

Basic Immunology

Lecture 7th - 8th

Communication between cellular components of the immune system

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

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.

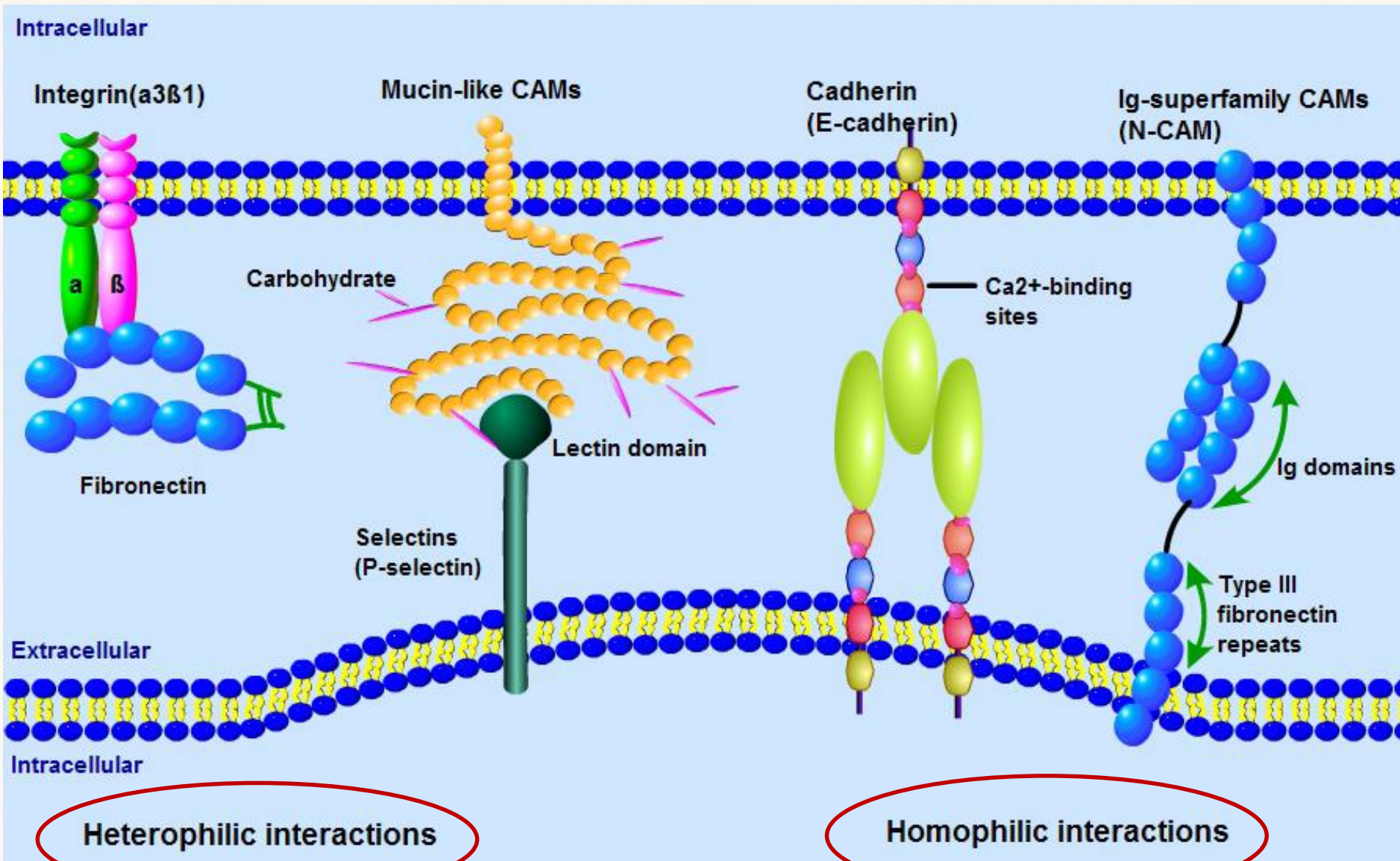
Leukocytes express various types of adhesion molecules, such as **selectins**, **integrins**, and members of the **Ig superfamily**, and these molecules play crucial role in cell migration and cellular activation both in innate and adaptive immune response.

Adhéziós molekulák

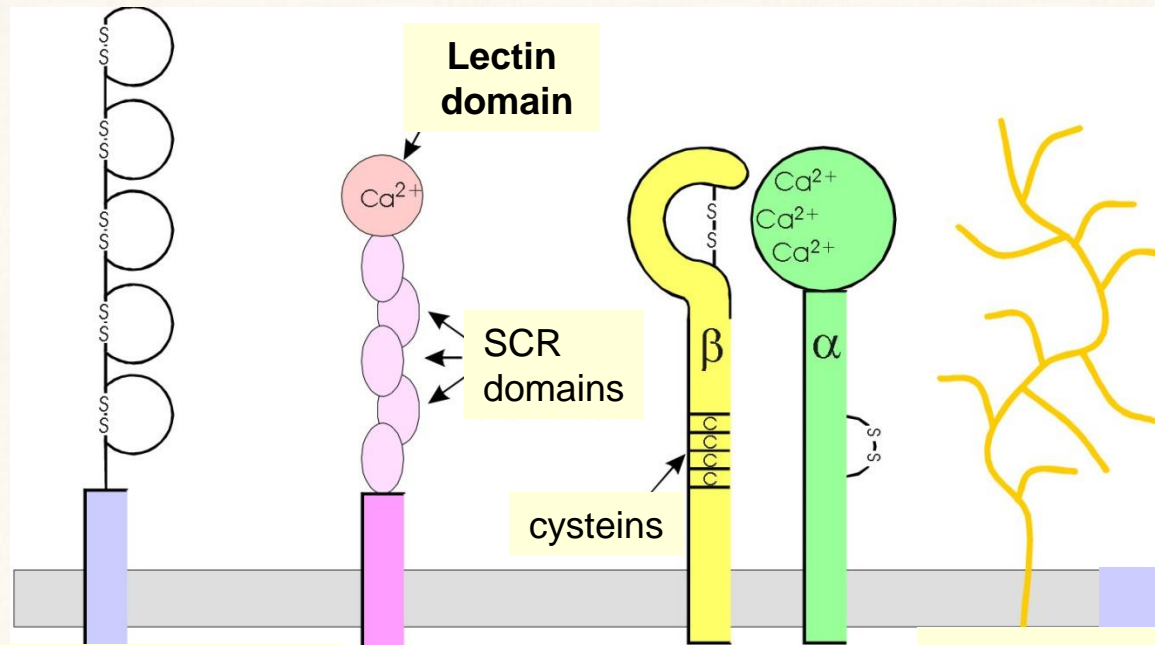
Sejtfelszíni molekulák, amelyek feladata a más sejtekkel vagy az extracelluláris mátrixszal való adhéziós kölcsönhatások elősegítése és a jelátvitel elindítása.

A leukociták különböző típusú adhéziós molekulákat, például **szelektineket**, **integrineket** és az **Ig supercsalád** tagjait expresszálnak, és ezek a molekulák döntő szerepet játszanak a sejt migrációban és a sejtaktivációban mind a veleszületett, mind az adaptív immunválaszban.

Types of cell adhesion molecules



Families of adhesion molecules



Ig-superfamily members

Selectins

Integrins

Mucin-like molecules

**„other”
accessory molecules**

CD2

CD4

CD8

B7

CD28

CTLA 4

ICAM

L selectin

E selectin

P selectin

VLA

LFA

Mac1

„vascular
addressins”

CD45

CD44

CD40, CD40L

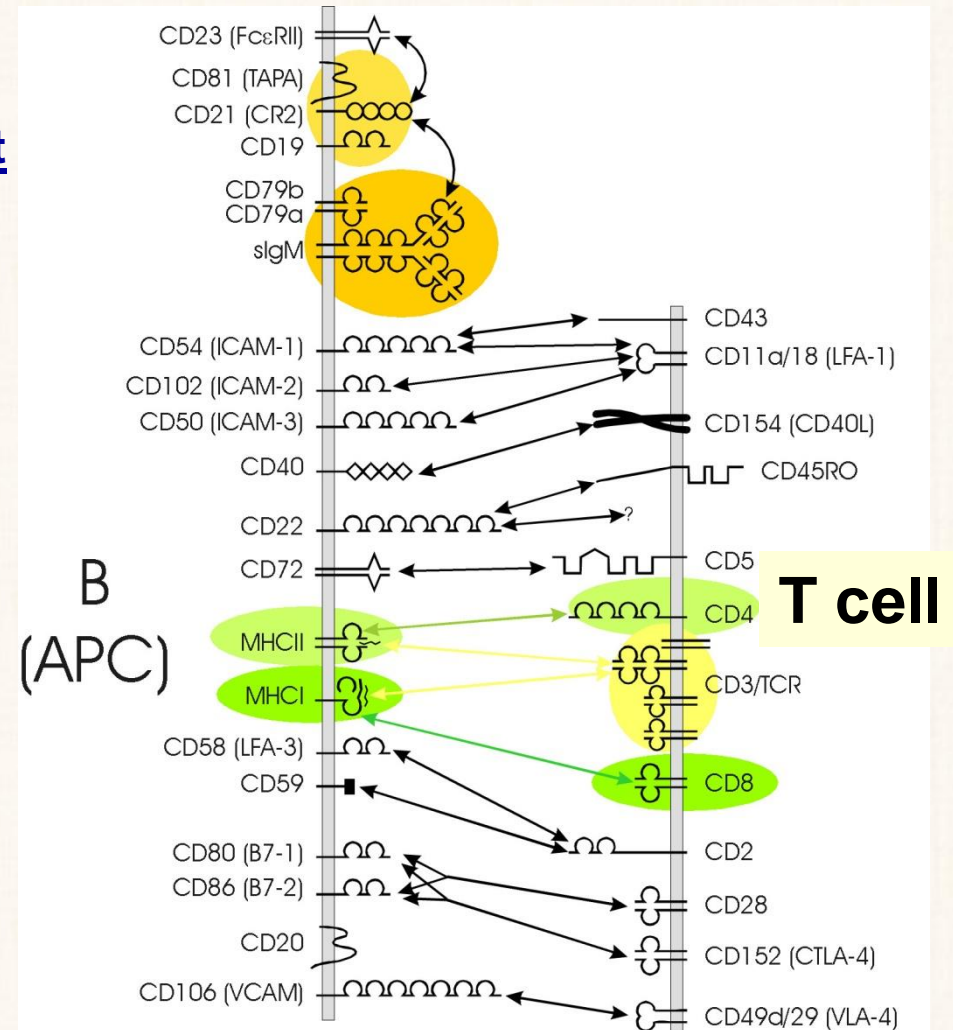
CD19/CD21/CD81

CD22

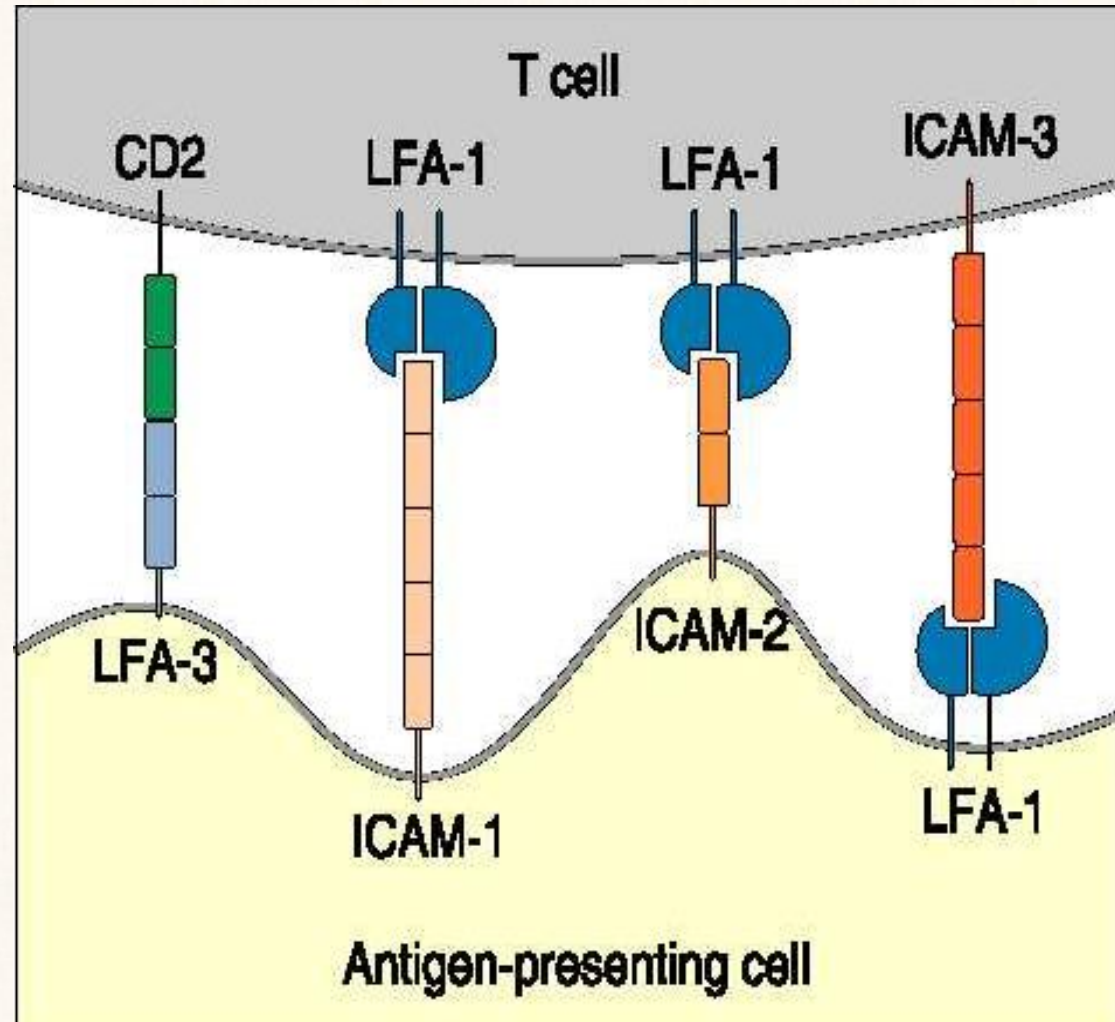
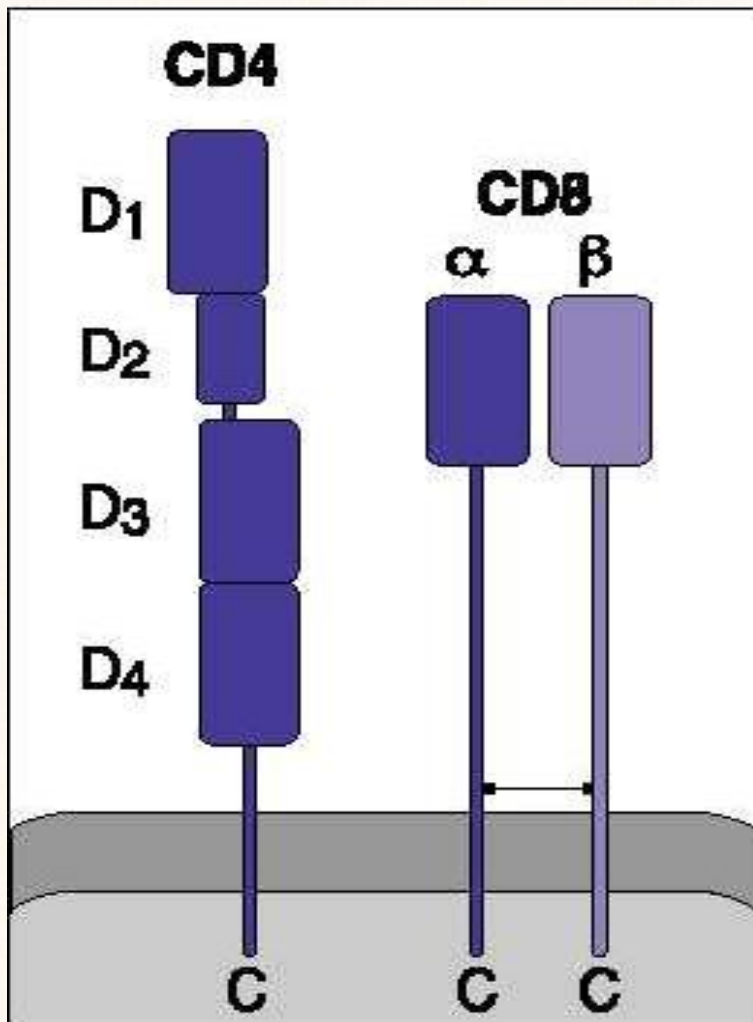
Family of accessory molecules, adhesion molecules, co-receptors

Common characteristics:

1. Molecules, responsible for the direct interaction 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

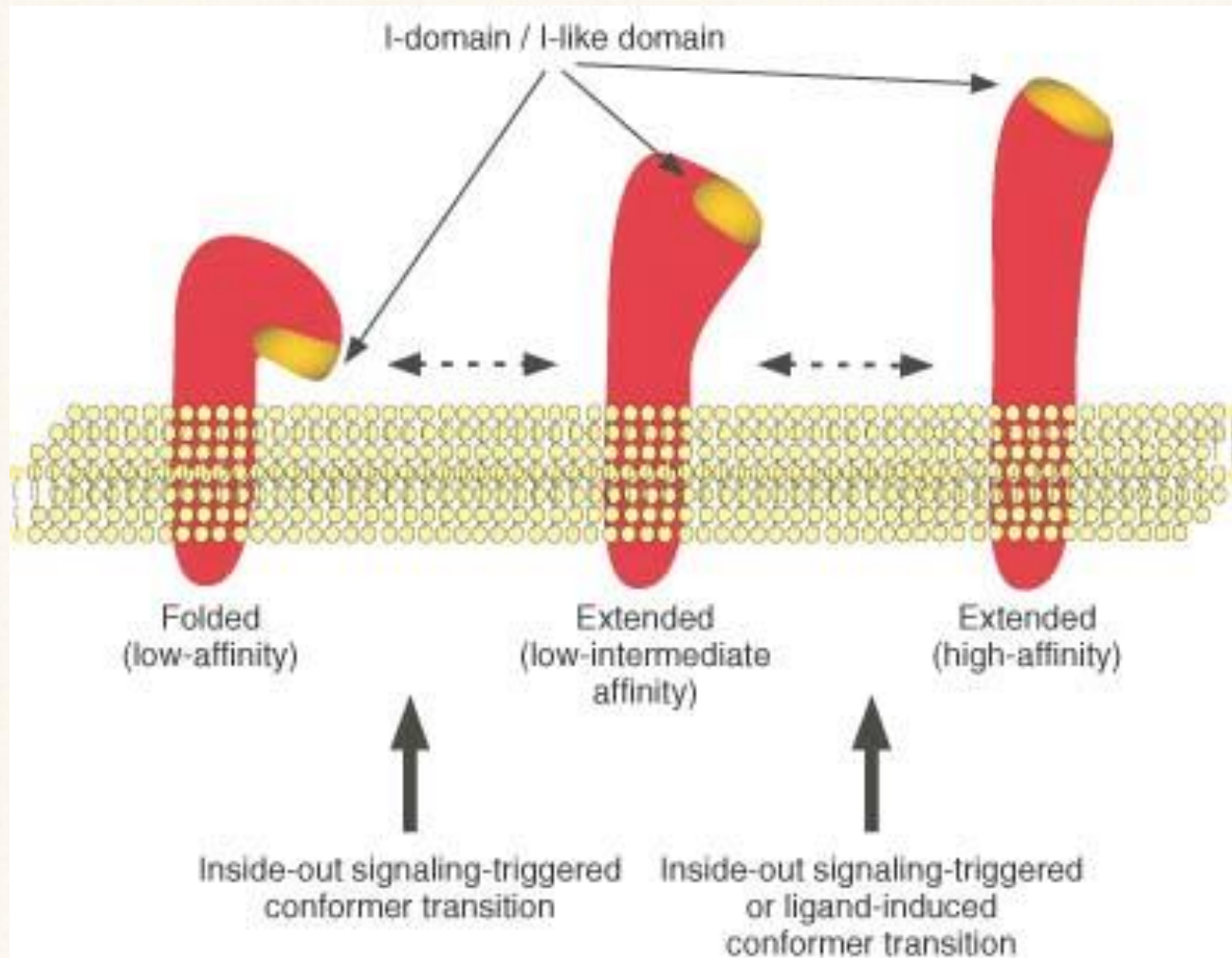


Accessory molecules on T cells

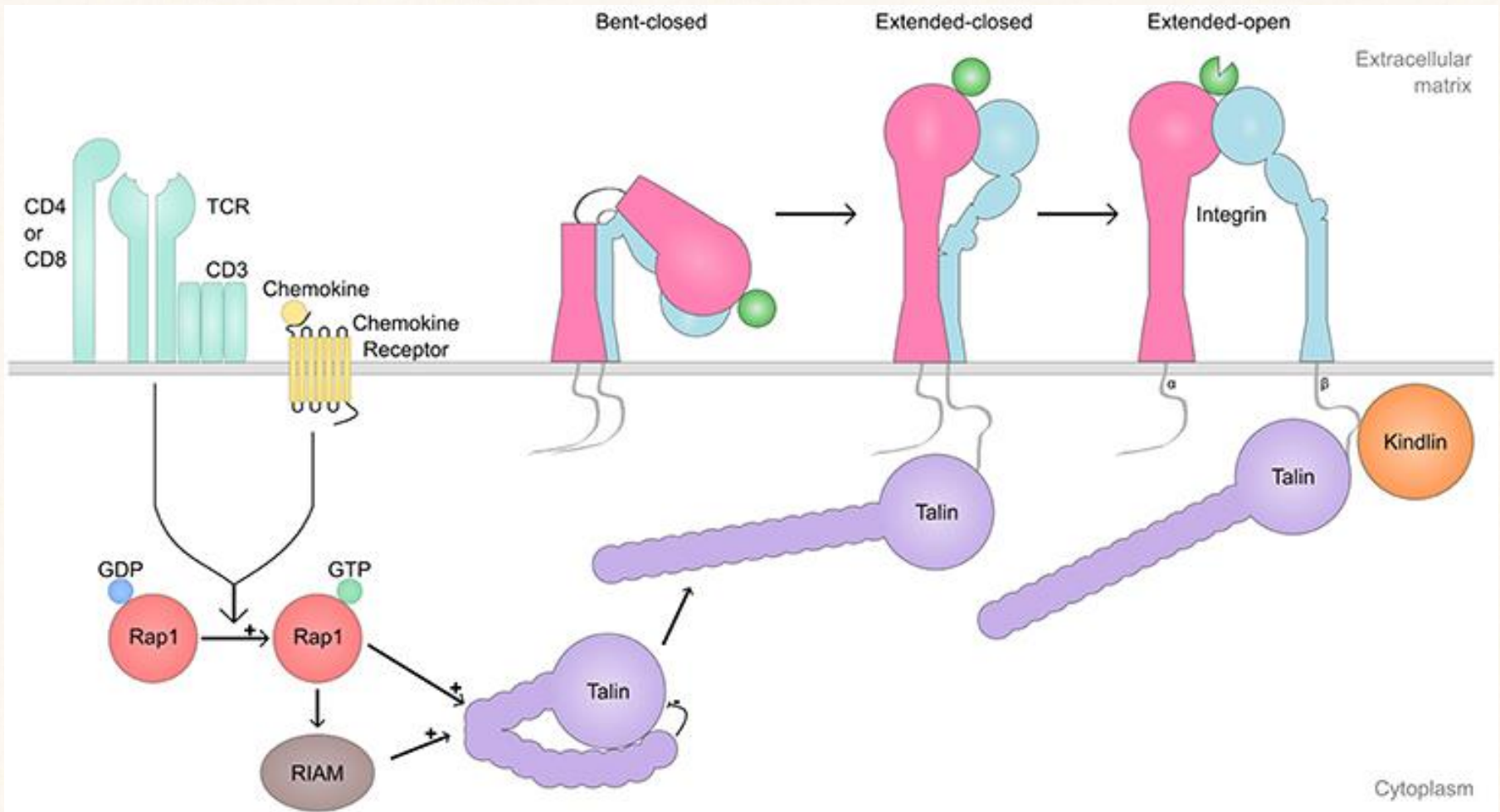


Activation of adhesion molecules

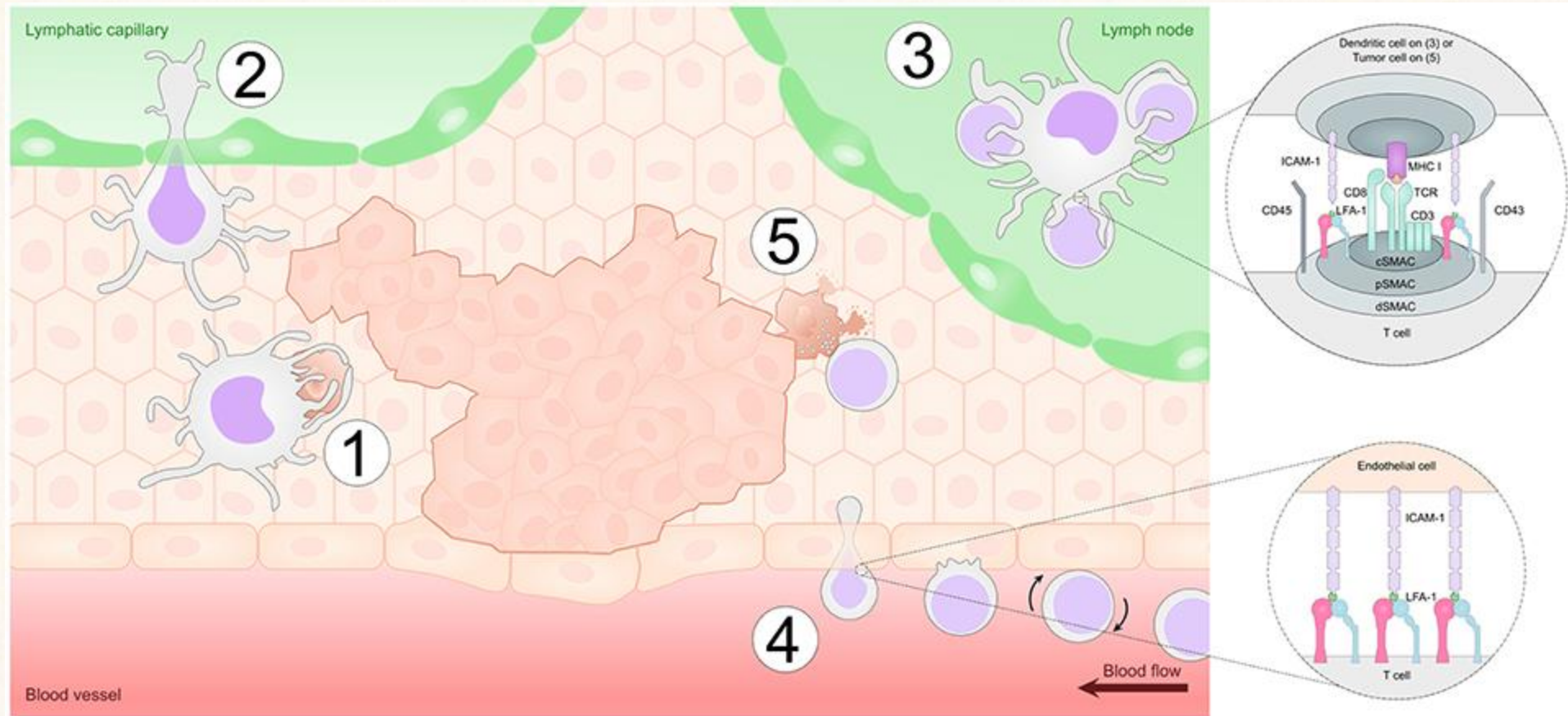
- Lymphocyte **F**unction-associated **A**ntigen
- Intra**C**ellular **A**dhesion **M**olecule



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.



Dendritic cells (DCs) take up tumor antigens in the tumor (Step 1). DCs then enter the lymphatic vessels partly in an LFA-1/ICAM-1-dependent manner and migrate to the draining lymph node (Step 2). DCs present the tumor antigen. LFA-1-ICAM interactions provide an additional co-stimulatory signal to the T cells (Step 3). Activated, T cells travel via the blood stream (Step 4). Finally, after reaching the tumor microenvironment, CD8+ T cells form an immunological synapse with tumor cells and kill the malignant cells via the release of cytotoxic granules (Step 5).

Ig-superfamily member CD2

CD2

„sheep red-blood cell receptor”

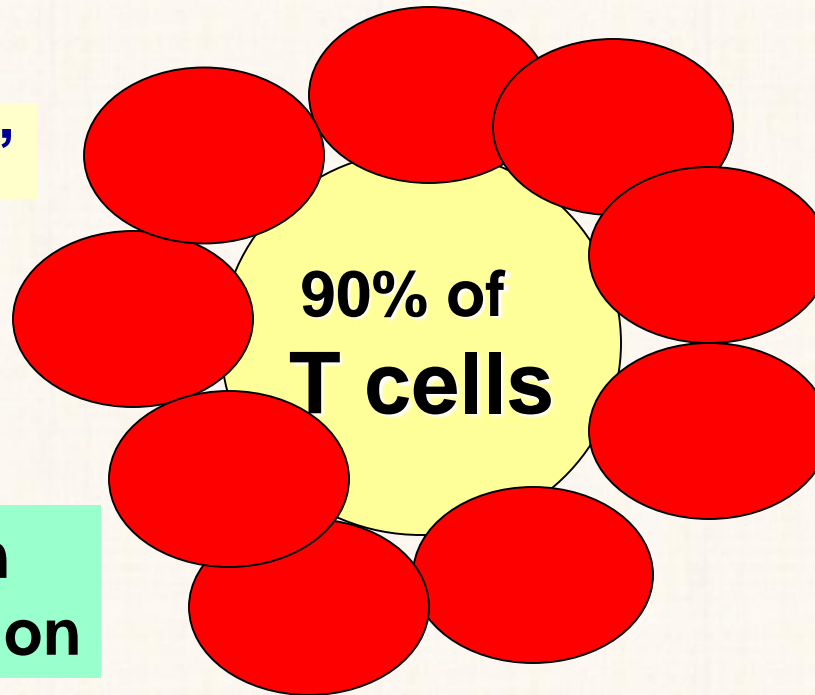


Binds to CD58

(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

Differentiation markers: CD4 - MHCII

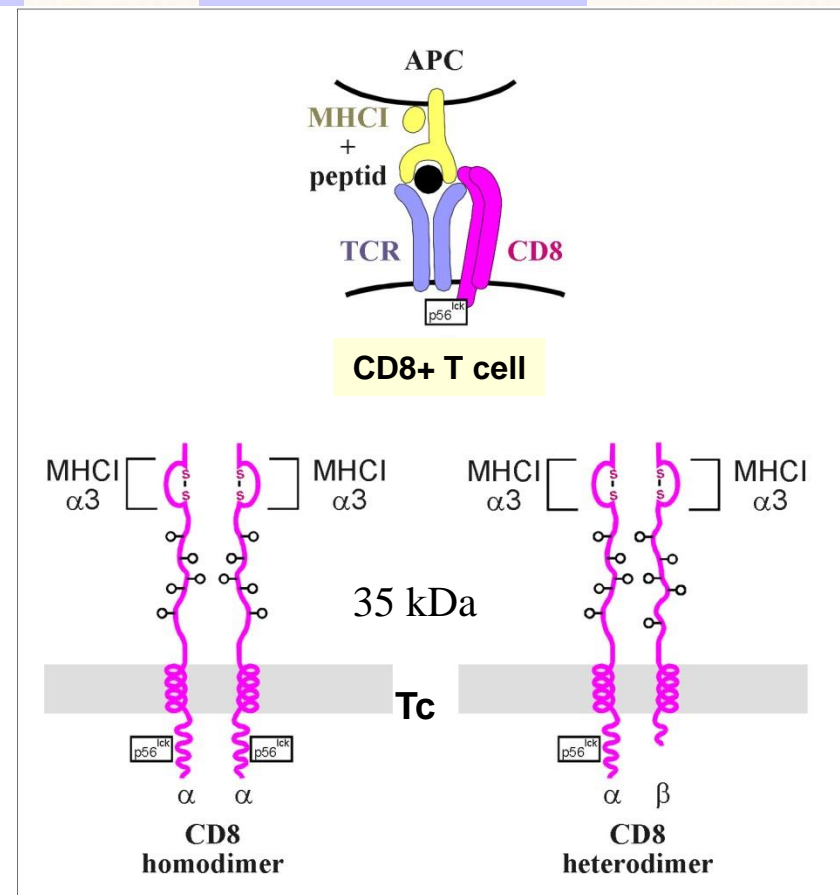
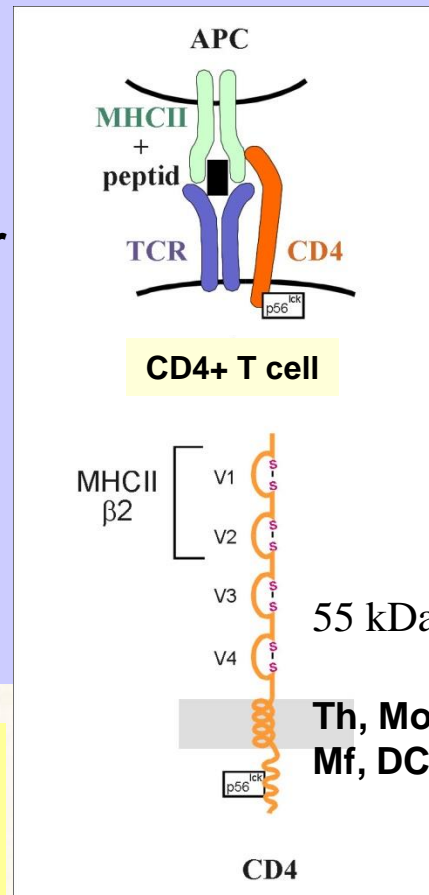
At different stages of T cell maturation

CD4 and CD8 together „double positive” in thymus

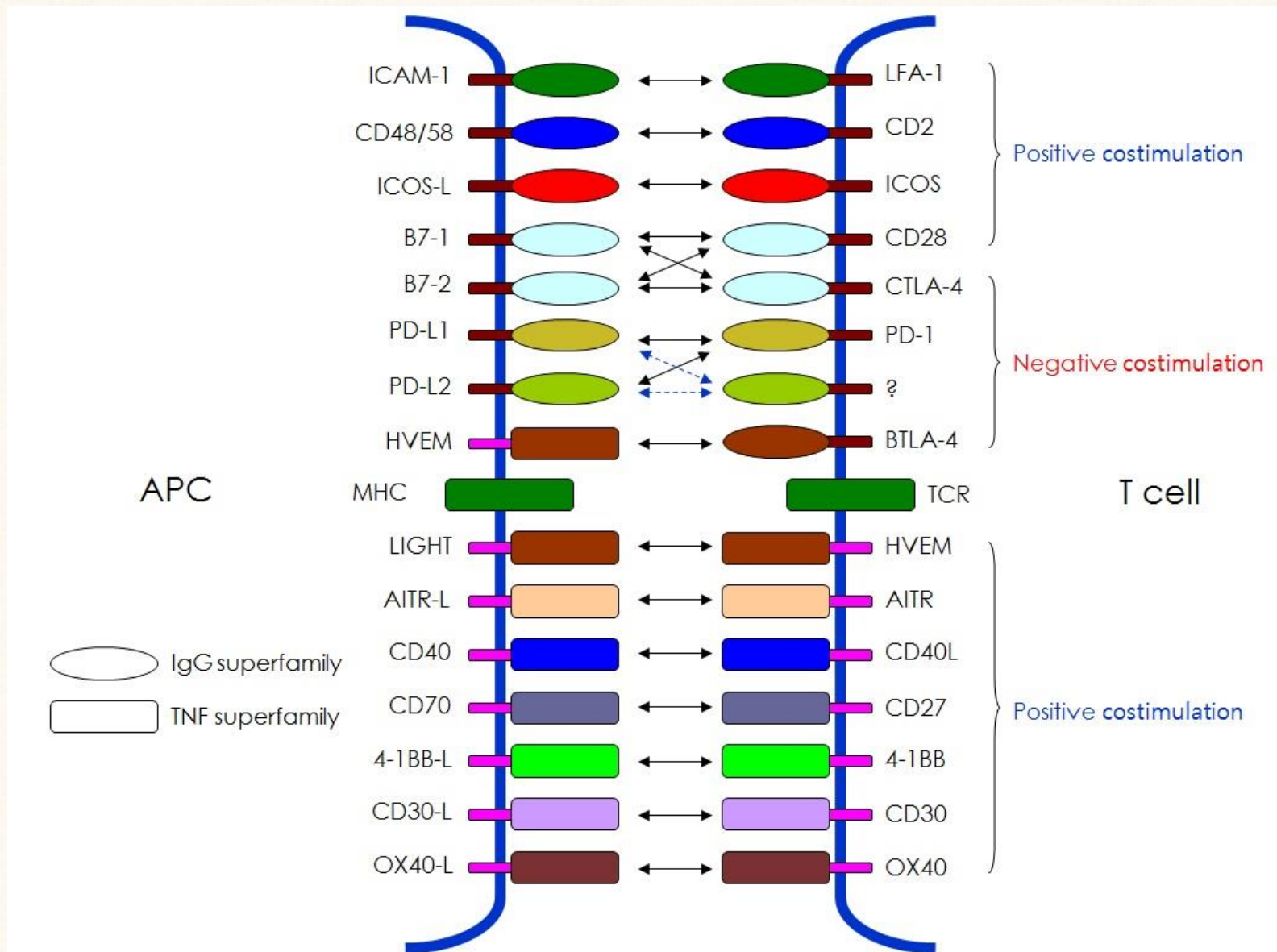
At the periphery:
„single positive”
T helper: CD4
T cytotoxic: CD8

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

CD8 - MHCI



Co-stimulatory molecules in APCs and T cells



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

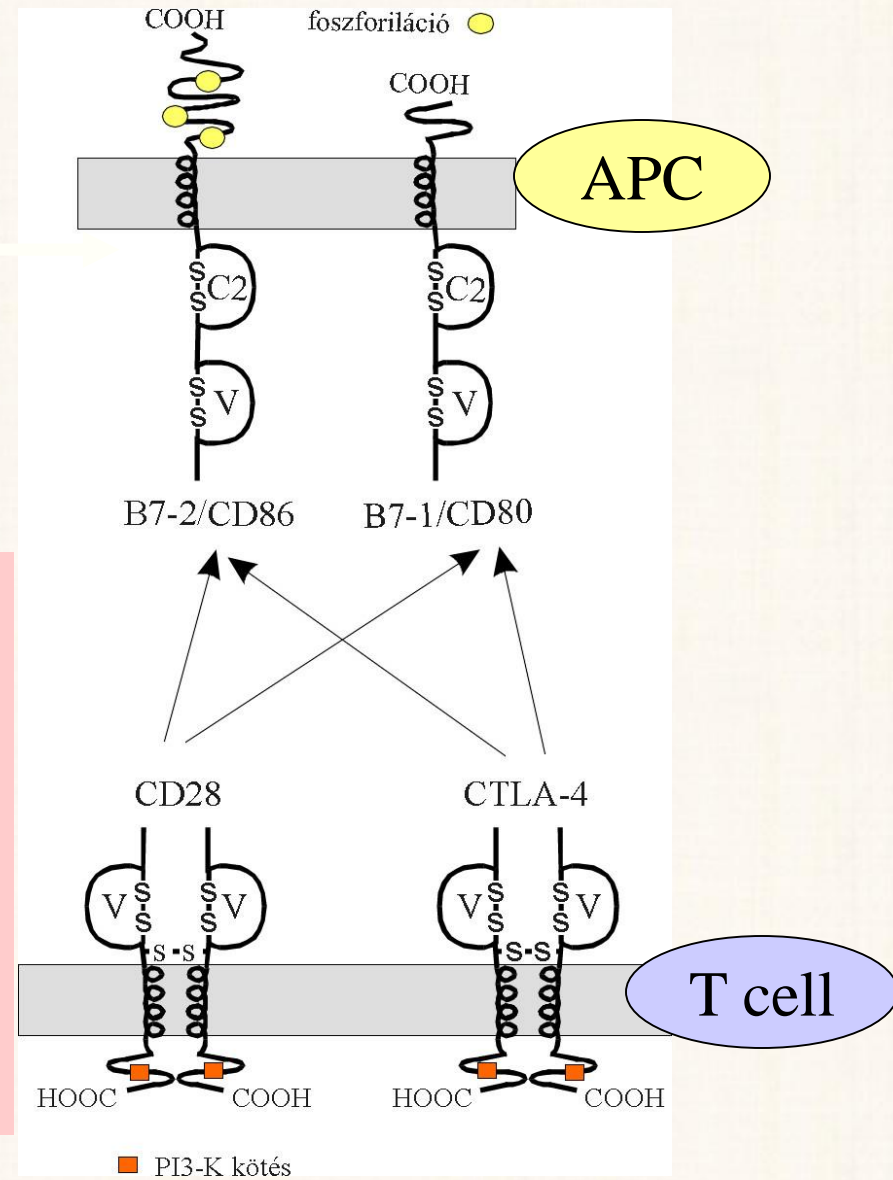
CD28 and CTLA-4 of T cells bind to the **B7-1** (CD80), **B7-2** (CD86) molecules of the APC

CD28: - co-stimulatory molecule in T cell activation

- Increases IL-2 and IL-2R expression,
- Induces T cell proliferation

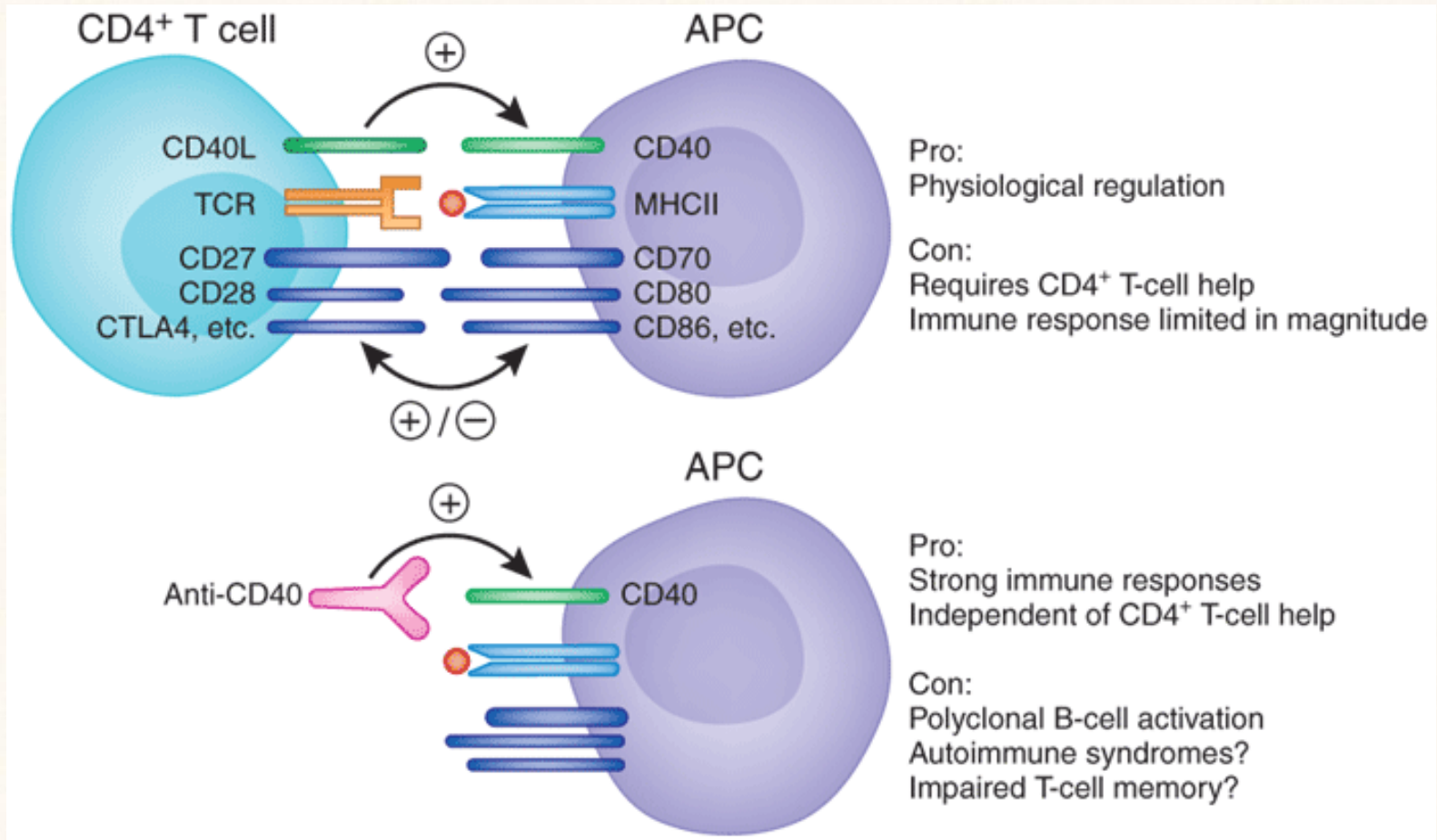
CTLA-4 (CD152): - expressed in a later phase of the T cell activation

- inhibitory function



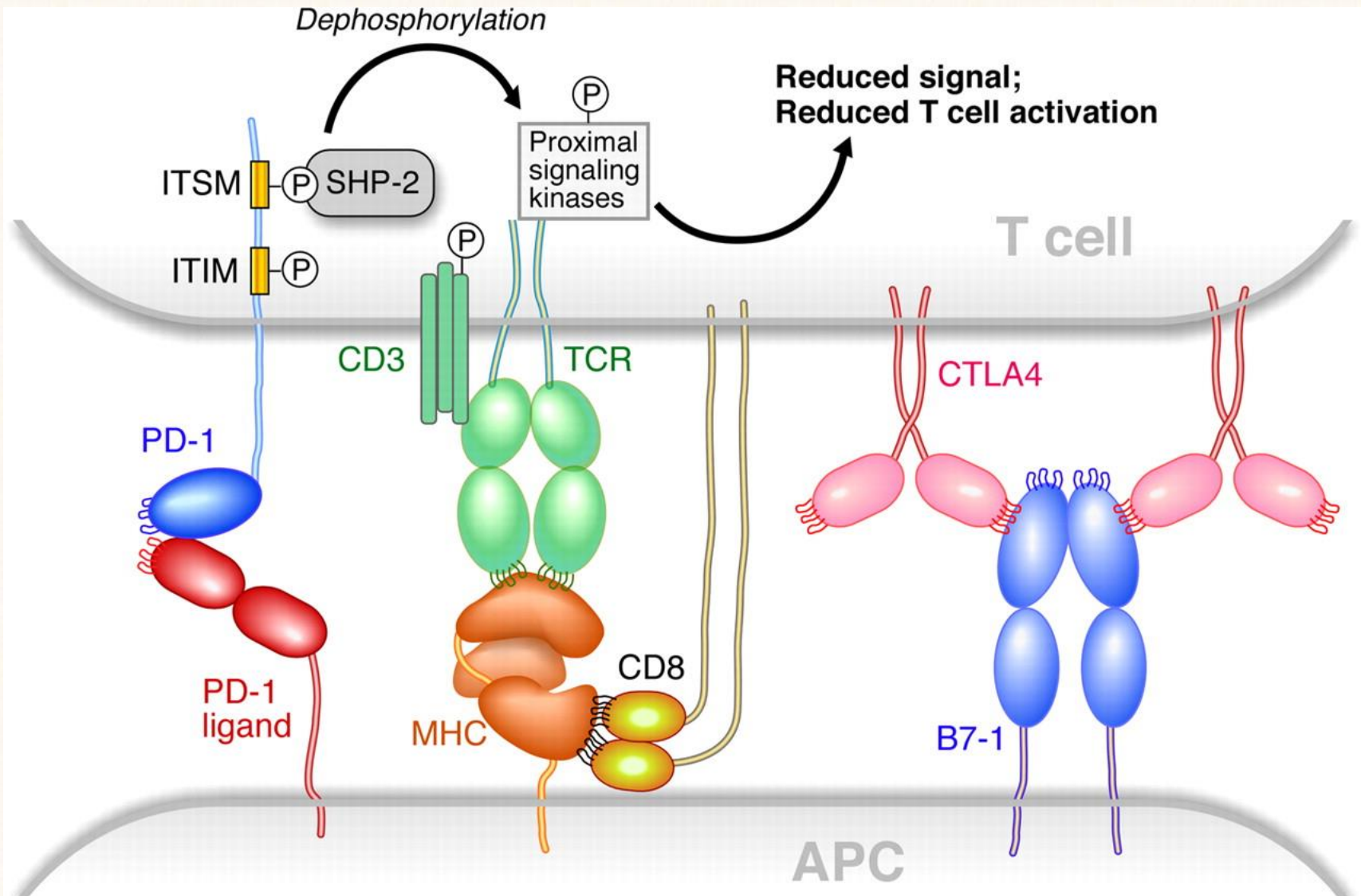
CTLA: Cytolytic T lymphocyte associated Antigen

CD40 and CD40L

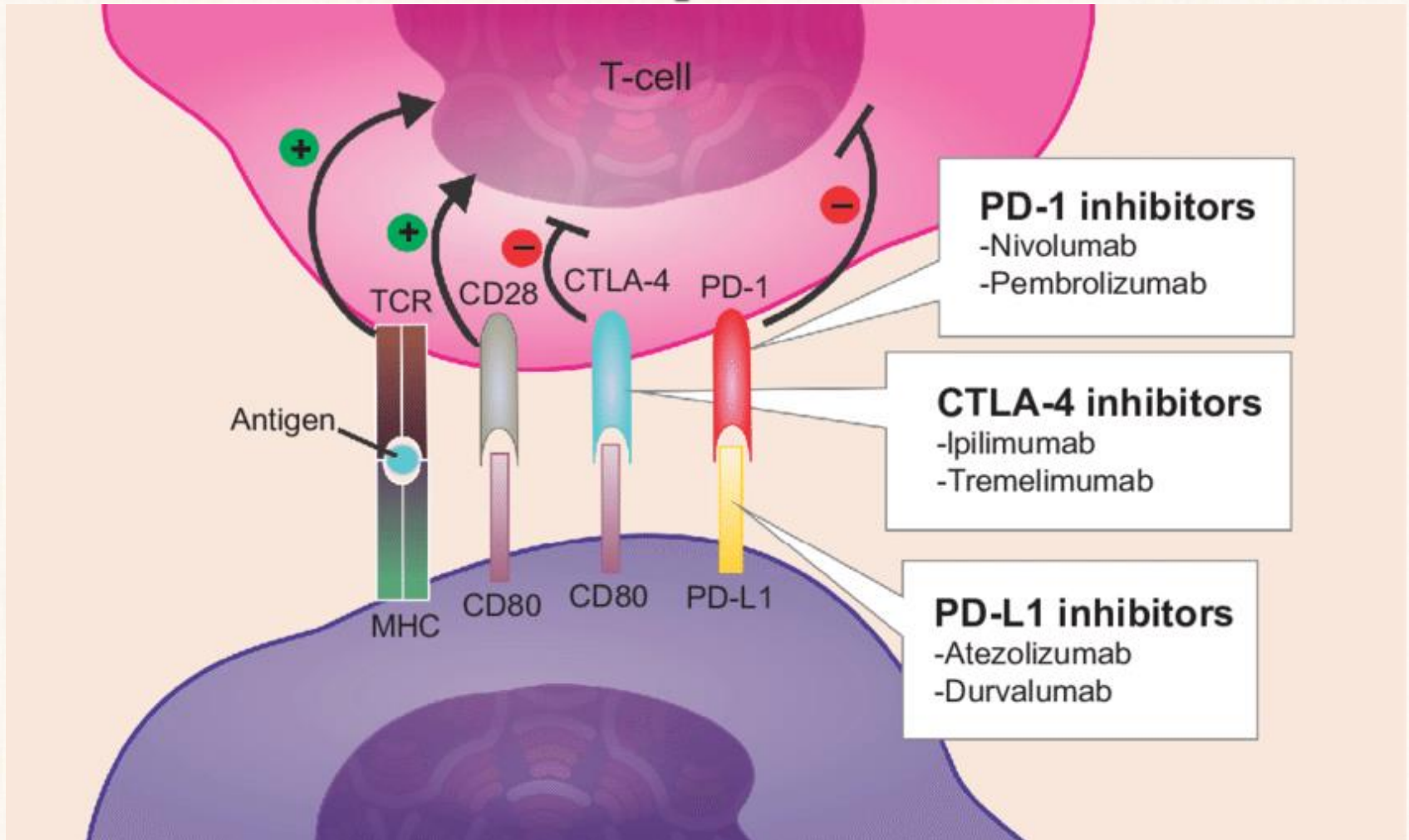


CD40 is a costimulatory protein found on antigen presenting cells and is required for their activation. The binding of CD154 (CD40L) on TH cells to CD40 activates antigen presenting cells and induces a variety of downstream effects

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.

„OTHER” accessory molecules

CD45

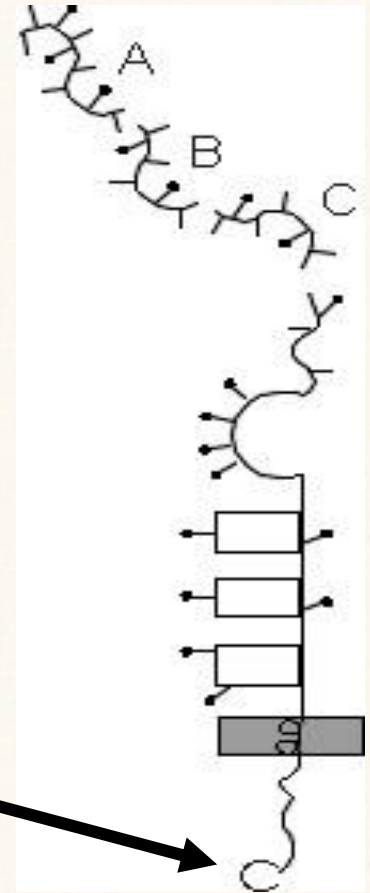
Expressed on every leukocyte

“pan-leukocyte marker”

- Highly glycosylated,
- More isoforms (180, 190, 200, 205, 220 kDa)
- alternate splicing

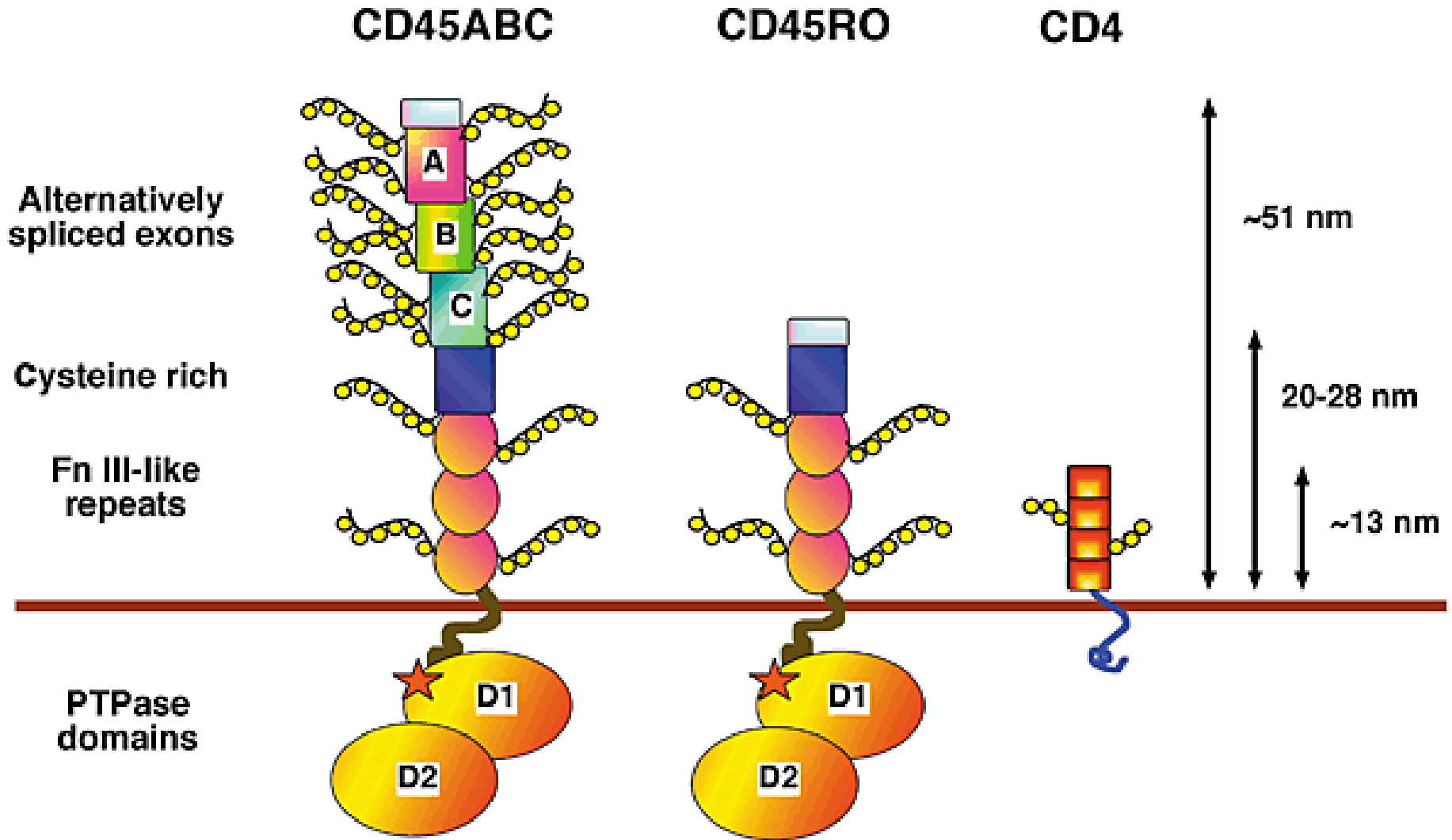
Plays important role in cell activation and in regulation of signal transduction

*- protein-tyrosine-phosphatase domain:
dephosphorylation*

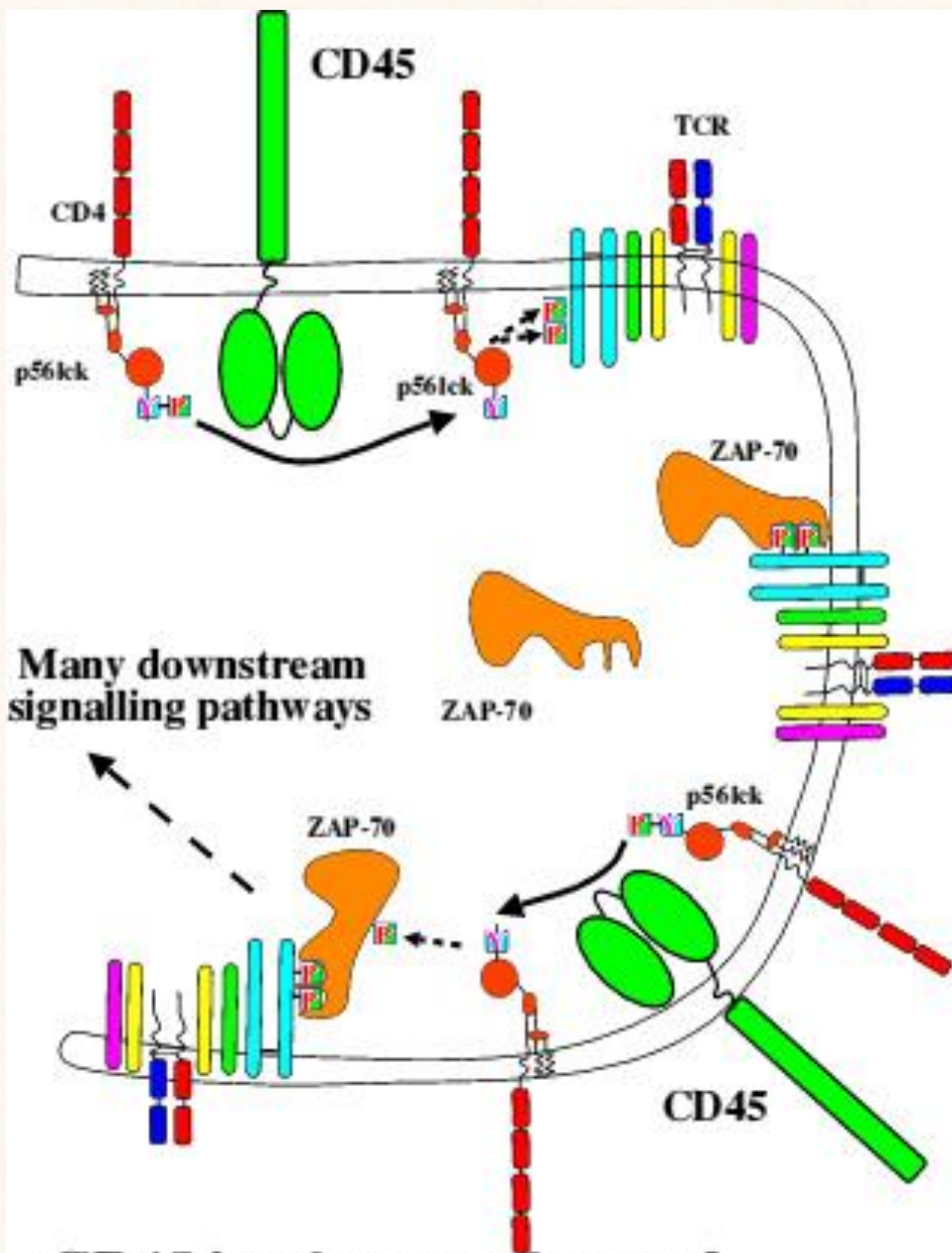


CD45

CD45 isoforms



CD45

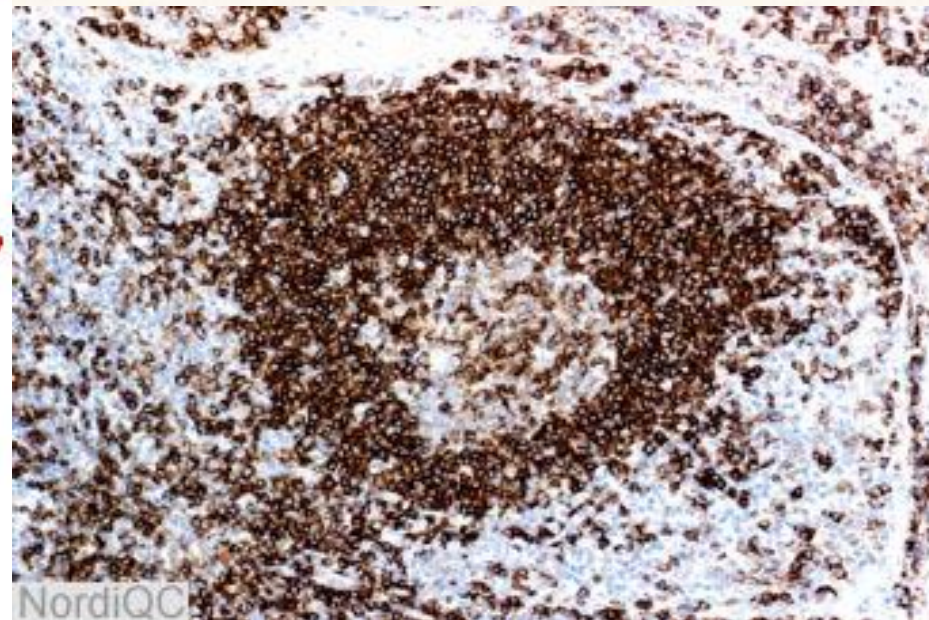


Many downstream signalling pathways

ZAP-70

CD45

CD45 is a key regulator of T lymphocyte activation



NordiQC

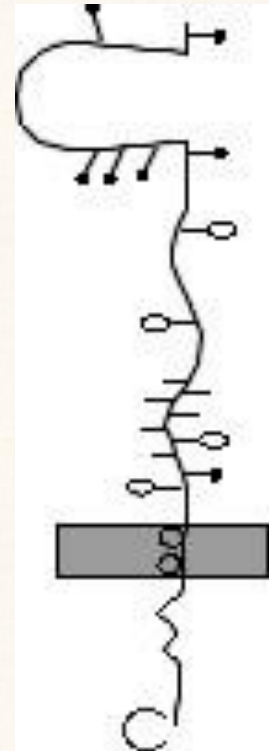
„OTHER” accessory molecules

CD44

Expressed on activated and memory T- and B-cells, phagocytes, fibroblasts, neuronal cells and tumor cells.

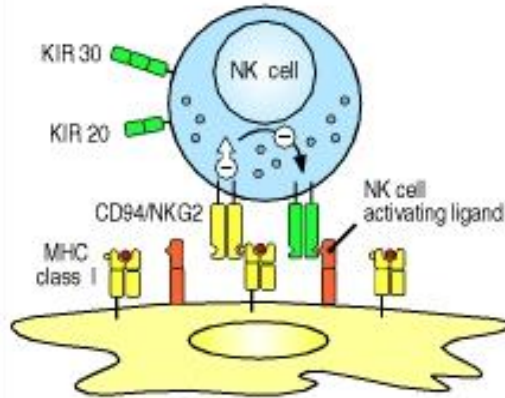
More isoforms - *alternate splicing*

Important in migration of cells including „homing” of leukocytes

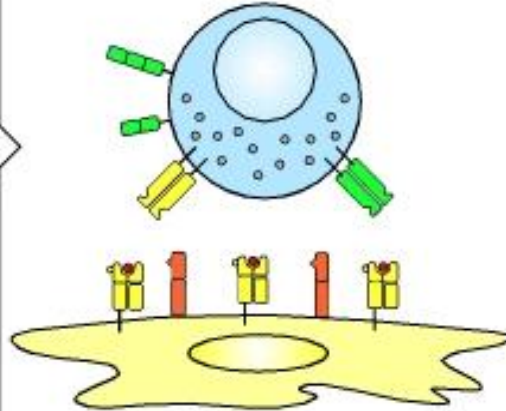


CD44

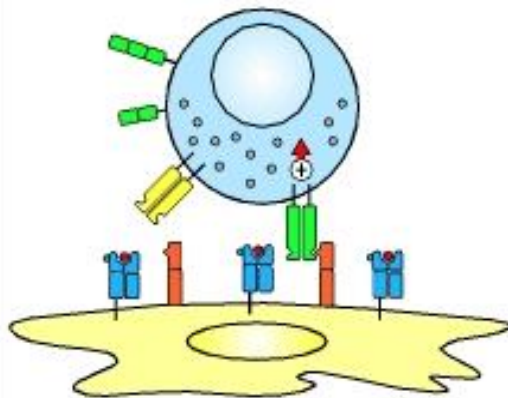
MHC class I on normal cells is recognized by killer inhibitory receptors (KIRs) or by lectinlike CD94: NKG2 heterodimers on NK cells, which inhibit signals from activating receptors



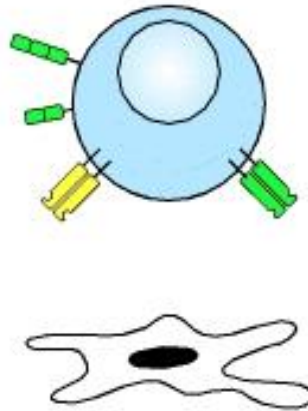
NK cell does not kill the normal cell



'Altered' or absent MHC class I cannot stimulate a negative signal. NK cell is triggered by signals from activating receptors



Activated NK cell releases granule contents, inducing apoptosis in target cell

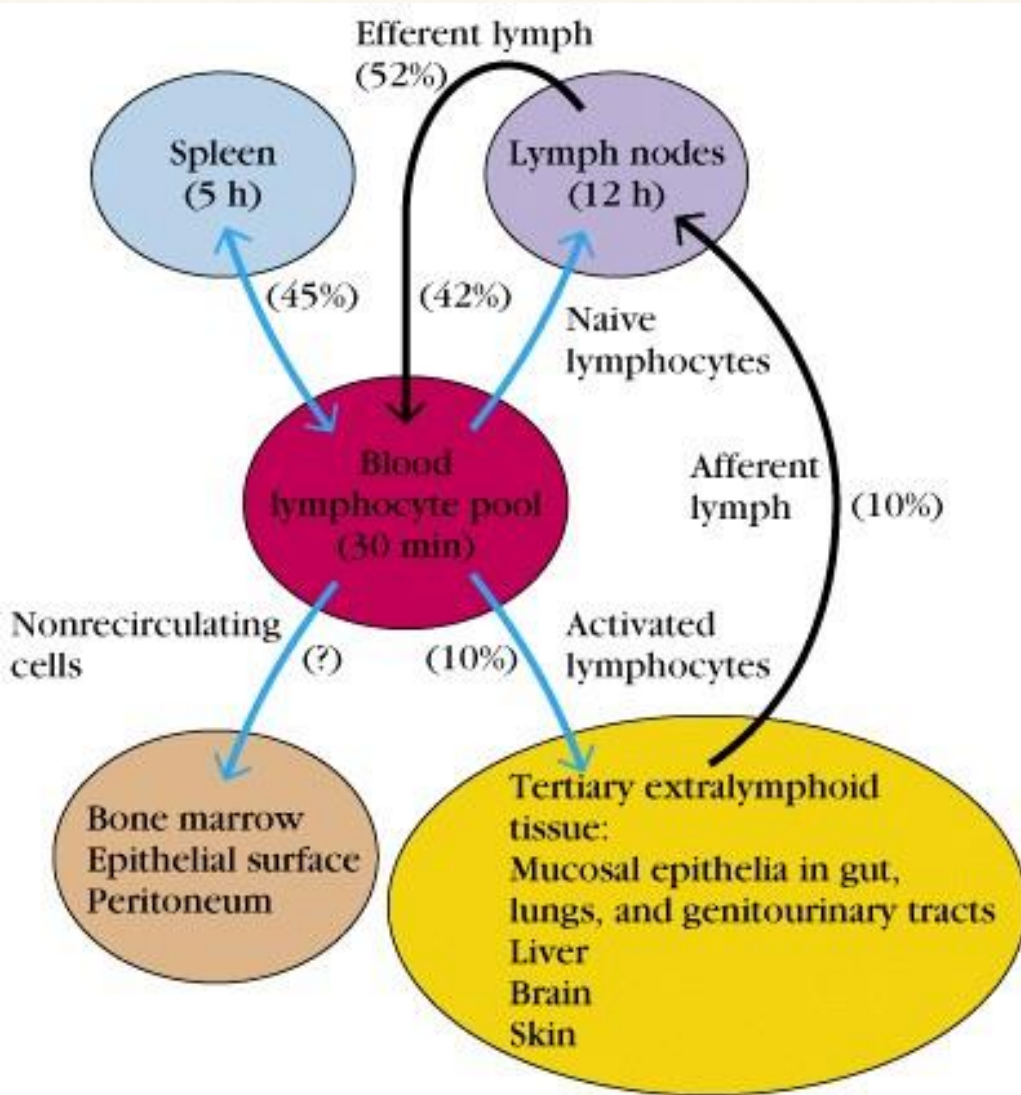


POSSIBLE MECHANISMS BY WHICH NK CELLS DISTINGUISH INFECTED FROM UNINFECTED CELLS

NK cells can use several different receptors that signal them to kill, including lectinlike activating receptors, or 'killer receptors,' that recognize carbohydrate on self cells. However, another set of receptors, called Ly49 in the mouse and **killer inhibitory receptors (KIRs)** in the human, recognize MHC class I molecules and inhibit killing by NK cells by overruling the actions of the killer receptors. This inhibitory signal is lost when cells do not express MHC class I and perhaps also in cells infected with virus, which might inhibit MHC class I expression or alter its conformation. Another possibility is that normal uninfected cells respond to IFN- α and IFN- β by increasing expression of MHC class I molecules, making them resistant to killing by activated NK cells. In contrast, infected cells can fail to increase MHC class I expression, making them targets for activated NK cells. Ly49 and KIR belong to different protein families—the C-type lectins in the case of Ly49 and the immunoglobulin superfamily for KIRs. The KIRs are made in two forms, p58 and p70, which differ by the presence of one immunoglobulin domain.

Lymphocyte recirculation:

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



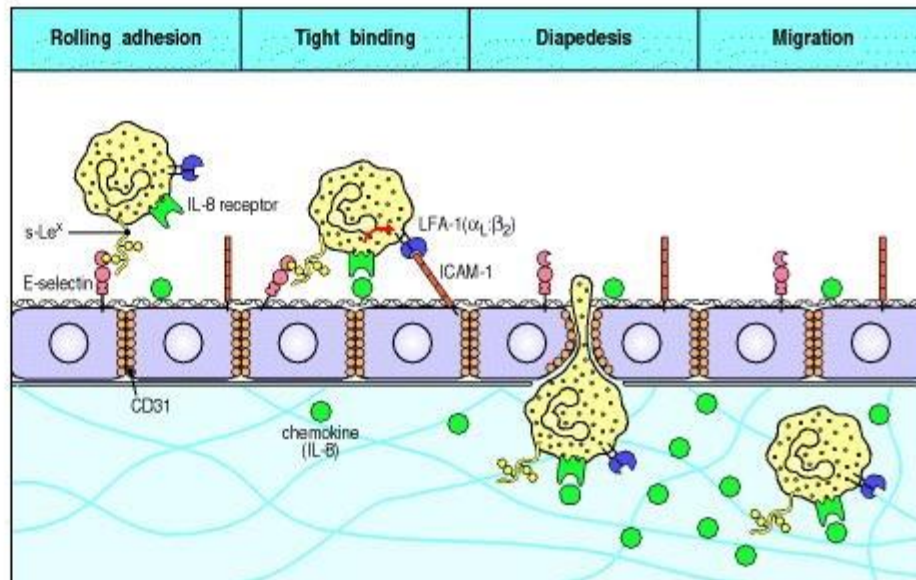
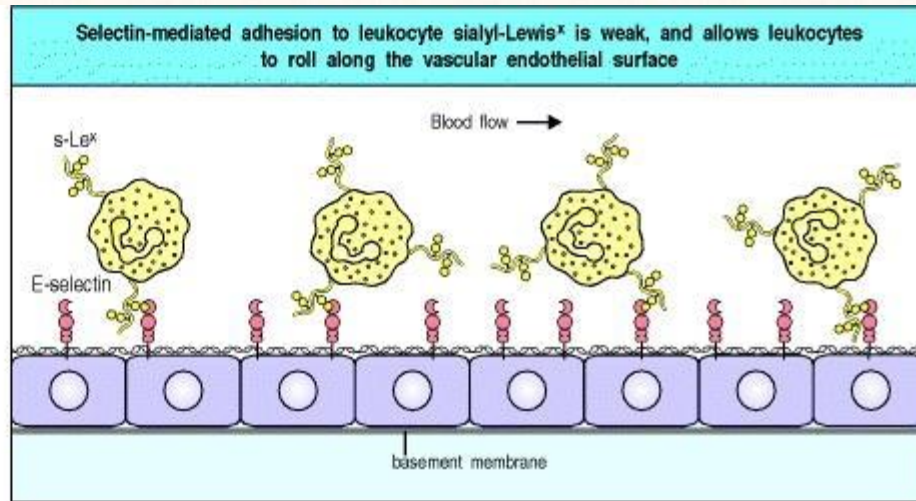
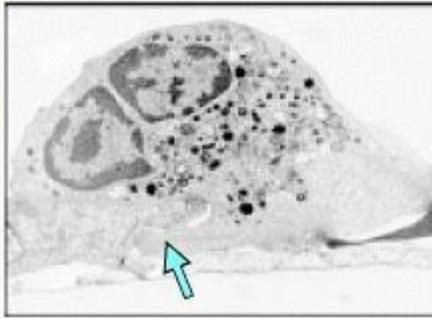
Role:

- Promotes the antigen capturing
- Promotes the development of inflammatory reactions

Mechanism:

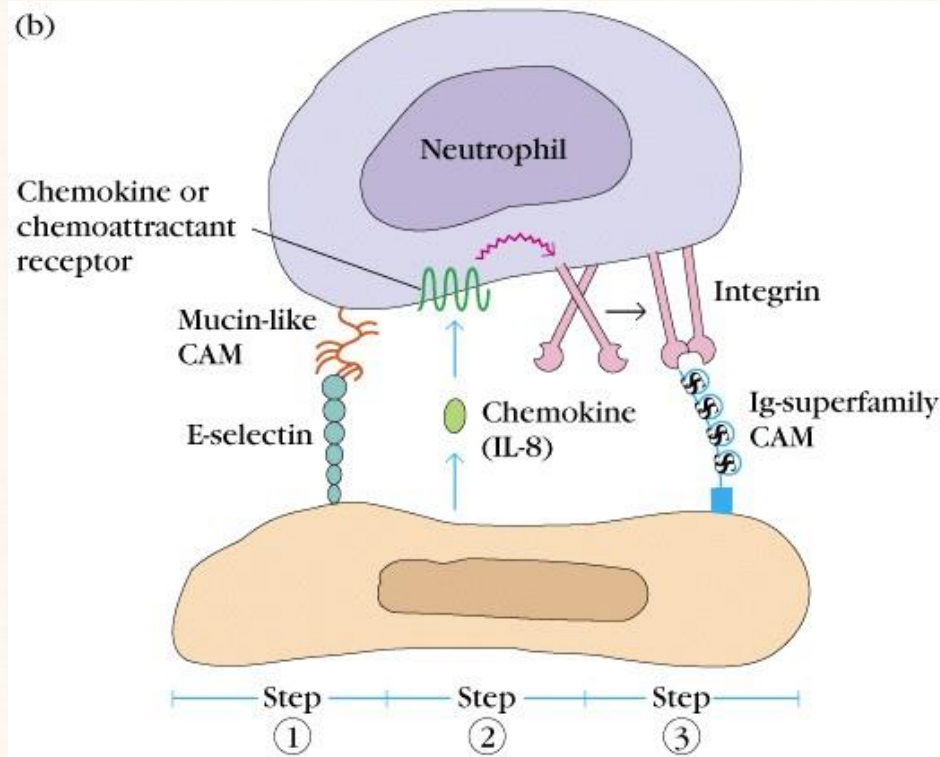
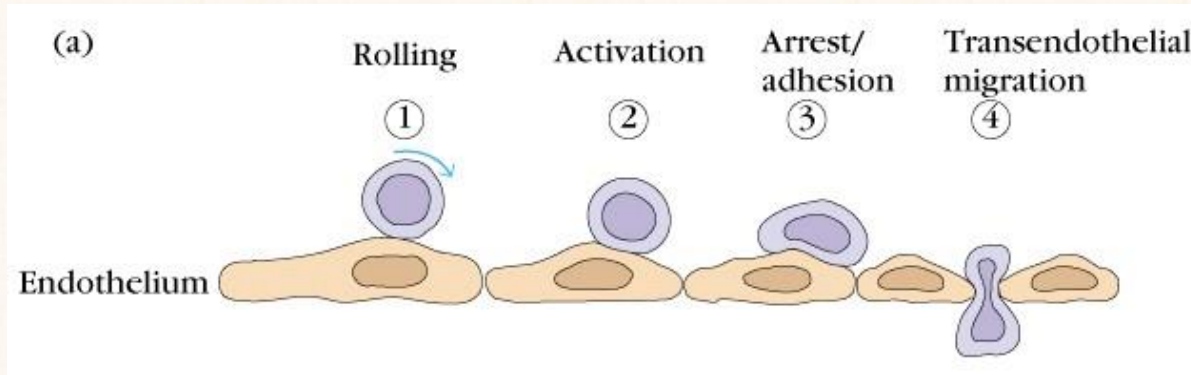
- Extravasation: leucocyte adhesion to the endothel, and migration across the wall of the blood vessels to the tissue

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



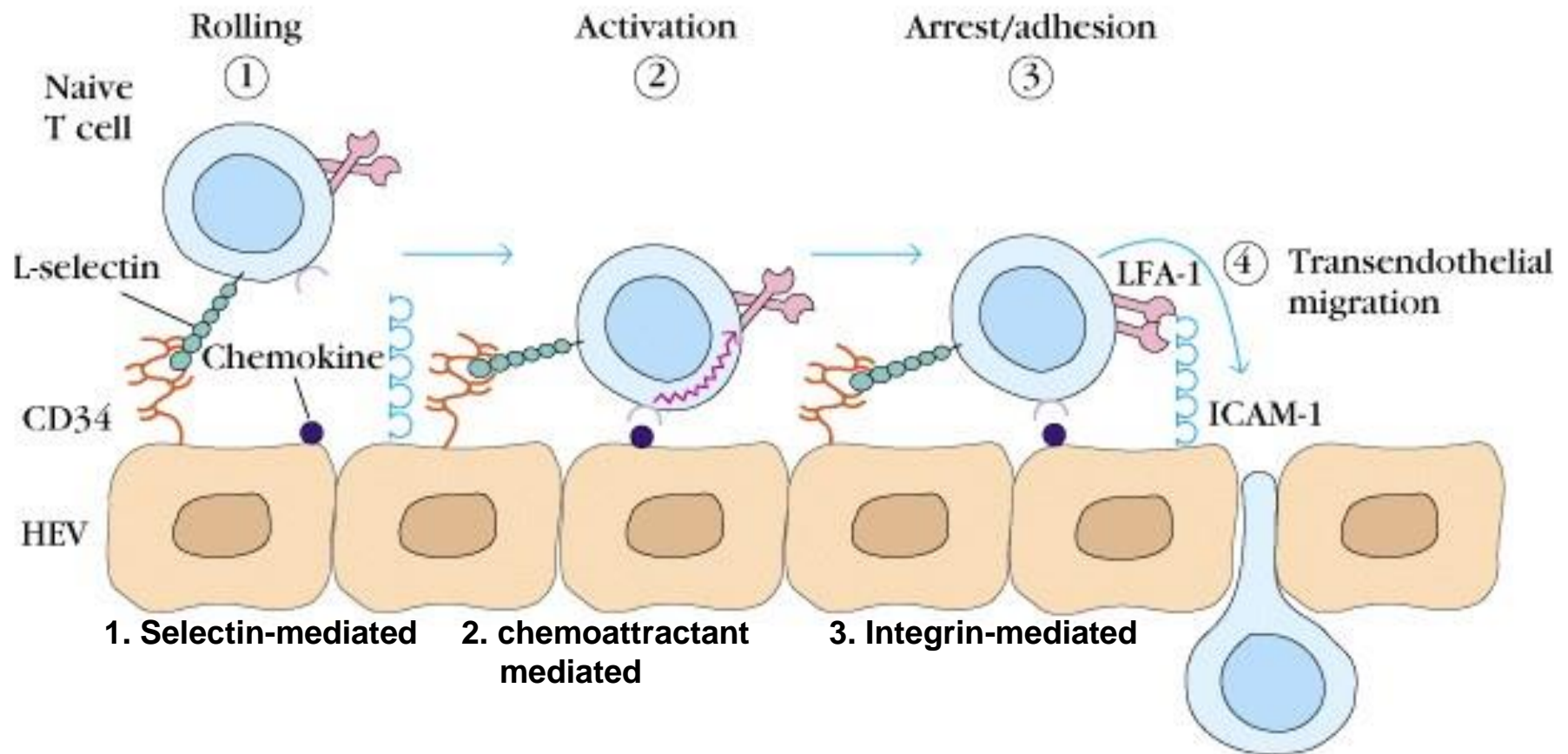
Neutrophils leave the blood and migrate to sites of infection in a multistep process mediated through adhesive interactions that are regulated by macrophage-derived cytokines and chemokines.

Migration of neutrophil granulocytes to the inflamed tissues through the endothelium

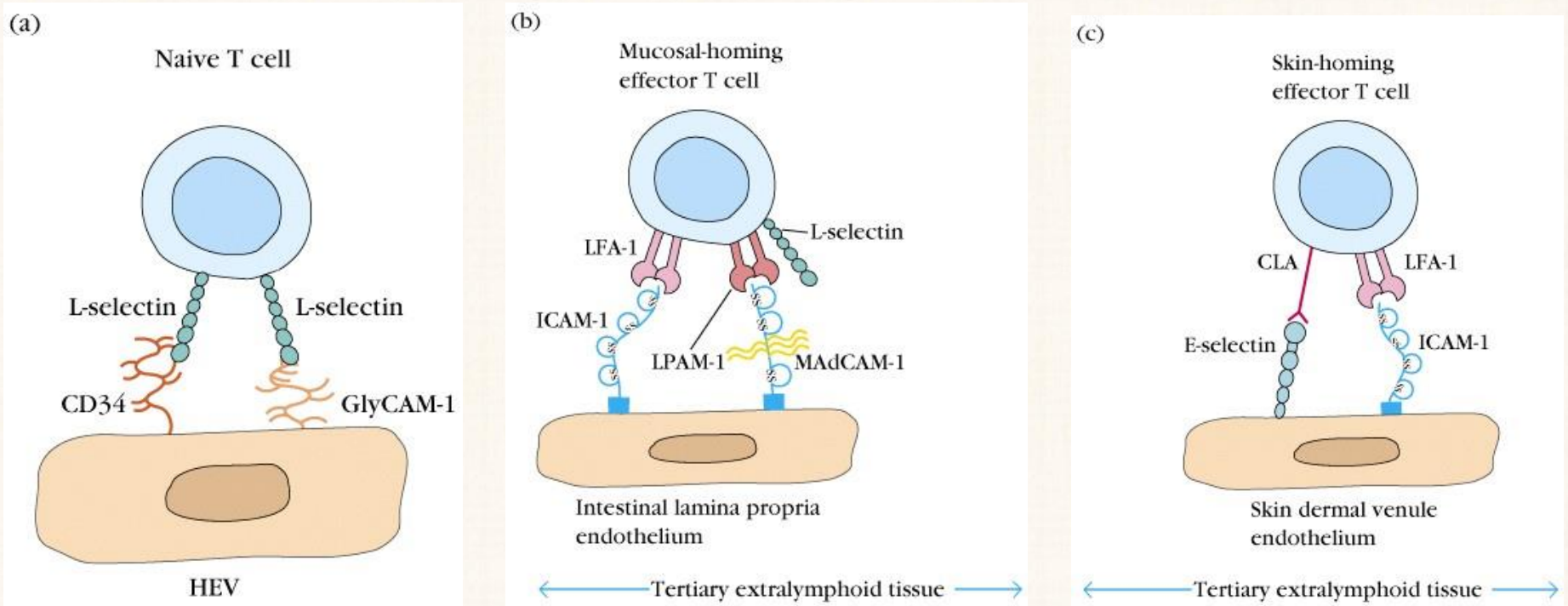


Naive lymphocytes migrating to the peripheral lymphatic tissues

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



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



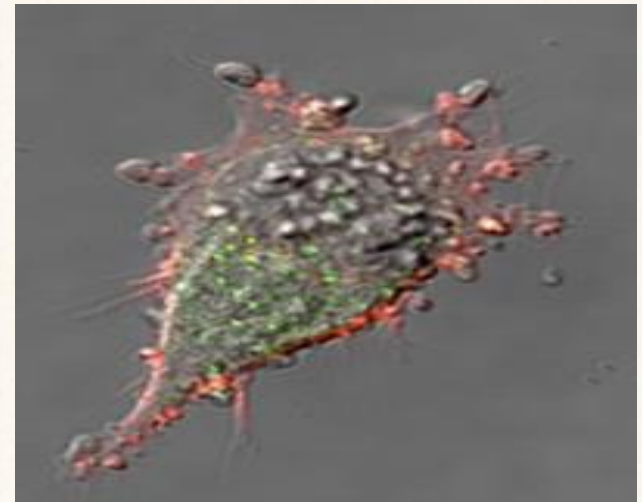
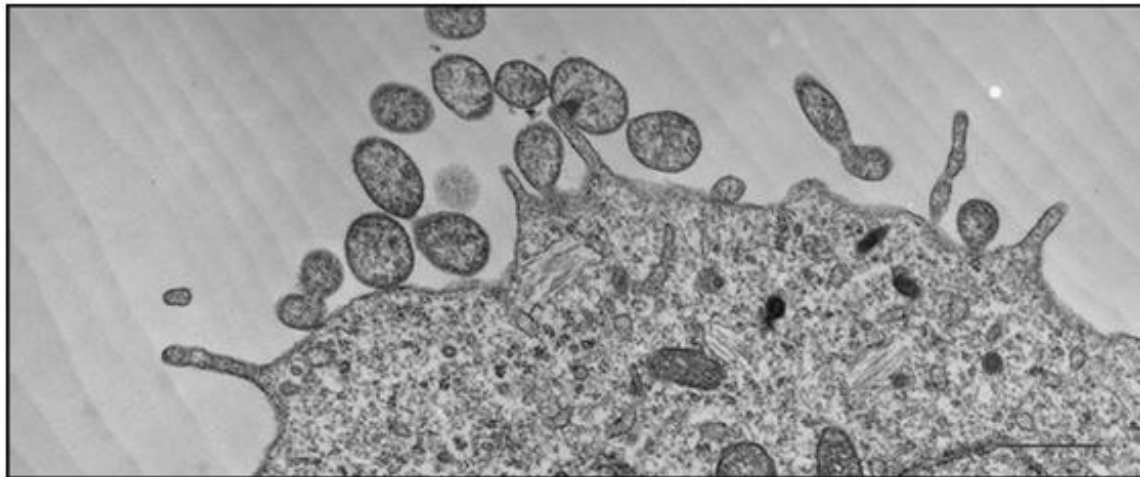
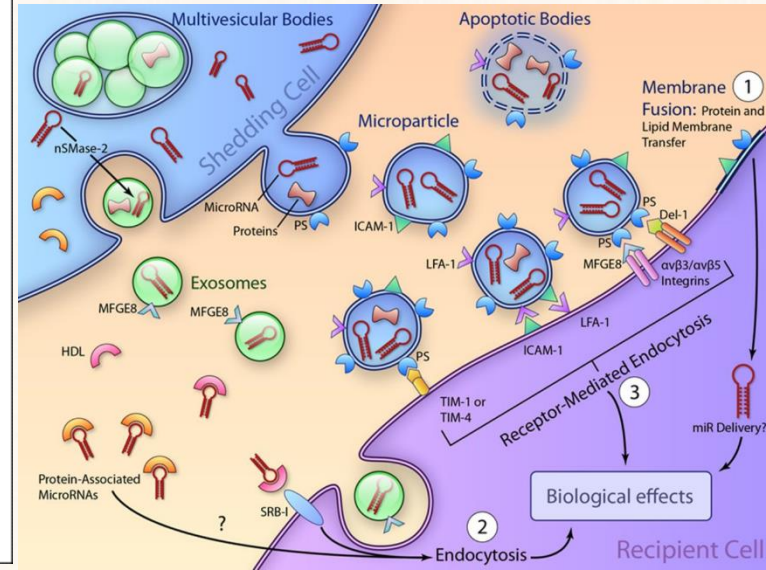
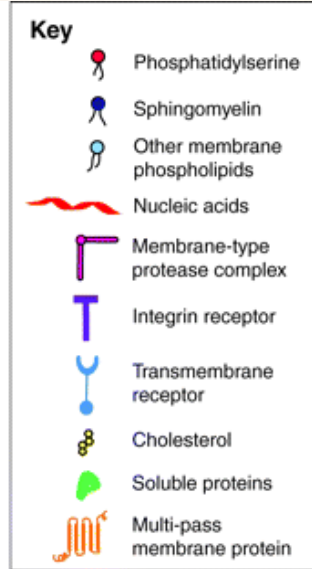
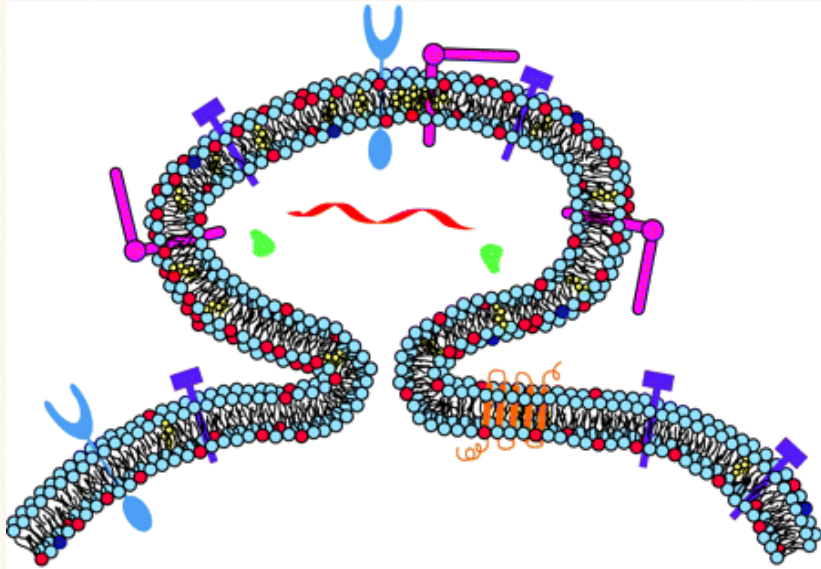
↓
Peripheral lymphatic tissue

↓
Inflammatory tissue

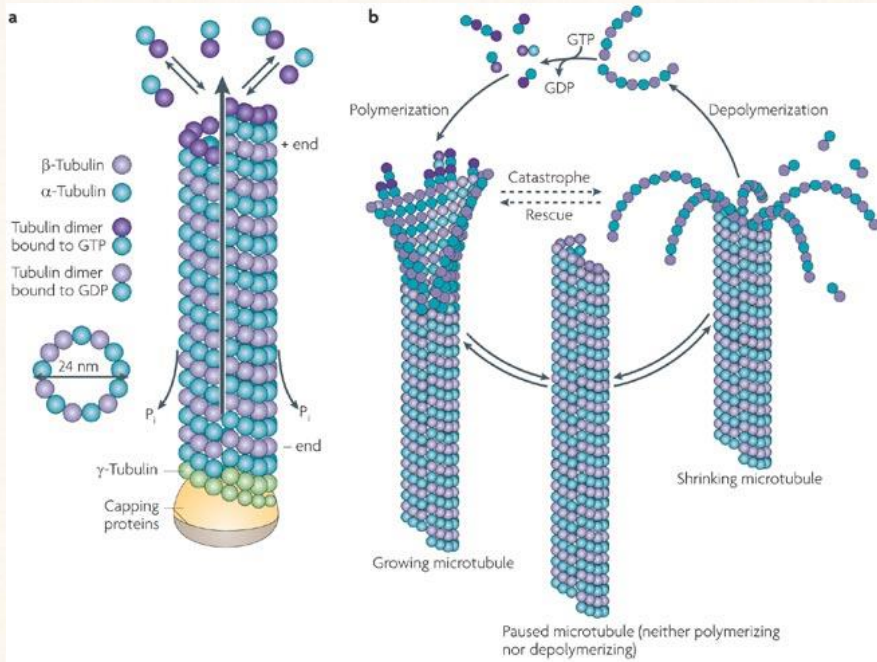
Some important accessory molecules

- **CD3**
- **CD4 and CD8**
- **CD28**
- **CD80/86 (B7.1 and B7.2)**
- **CD152 (CTLA4)**
- **CD25 (IL-2 Receptor)**
- **CD45RA/RO**
- **CD154 (CD40 Ligand)**

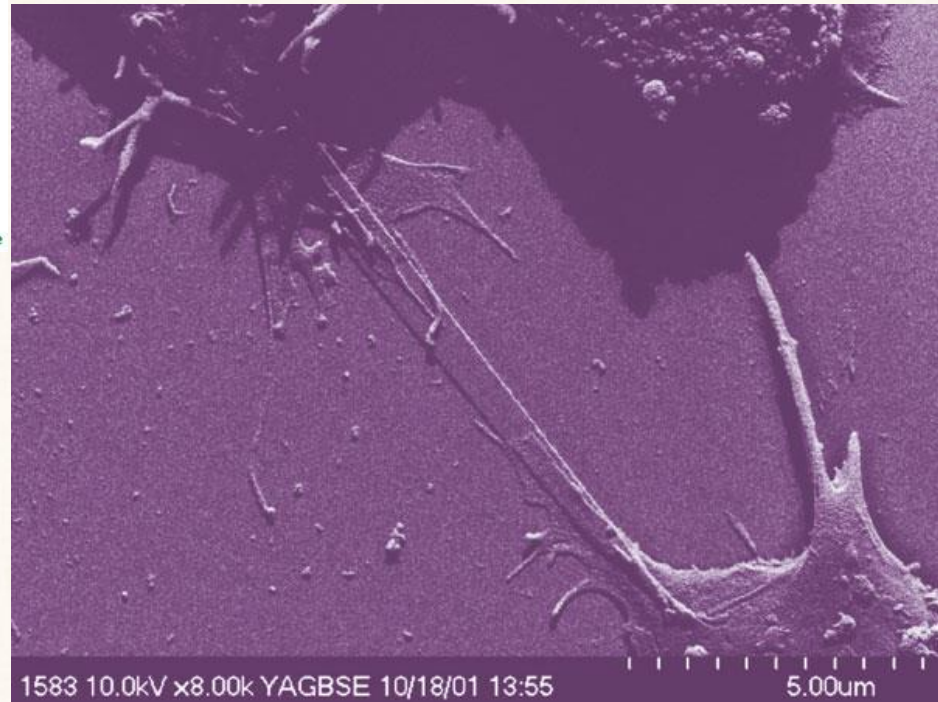
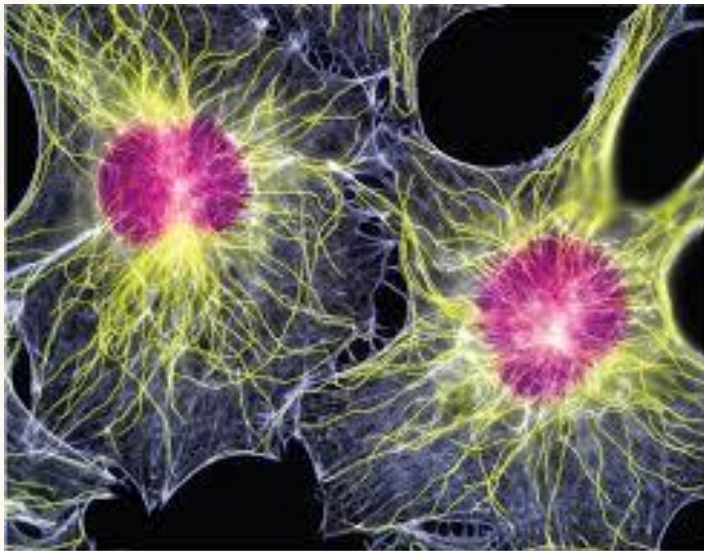
Microvesicles



Mikrotububes



Direct cell-cell communication?



Cell-cell communication through cytokines and their receptors

- **Cytokines**
- **Chemokines**
- **Interferons**
- **Growth factors**
- **Tissue hormones**

Basic characteristics of cytokines

- **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**

A citokinek általános jellemzői

Alacsony molekulatömegű (10-40 kDa), genetikailag konzervált glikoproteinek.

Génaktiválást követően szekretálják a sejtek.

Sejt-sejt kölcsönhatást közvetítenek:

- Információ küldés
- Biológiai homeosztázis általános szabályozása,

beleértve az immunválaszt is.

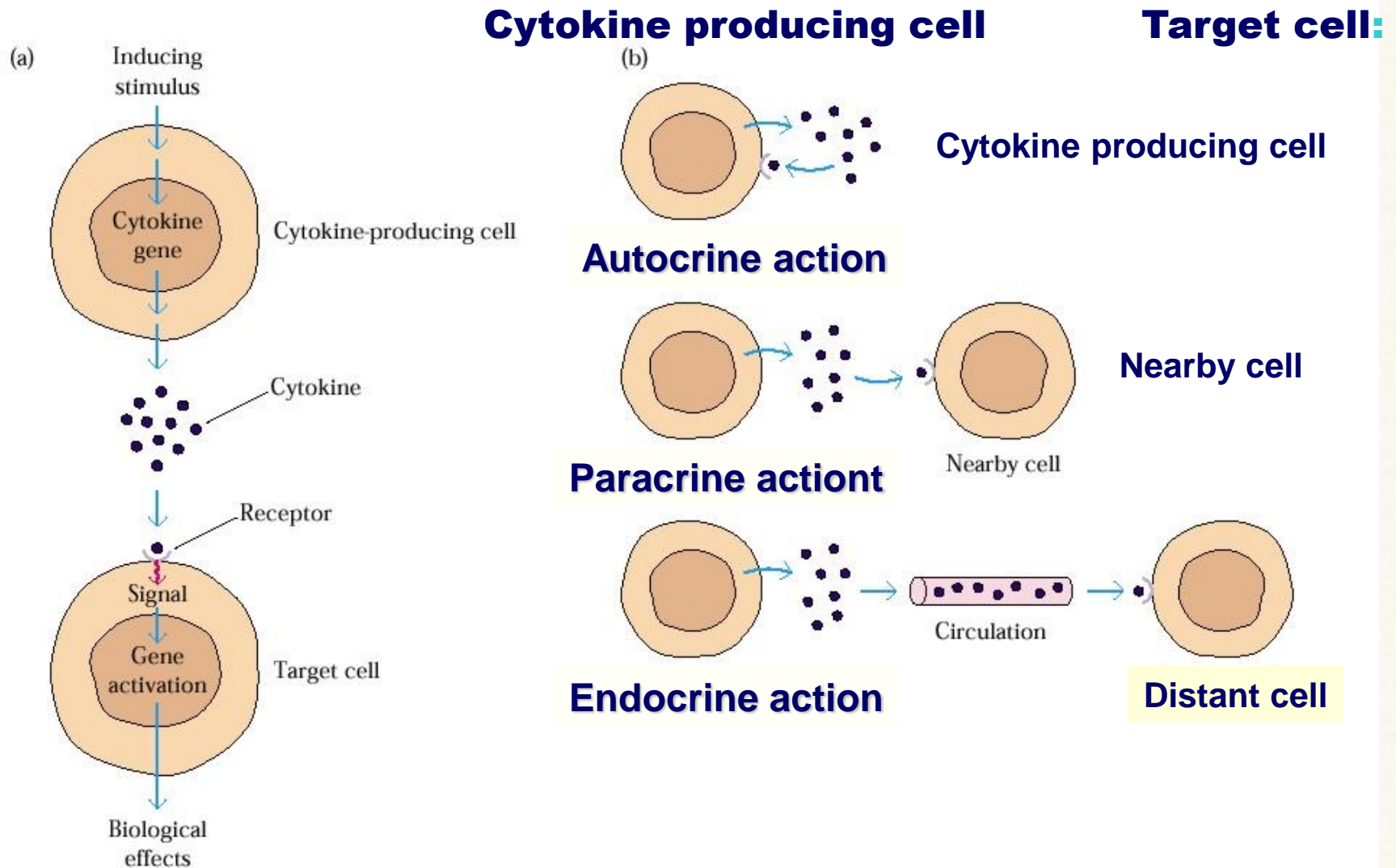
Hatásmechanizmus:

- átmeneti génaktiválást követően termelődnek
- receptorokon keresztül hatnak, amelyek jelátvitelt

indítanak el.

- nagy affinitás
- pikomoláris koncentráció
- főként lokálisan hatnak

Mechanism of cytokine action I.



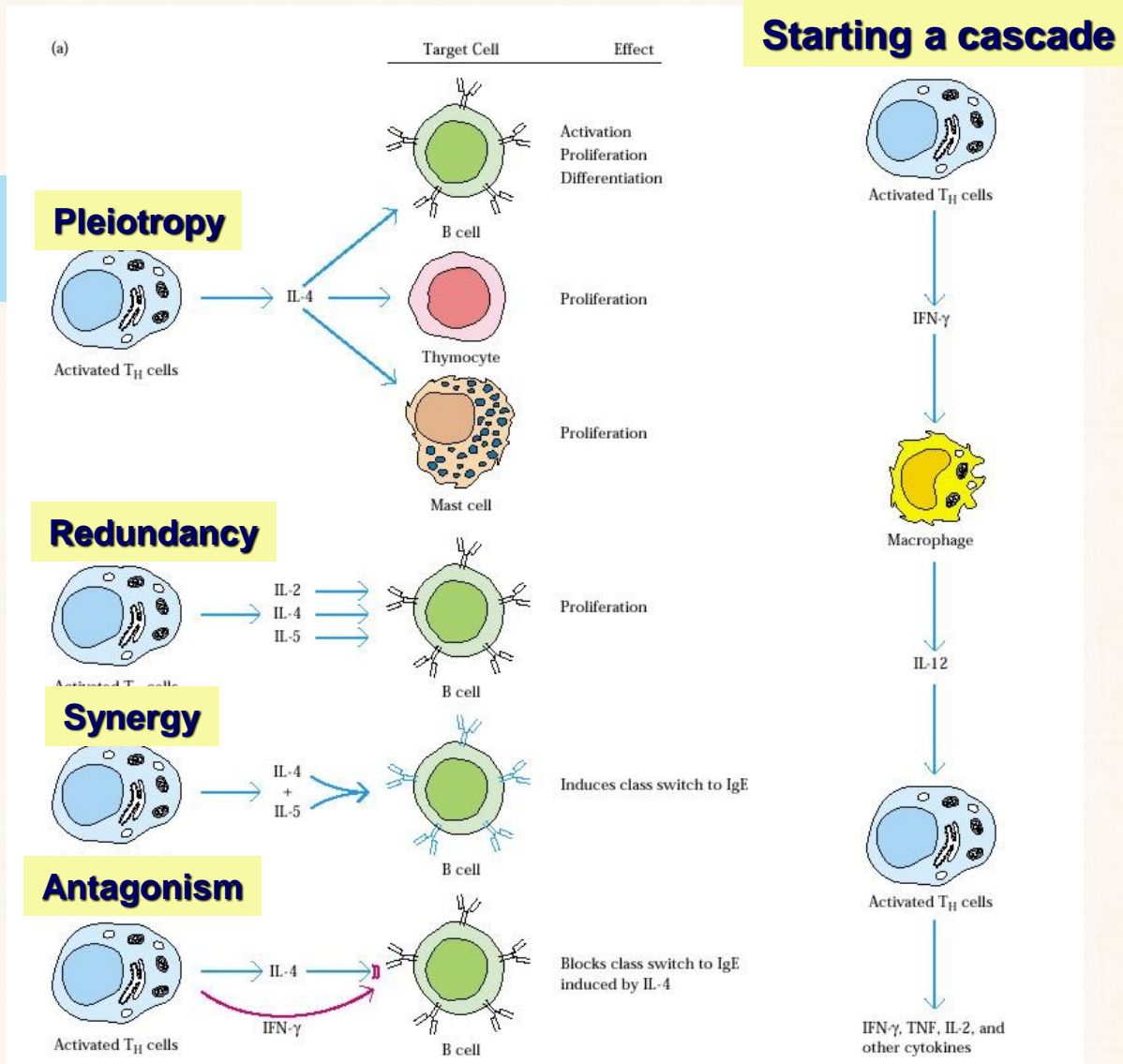
Mechanism of cytokine action II.

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

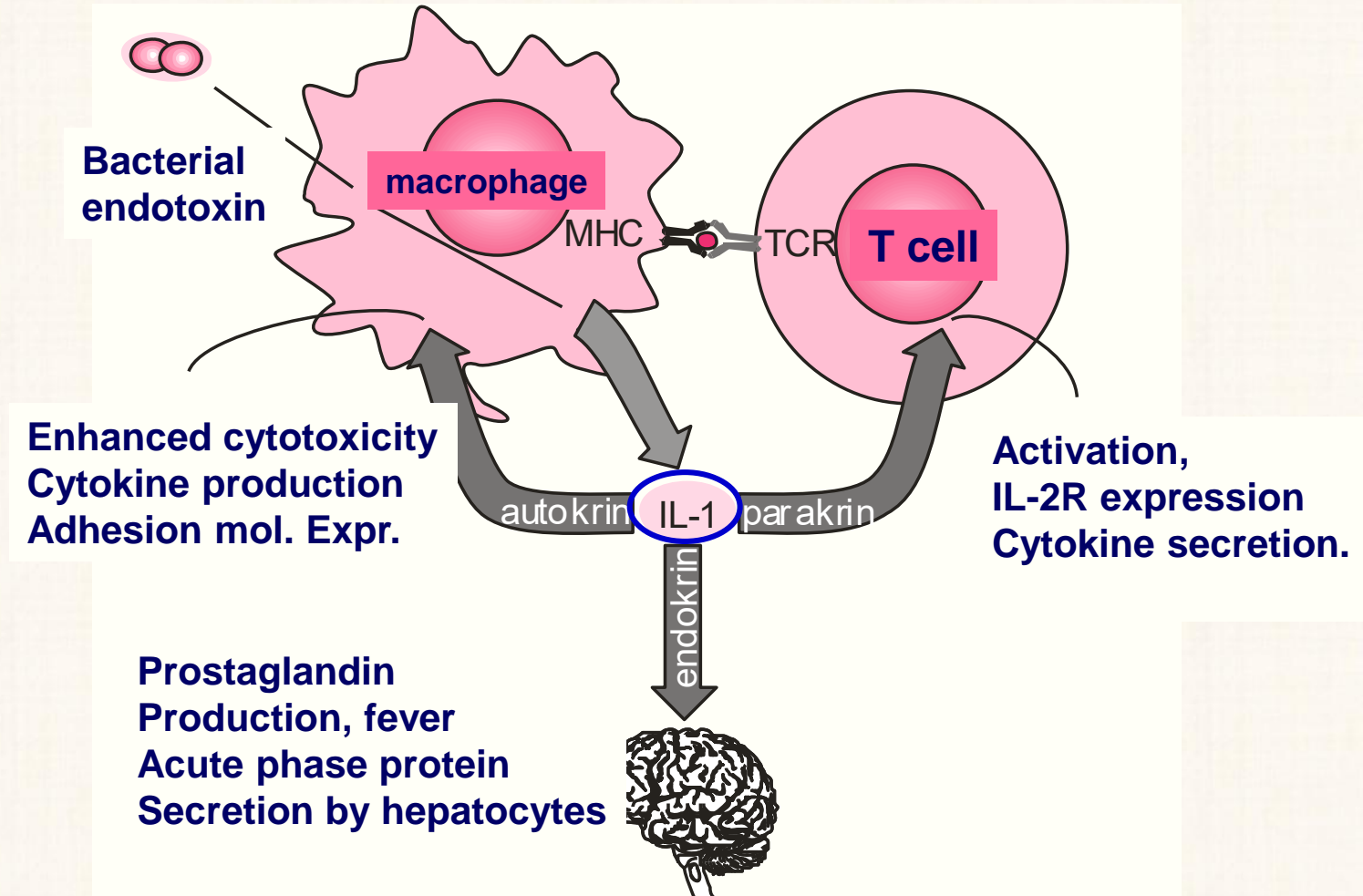
One cytokine inhibits the effects of another cytokine



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

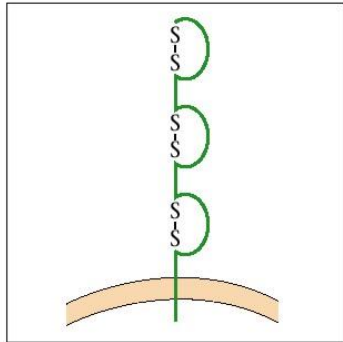
Autocrine, paracrine and endocrine action of IL-1



Cytokine receptors

RECEPTOR FAMILY

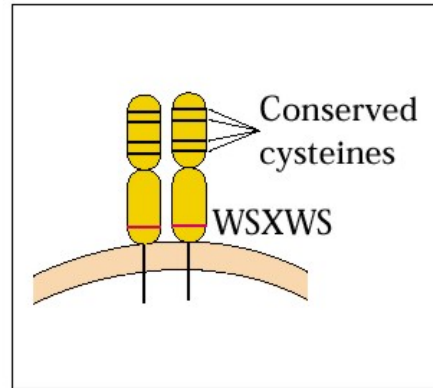
(a) Immunoglobulin superfamily receptors



LIGANDS

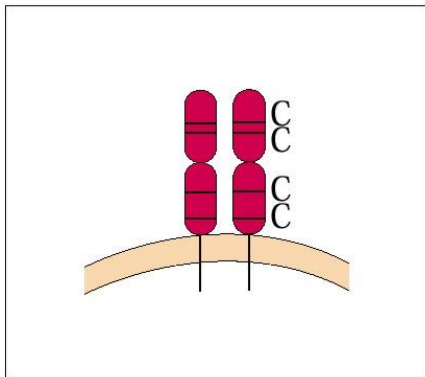
IL-1
M-CSF
C-Kit

(b) Class I cytokine receptors (hematopoietin)



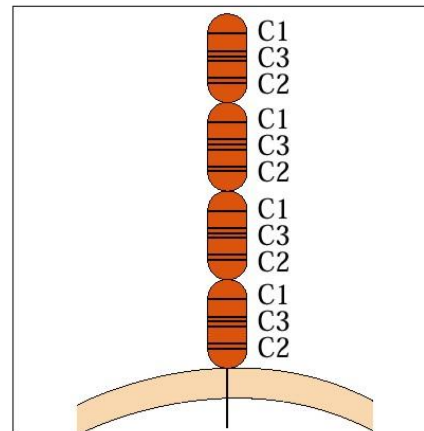
IL-2	IL-13
IL-3	IL-15
IL-4	GM-CSF
IL-5	G-CSF
IL-6	OSM
IL-7	LIF
IL-9	CNTF
IL-11	Growth hormone
IL-12	Prolactin

(c) Class II cytokine receptors (interferon)



IFN- α
IFN- β
IFN- γ
IL-10

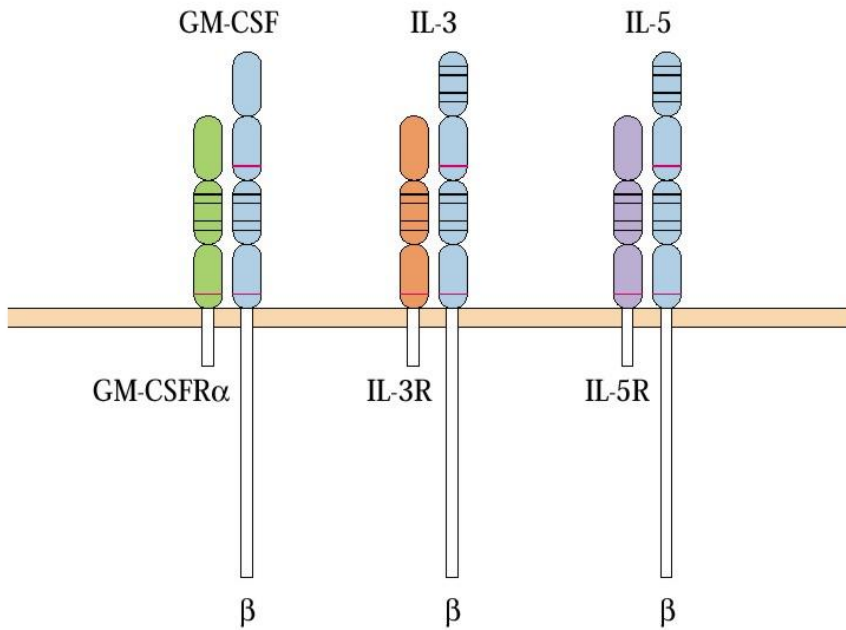
(d) TNF receptors



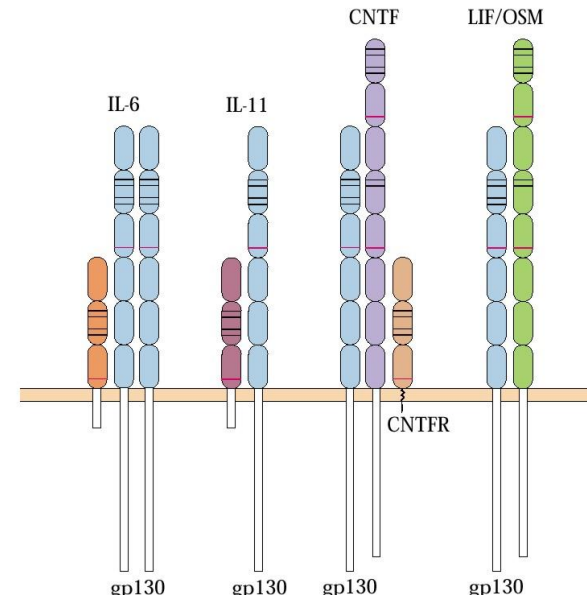
TNF- α
TNF- β
CD40
Nerve growth factor (NGF)
FAS

Characteristics of multichain cytokine receptors

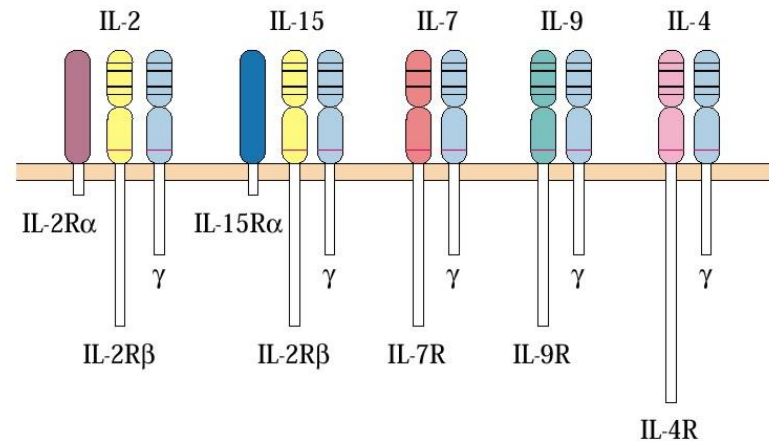
(a) GM-CSF receptor subfamily (common β subunit)



(b) IL-6 Receptor subfamily (common gp130 subunit)



(c) IL-2 receptor subfamily (common γ subunit)



Chemokines

- 90-130 aa. Polypeptides
- Receptorial action
- Produced by lymphatic and none-lymphatic tissues

Functions:

- chemotaxis for different leukocytes
- regulation of normal leukocyte traffic
- recruitment of cells to inflammatory sites
- enhancement of cell adhesion
- activation of effectors leukocytes
- development of the inflammatory reaction
- development of normal lymphoid tissues

