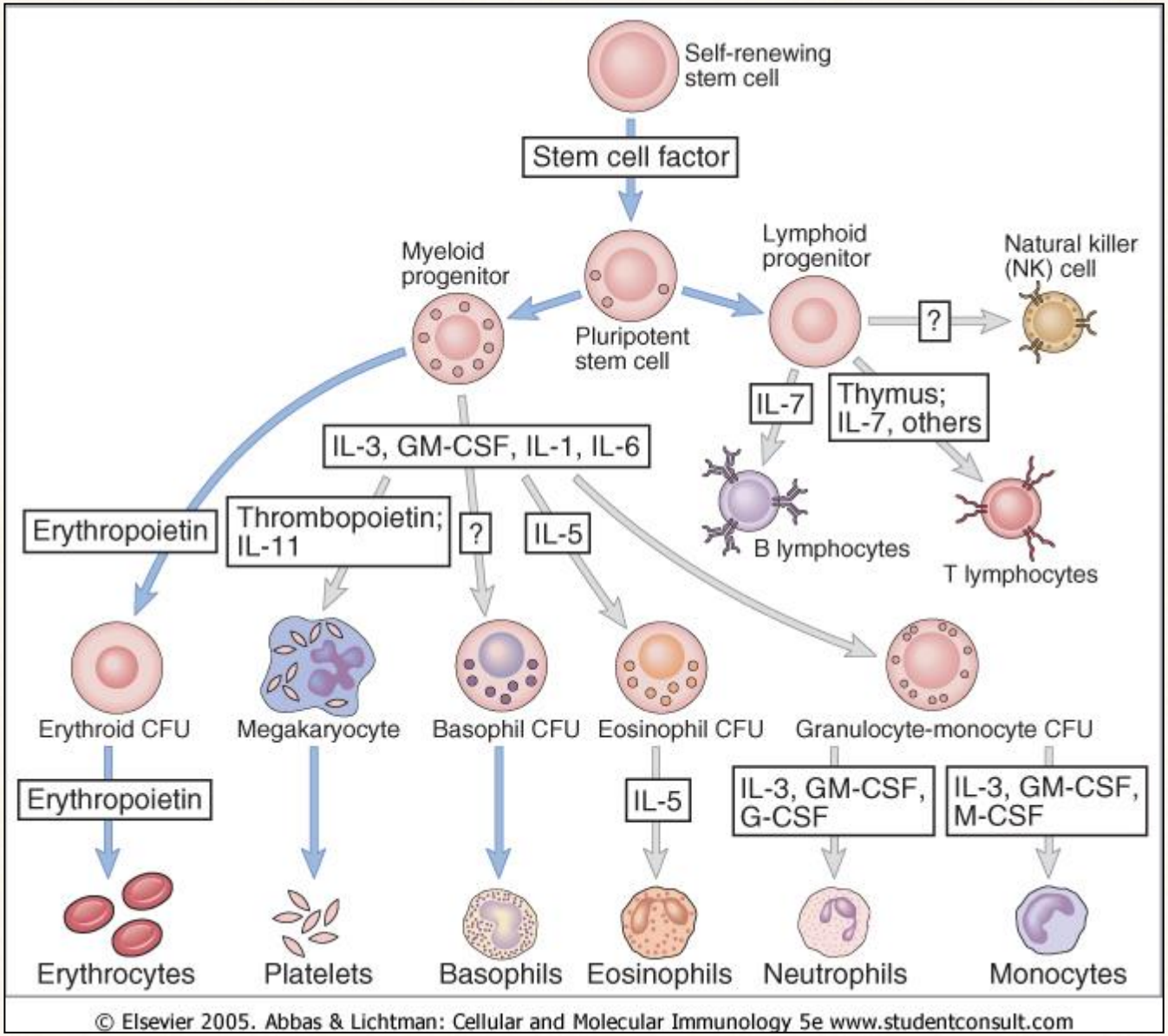


Fig. 7-24

Functional groups of cytokines:

1. Haemopoetic cytokines

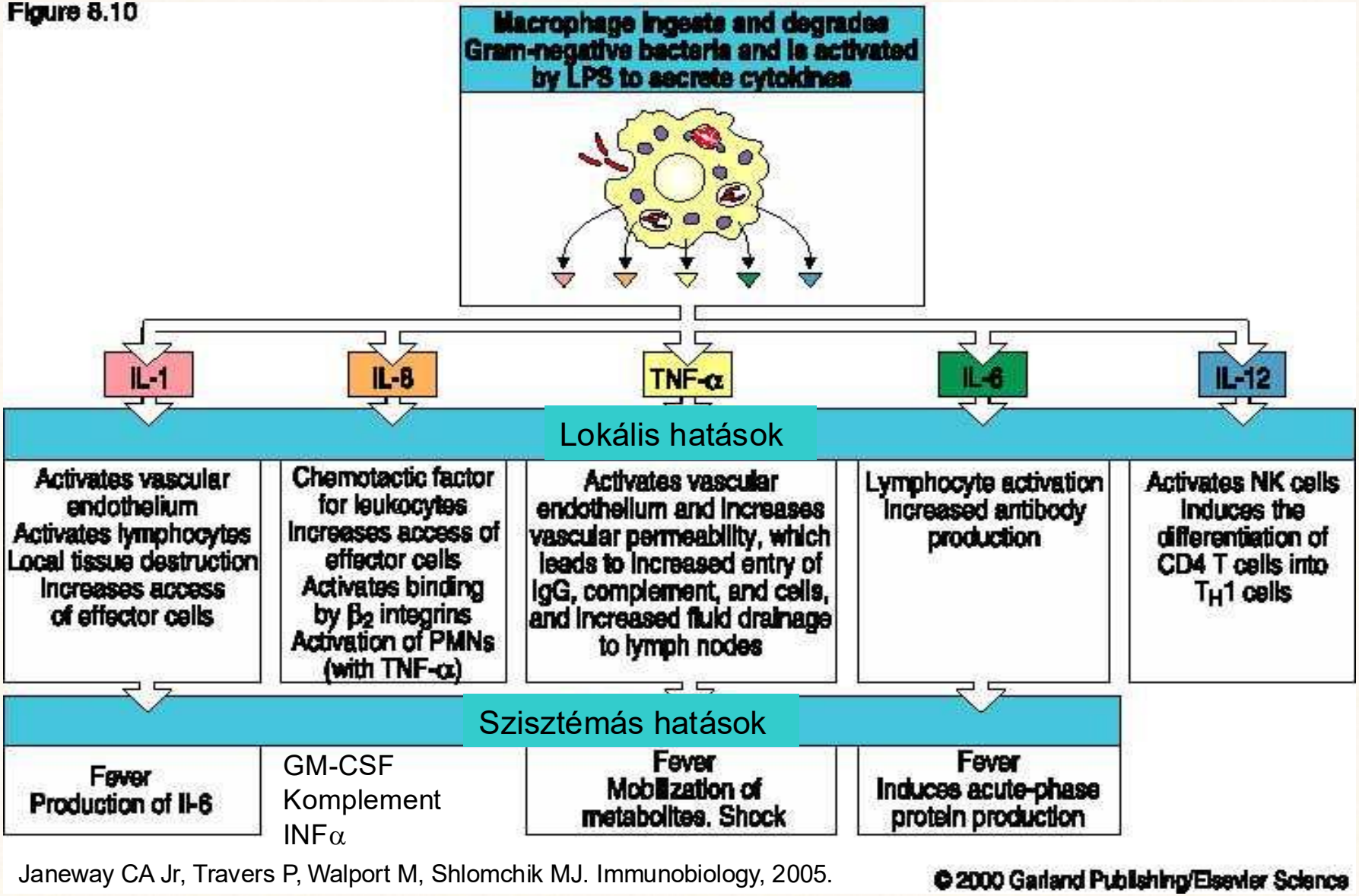
Cytokines regulating the production of the cells in the immune system



Functional groups of cytokines:

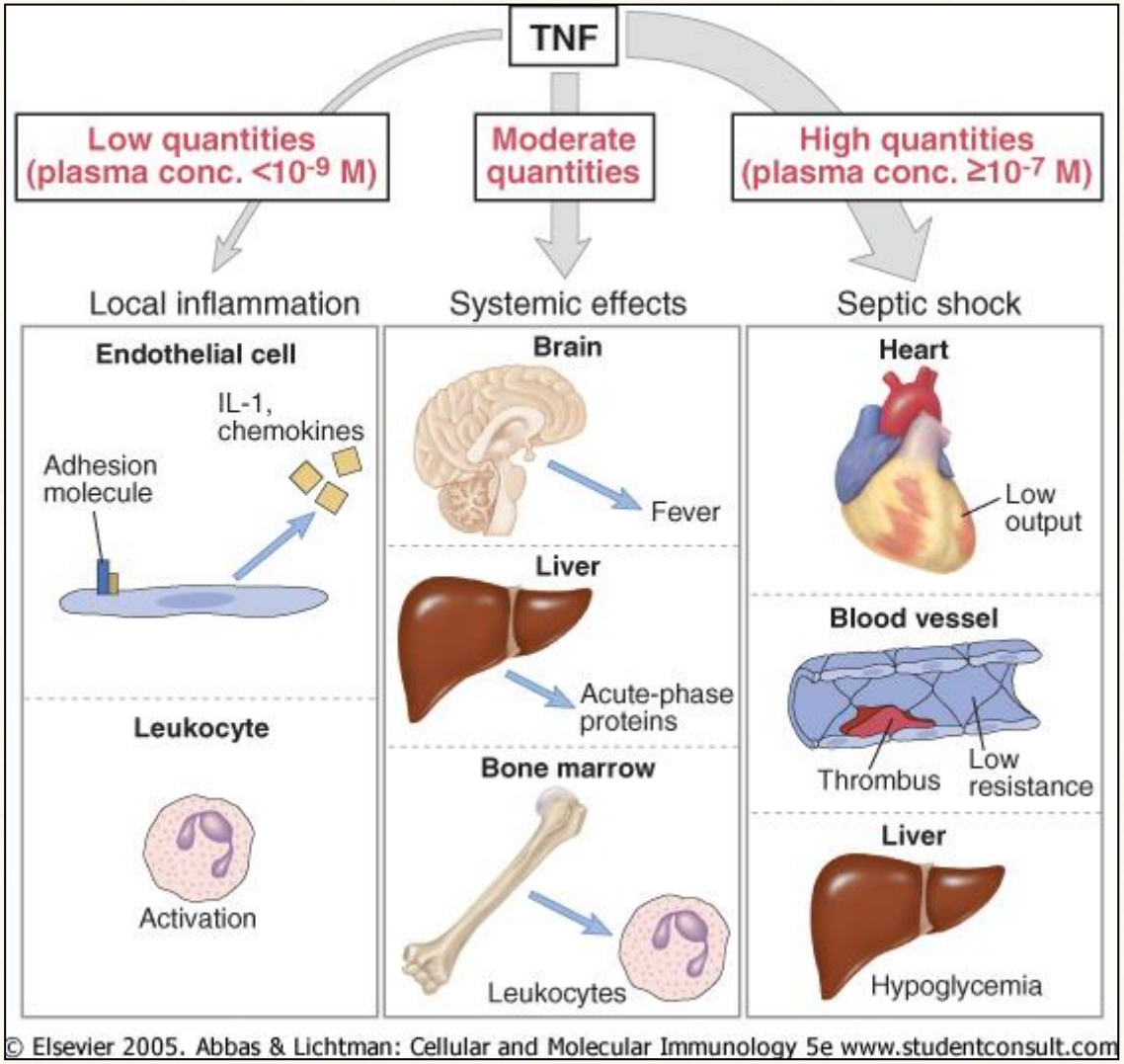
2. Inflammatory cytokines, chemokines

Role of macrophages in acute inflammation: inflammatory cytokines



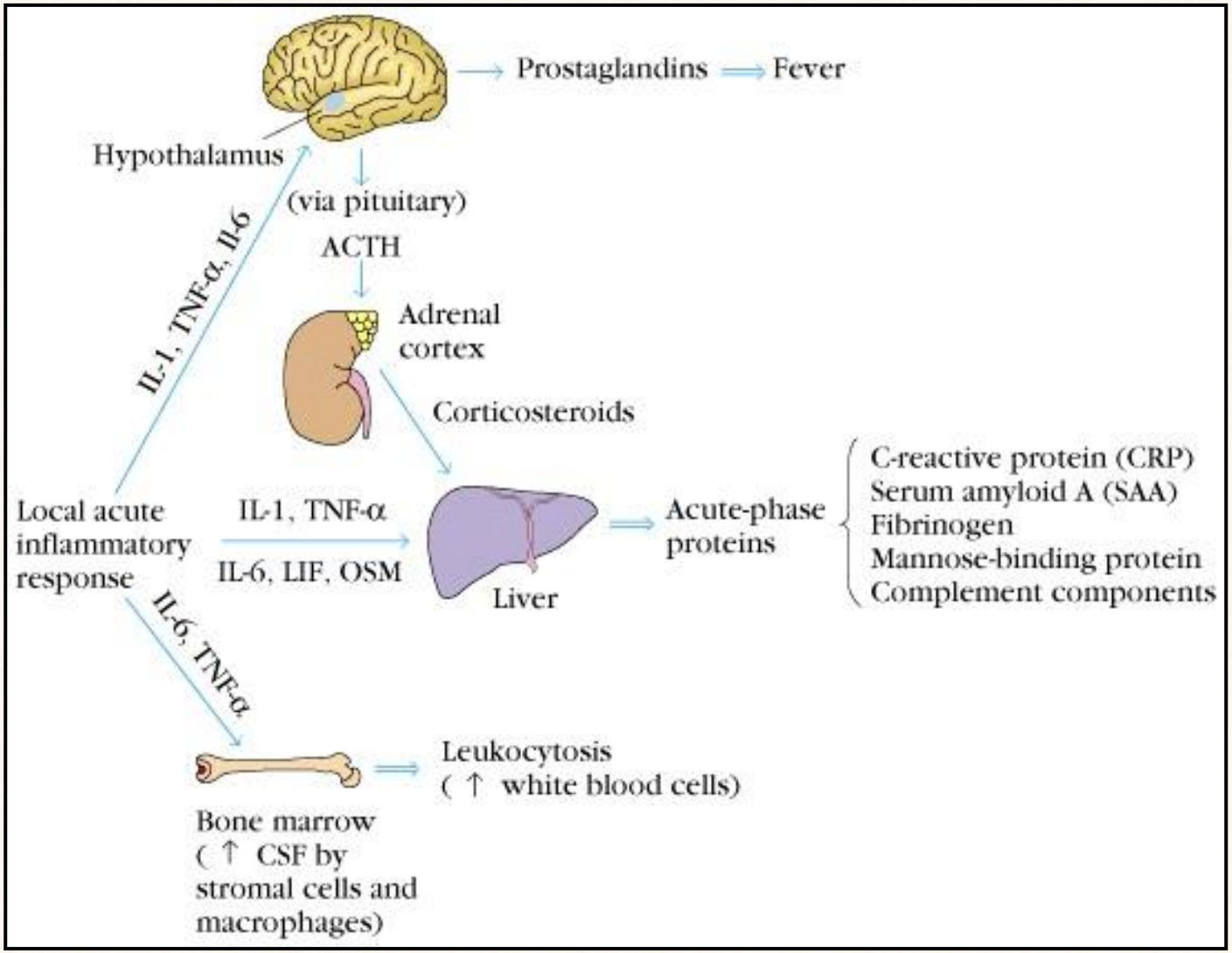
Janeway CA Jr, Travers P, Walport M, Shlomchik MJ. Immunobiology, 2005.

Concentration-dependent effects of TNF in the inflammatory reaction



Cytokine "storm" (tsunami):
Extreme overproduction of the inflammatory cytokines leads to organ damage and dysfunction.

Systemic effects of the infalmmatory cytokines

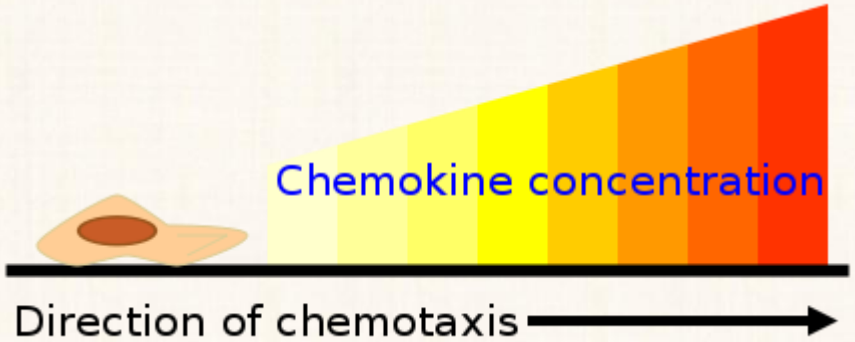


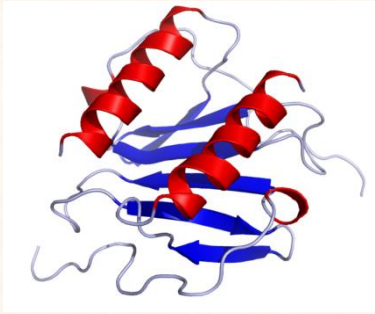
Chemokines

- Chemotactic cytokines: „attractant” molecules

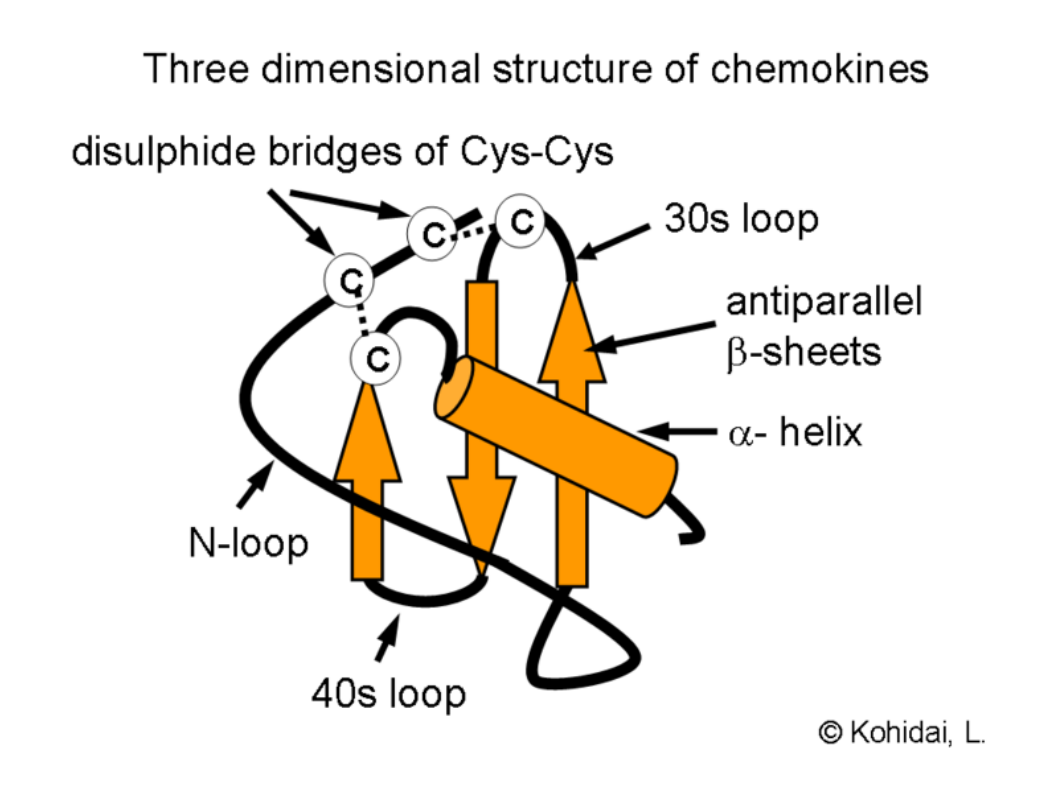
Function: Induction of chemotaxis: - migration of cells
- recruitment
- increasing adhesion

- Lymphocyte migration to the lymph nodes
- Homing of effector lymphocytes
- Migration of phagocytes to the inflammatory tissue
- Homeostatic chemokines: normal lymphatic tissue structure





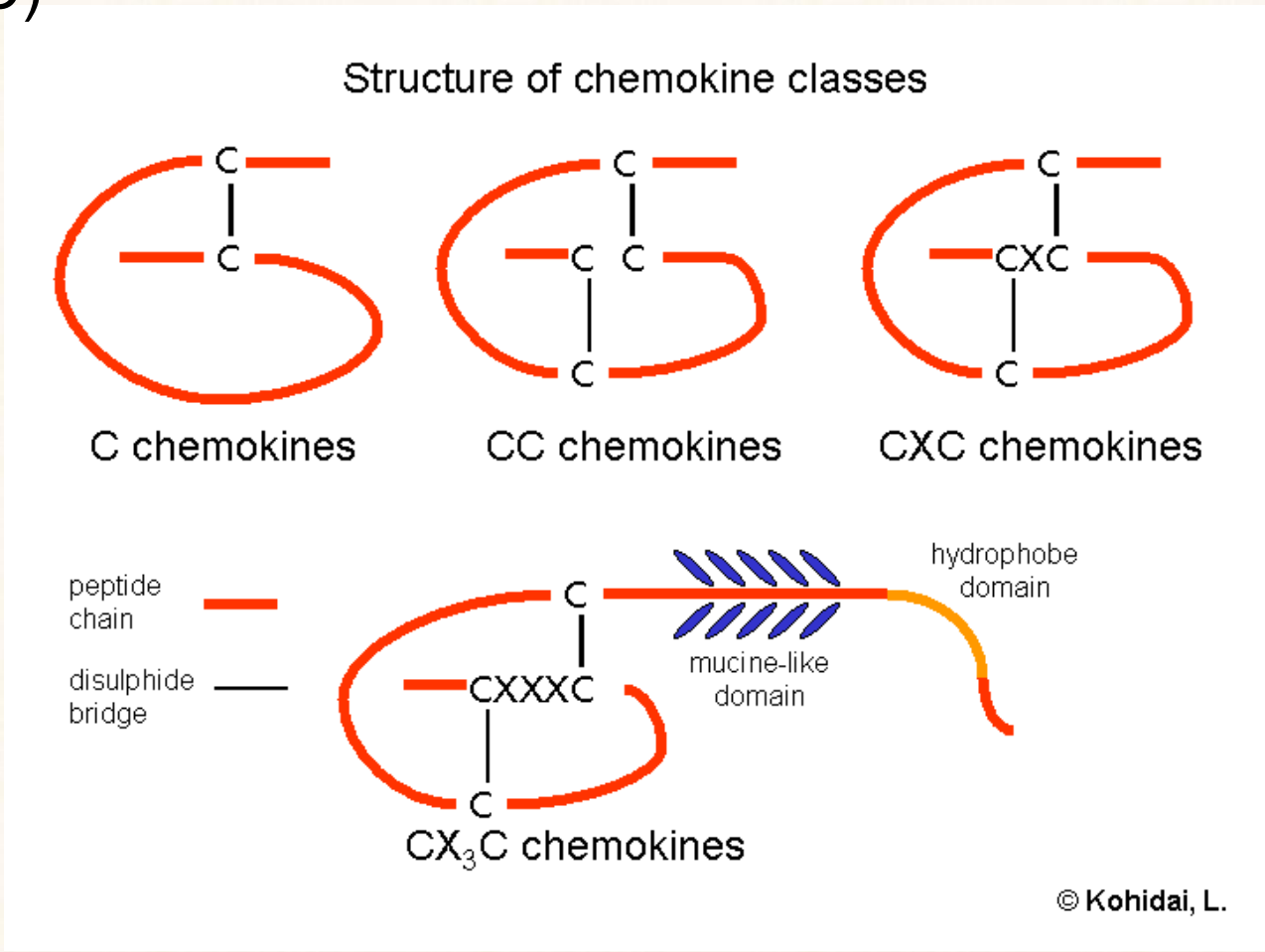
Chemokine structure



- „small cytokines”: MW: (8-10 kD)
- 4 cysteins (C) in conserved positions →
- Tertiary structure like a greek key

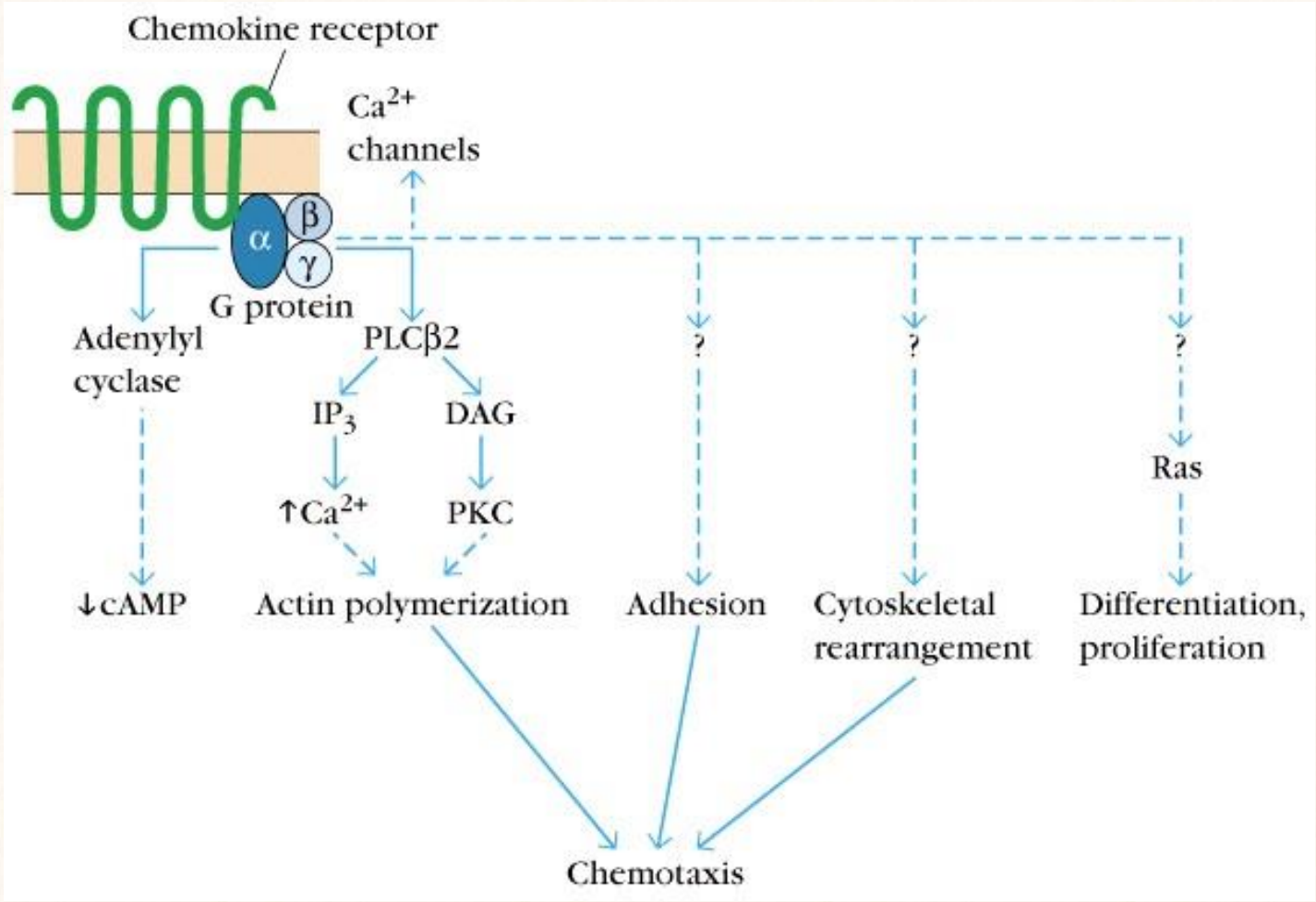
Groups based on the position of „C”:

a chemokines (CXC)
b chemokines (CC)
g, d chemokines



CXCL8(IL-8), CCL3,4 (MCP, MIF)

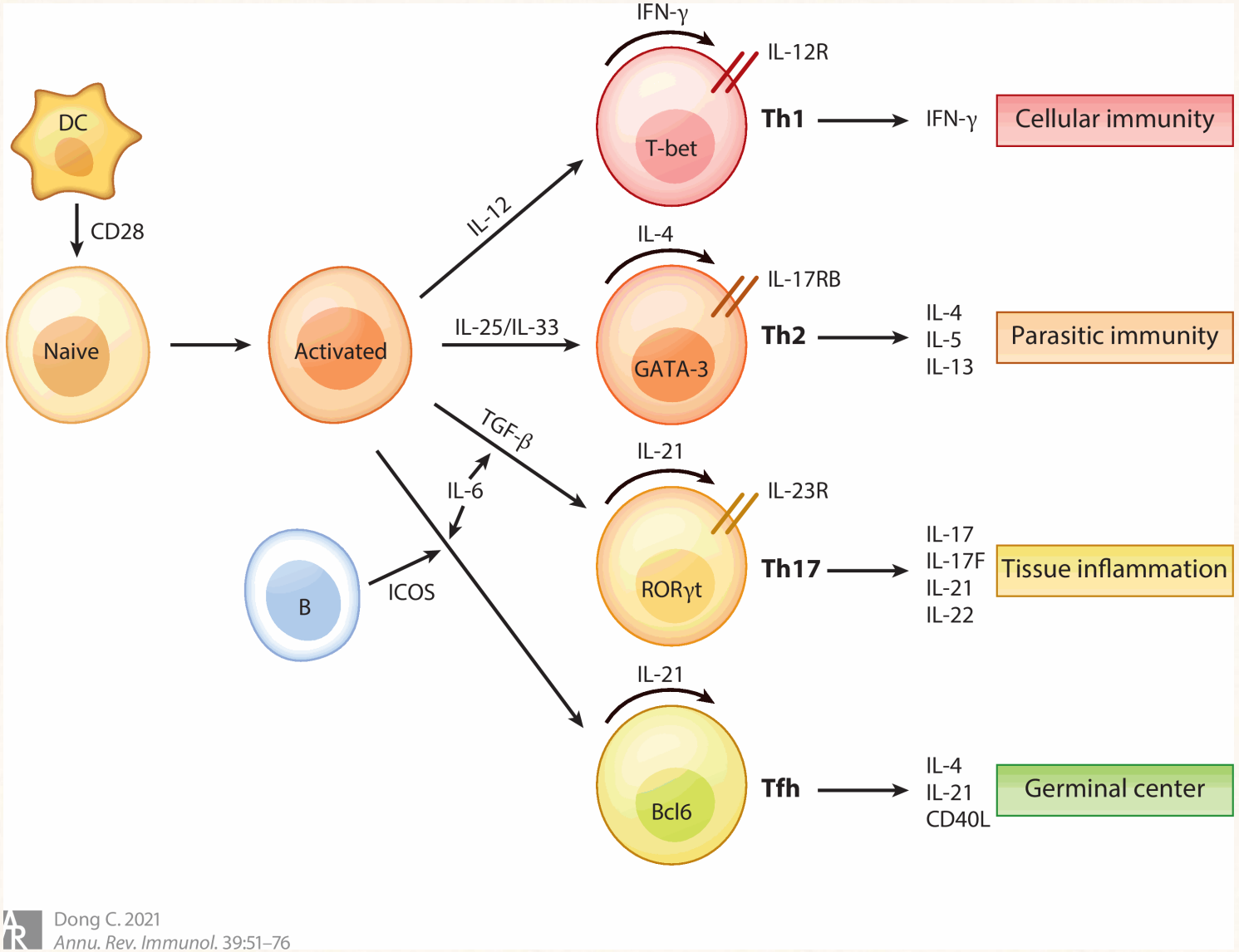
Chemokines signal through receptors coupled with G-proteins



Functional groups of cytokines:

3. Cytokines regulating the specific immune response

T helper cell polarization



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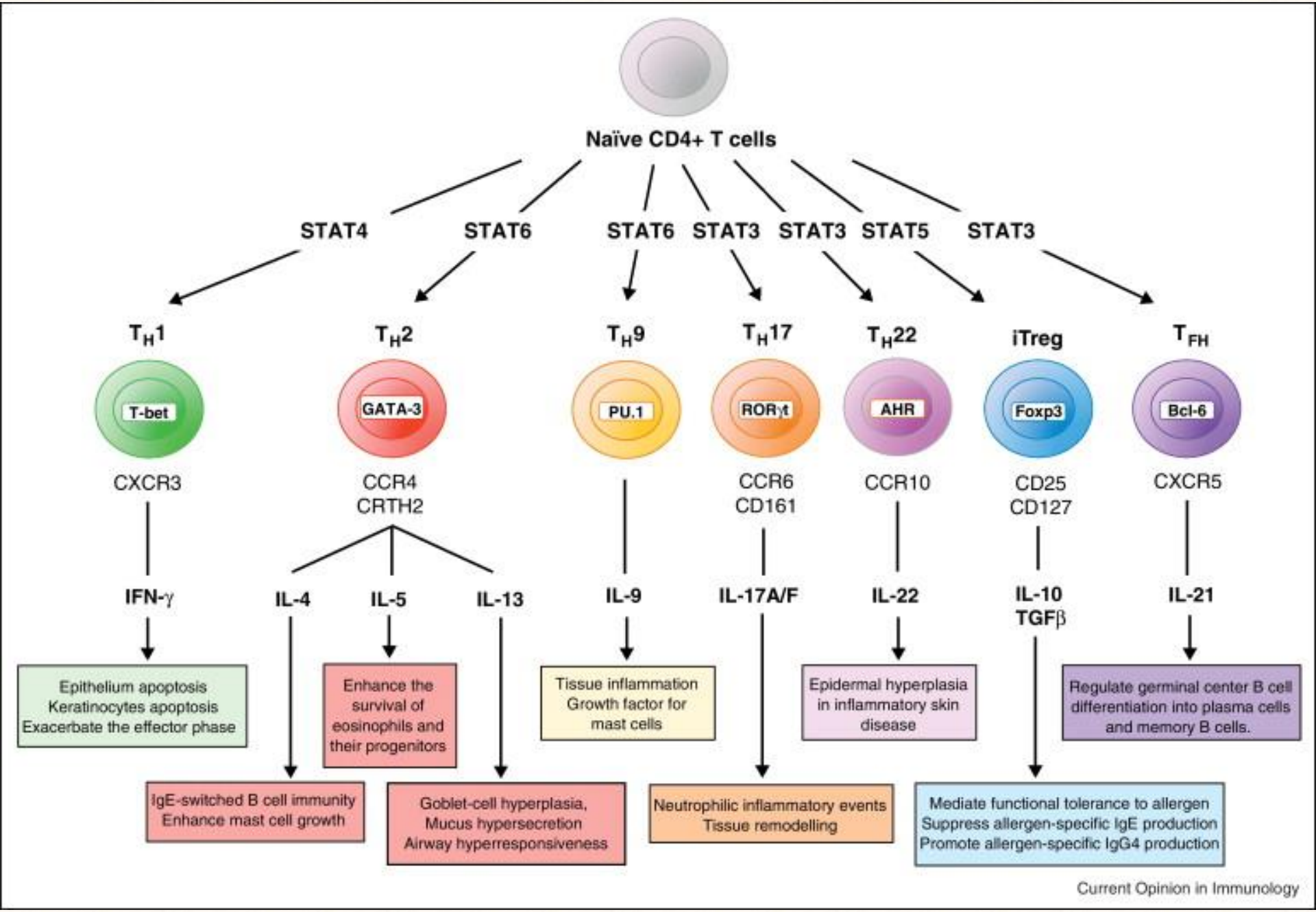
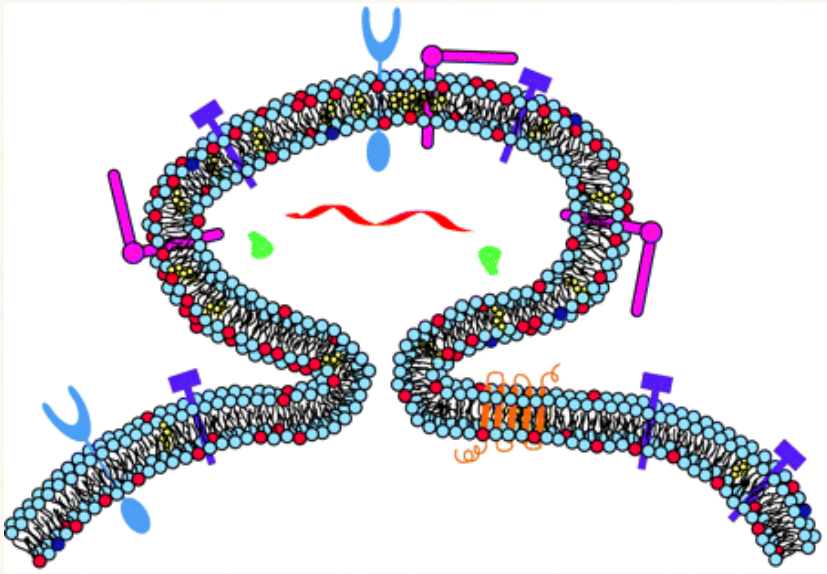
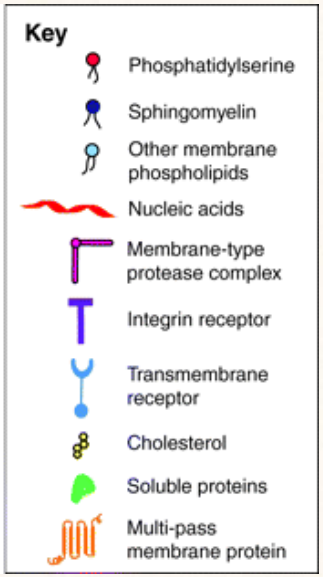
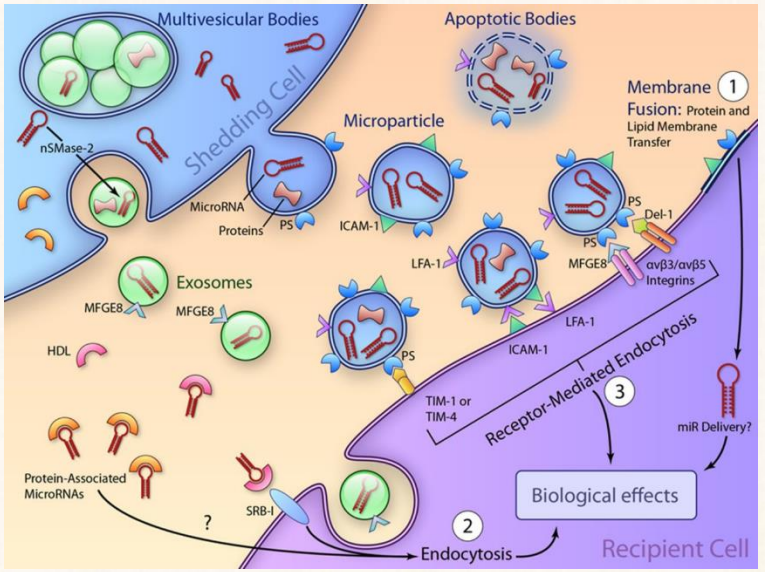
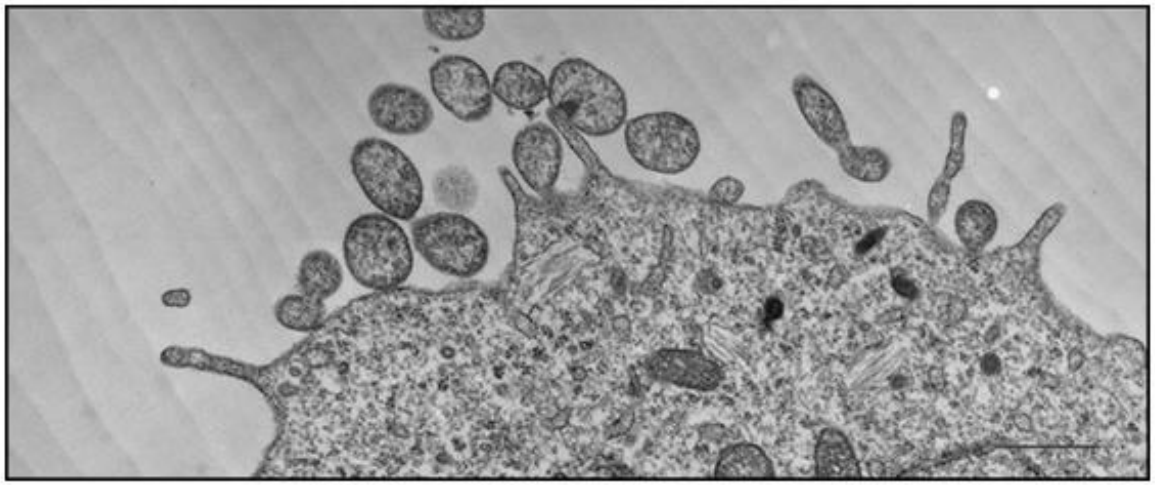

Naïve CD4+ T cells
STAT4
STAT6
STAT6
STAT3
STAT3
STAT5
STAT3
T_H1
T_H2
T_H9
T_H17
T_H22
iTreg
T_{FH}
T-bet
GATA-3
PU.1
RORγt
AHR
Foxp3
Bcl-6
CXCR3
CCR4
CRTH2
CCR6
CD161
CCR10
CD25
CD127
CXCR5
IFN-γ
IL-4
IL-5
IL-13
IL-9
IL-17A/F
IL-22
IL-10
TGFβ
IL-21
Epithelium apoptosis
Keratinocytes apoptosis
Exacerbate the effector phase
IgE-switched B cell immunity
Enhance mast cell growth
Enhance the survival of eosinophils and their progenitors
Goblet-cell hyperplasia,
Mucus hypersecretion
Airway hyperresponsiveness
Tissue inflammation
Growth factor for mast cells
Neutrophilic inflammatory events
Tissue remodelling
Epidermal hyperplasia in inflammatory skin disease
Mediate functional tolerance to allergen
Suppress allergen-specific IgE production
Promote allergen-specific IgG4 production
Regulate germinal center B cell differentiation into plasma cells and memory B cells.
Current Opinion in Immunology

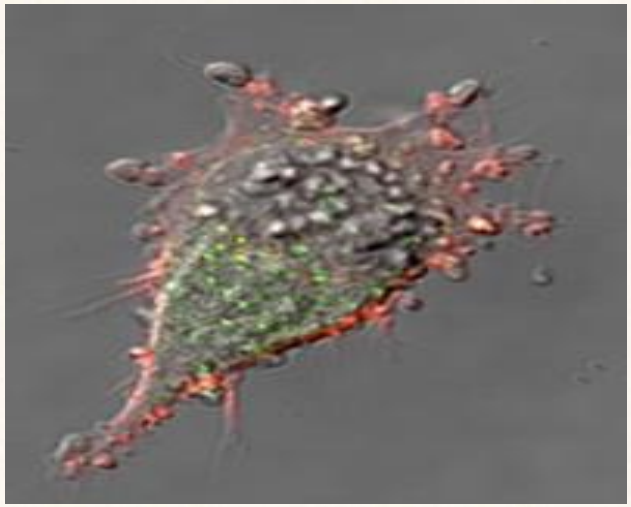
Microvesicles



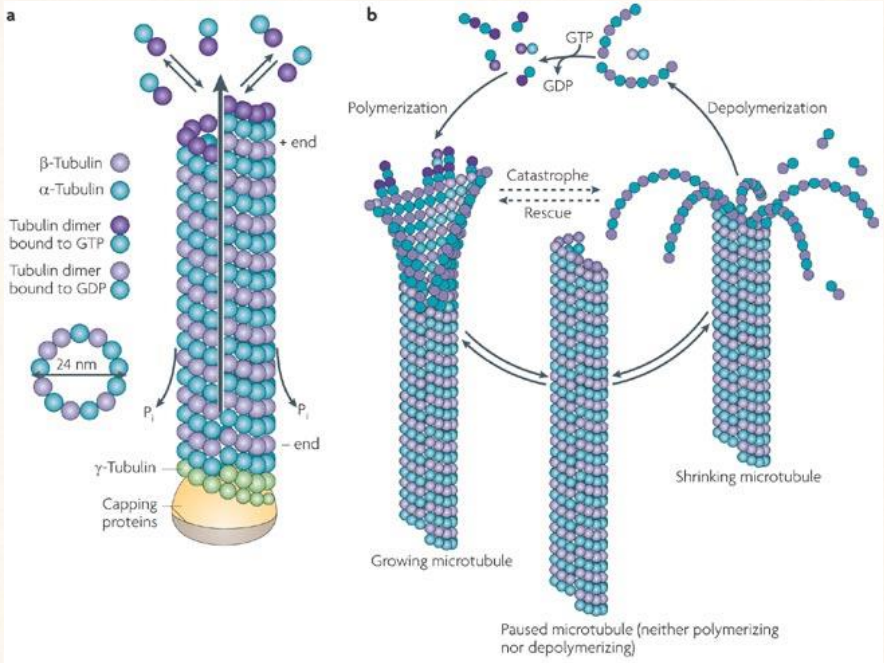








Microtubules



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Direct cell-cell communication?