Basic Immunology

Lecture *5th - 6th*

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 hormons,complement factors, etc.

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

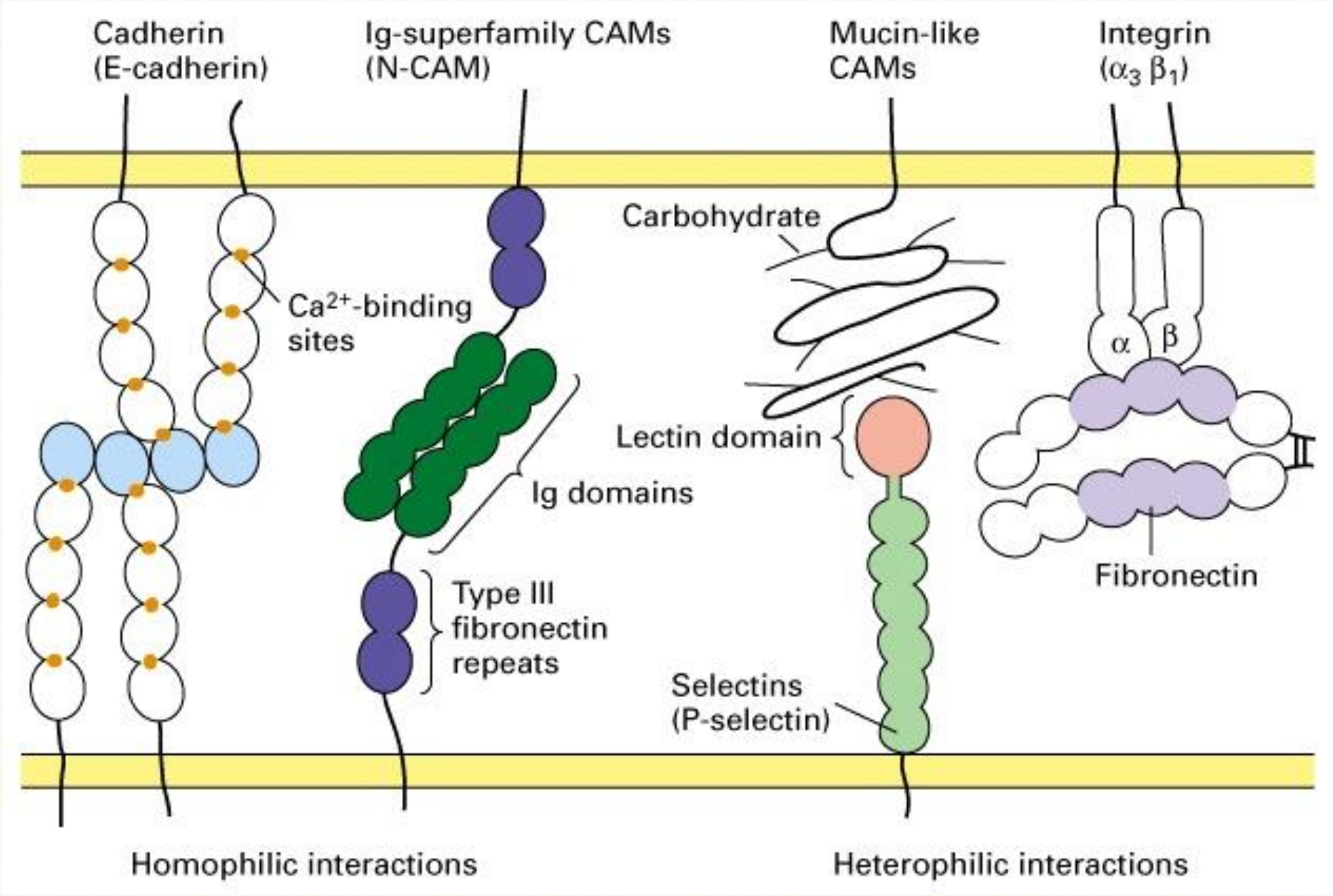
-Immune response: T cell and APC/B cell interactions during antigen presentation, activation and differentiation of immune cells, cytotoxic effector reactions

Adhesion molecules

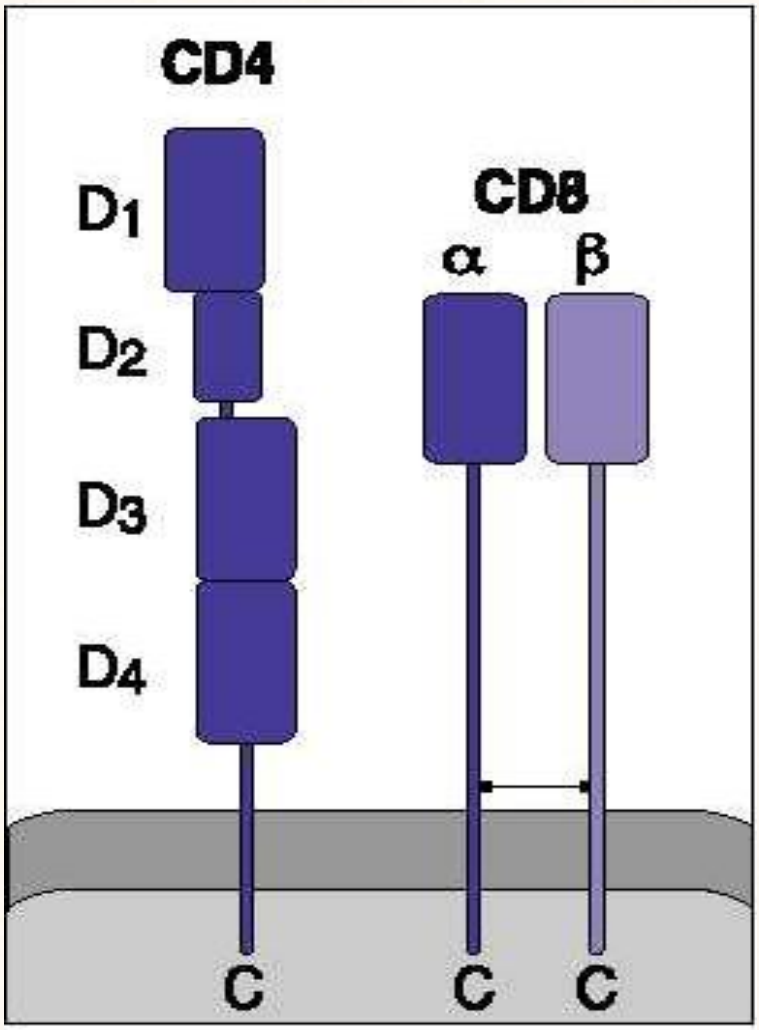
Cell surface molecules whose function is to promote adhesive interactions with other cells or the extracellular matrix and initiate signal transduction.

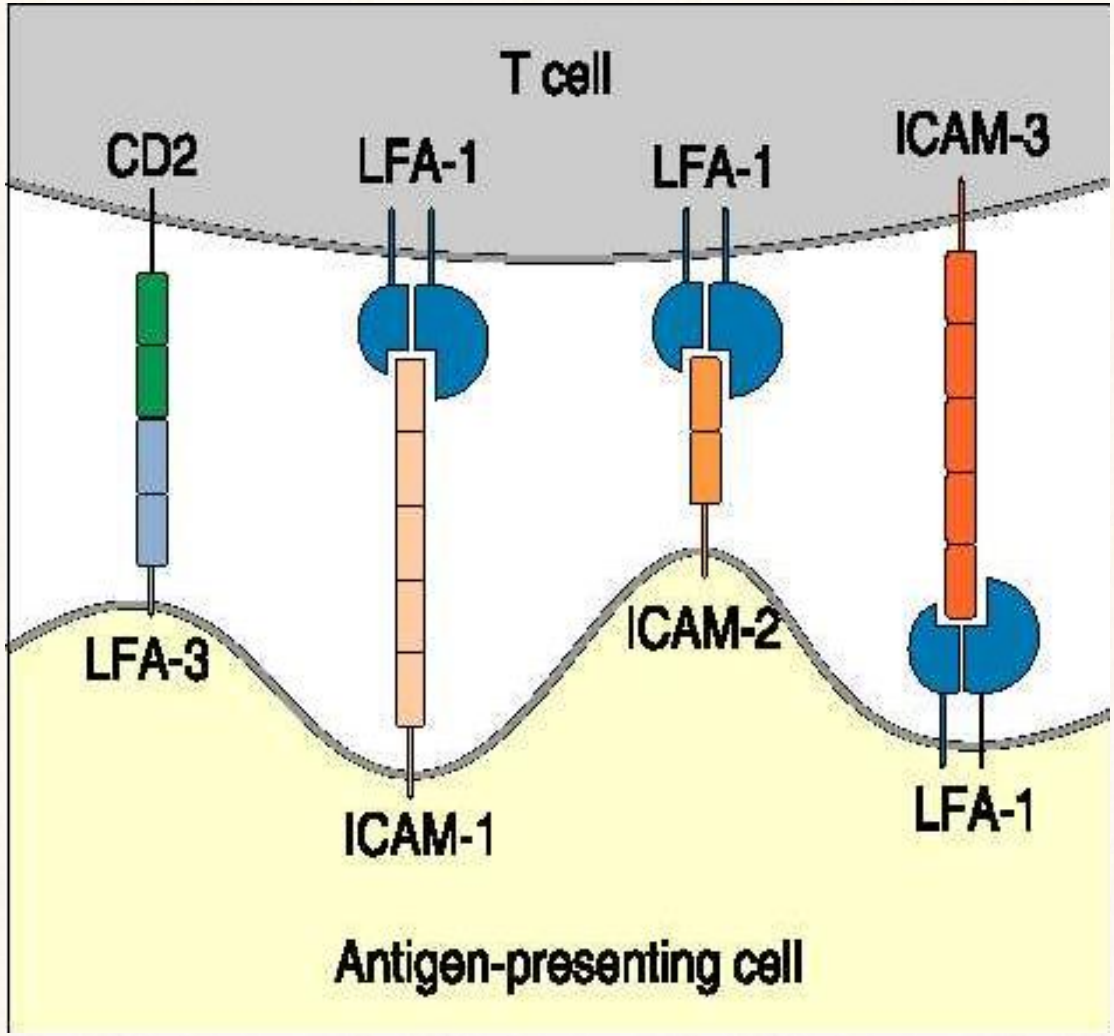
Leukocytes express various types of adhesion molecules, such as selectins, integrins, and members of the Ig superfamily, and these molecules play crucial role in cell migration and cellular activation both in innate and adaptive immune response.

Cell adhesion molecules



Accessory molecules on T cells

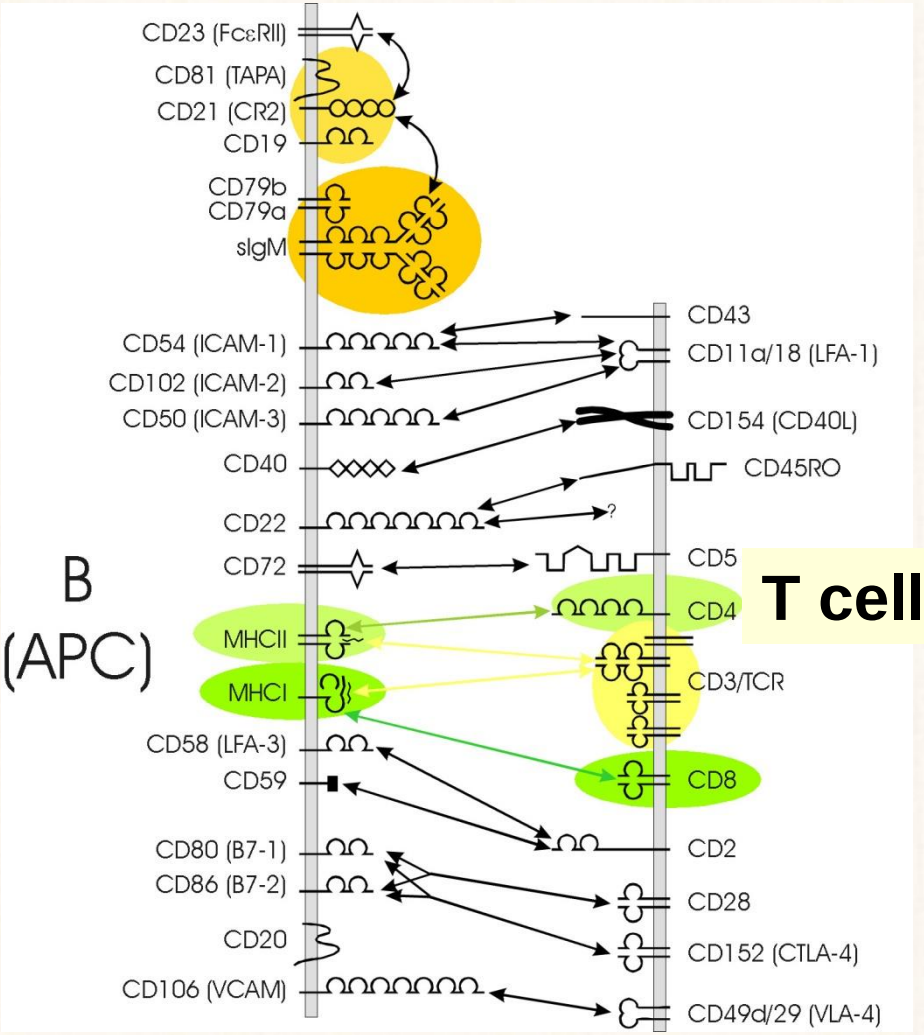




Family of accessory molecules, adhesion molecules, co-receptors

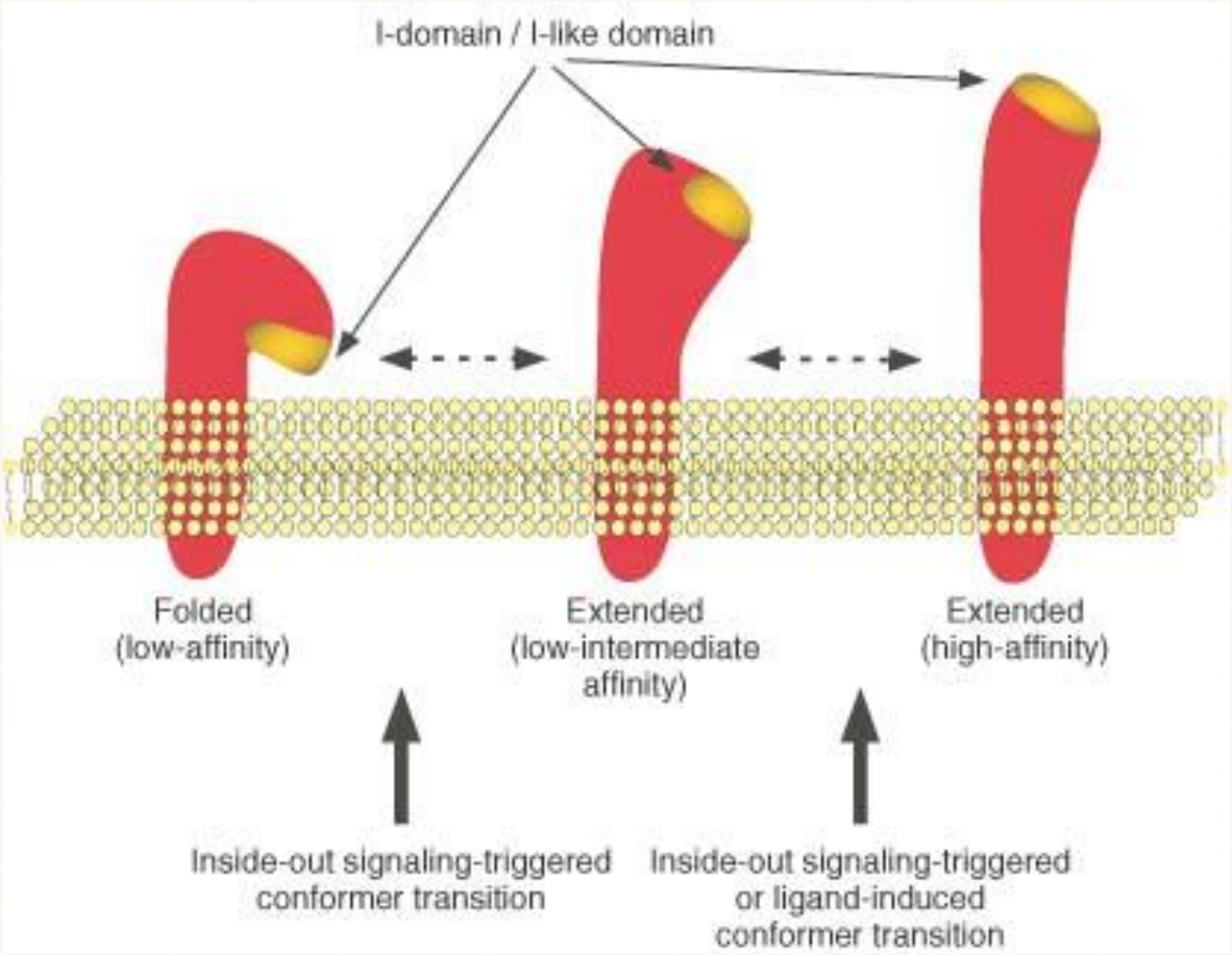
Common characteristics:

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**

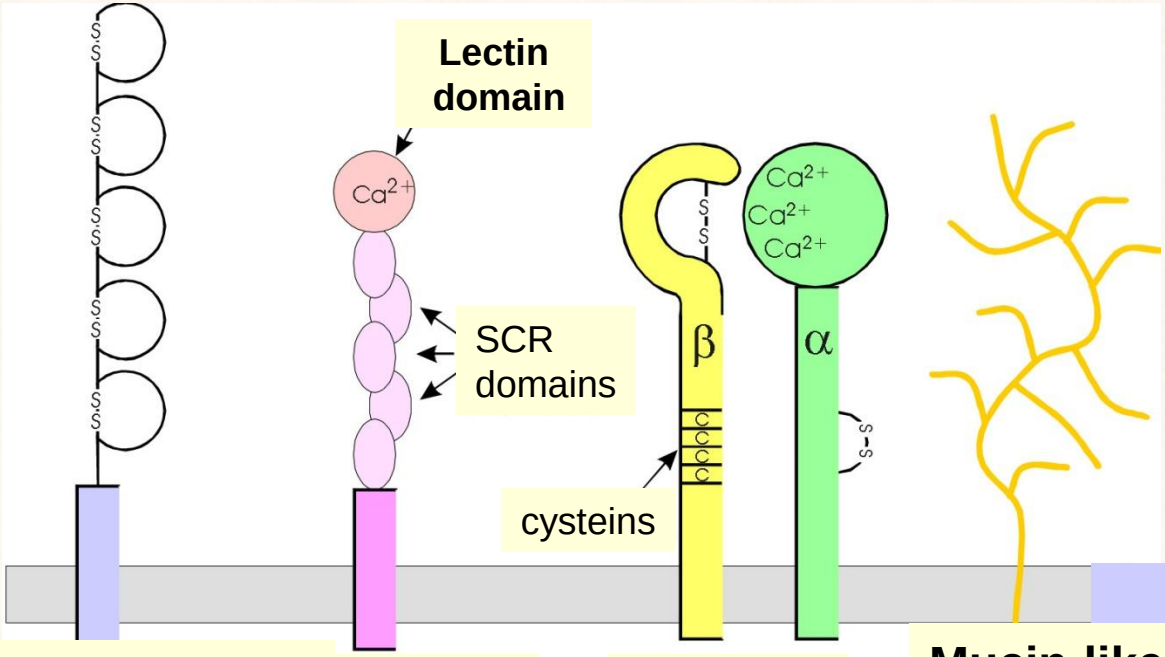


Activation of adheseion molecules

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



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

Ig-superfamily member CD2

CD2

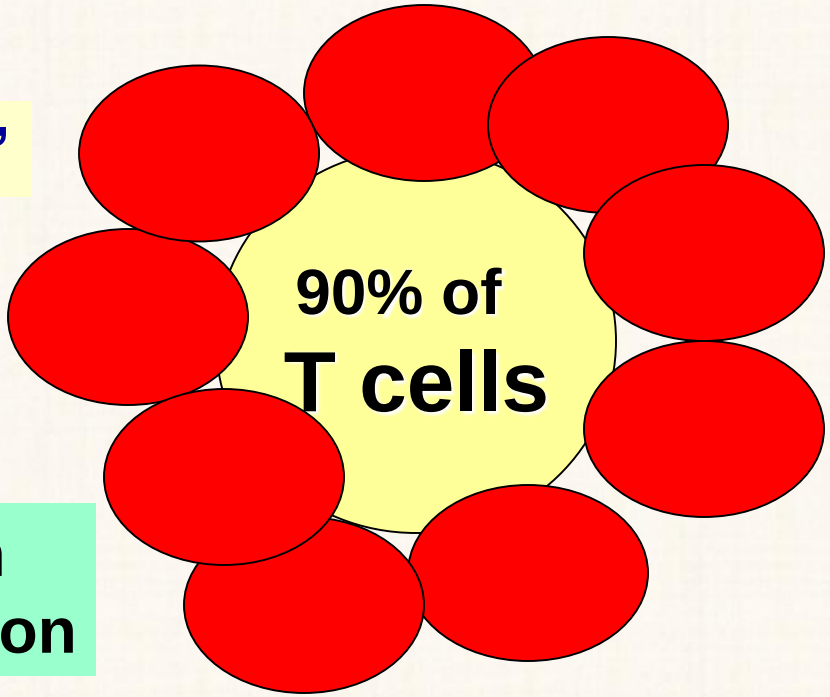
„sheep red-blood cell receptor”

→ **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

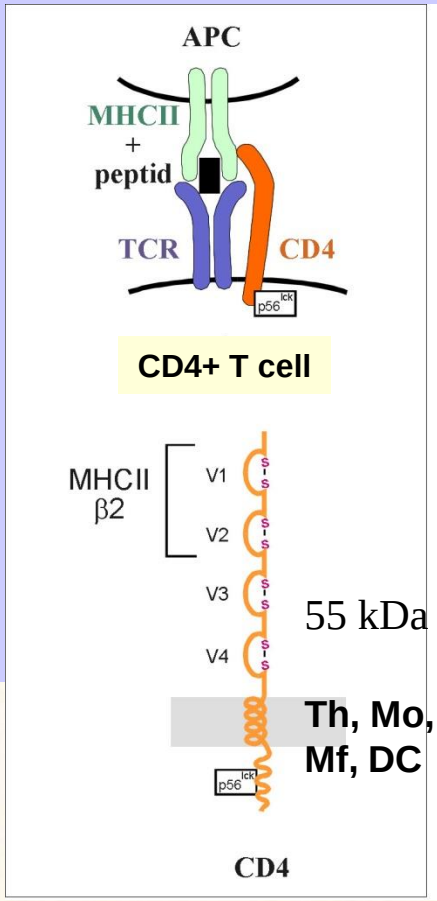
CD8 - MHCI

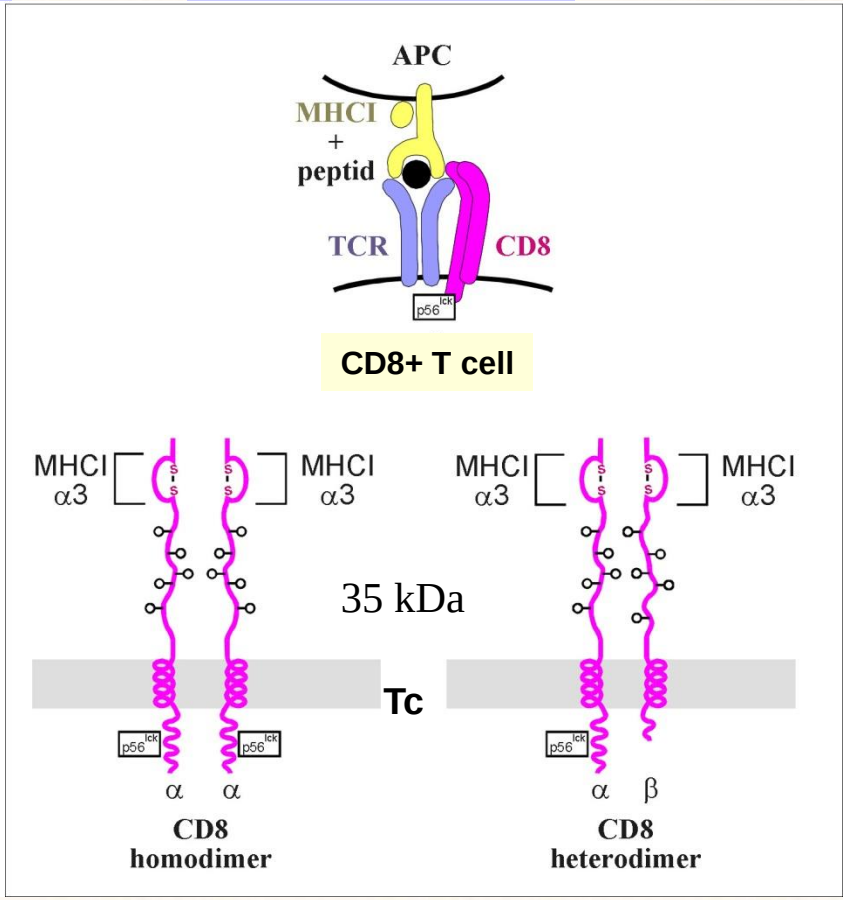
At different stages of T cell maturation

CD4 and **CD8 together**
„double positive"
in thymus

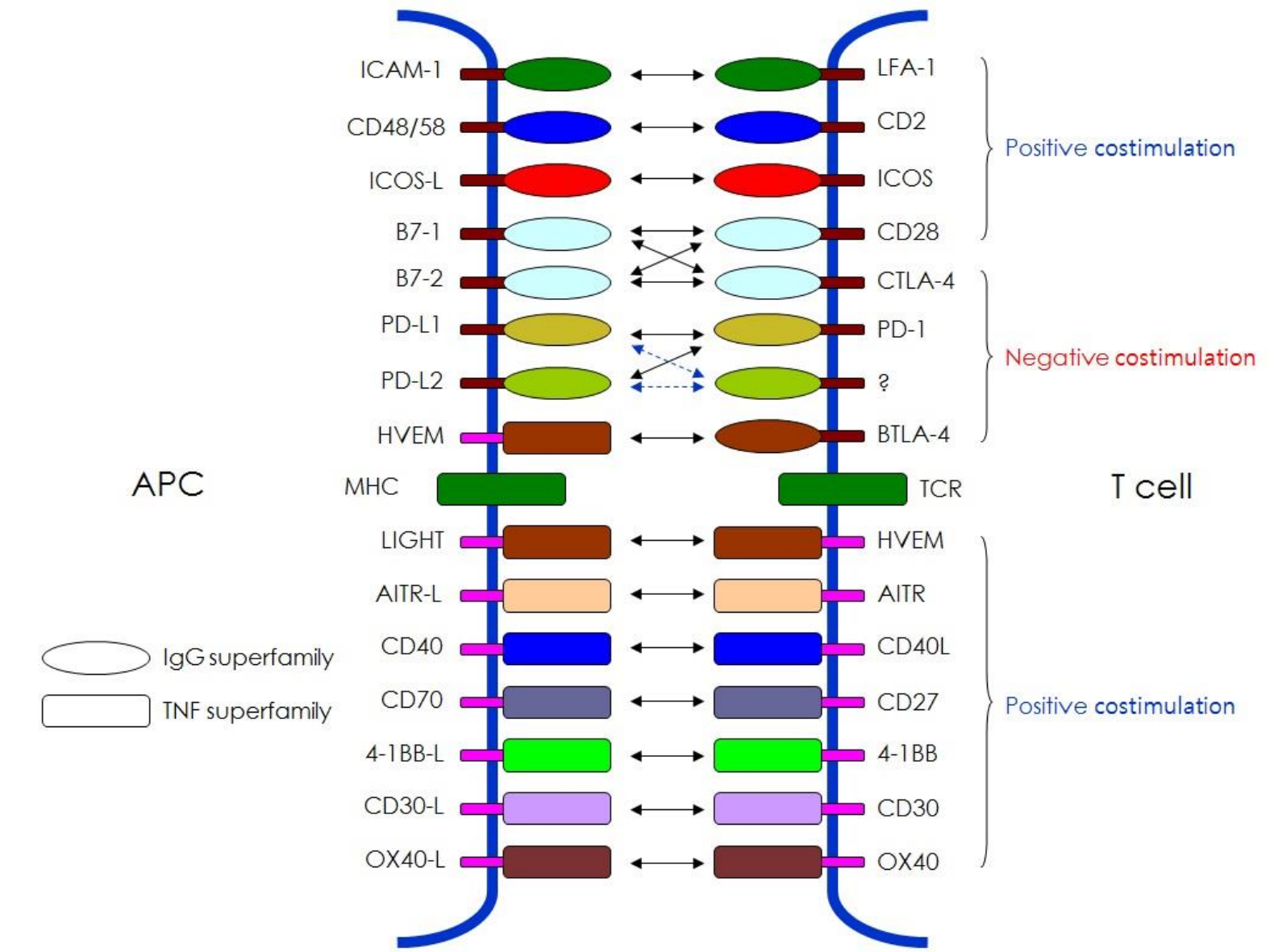
At the periphery:
„single positive"
T helper: CD4
T cytotoxic: CD8

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





Co-stimulatory molecules in APCs and T cells

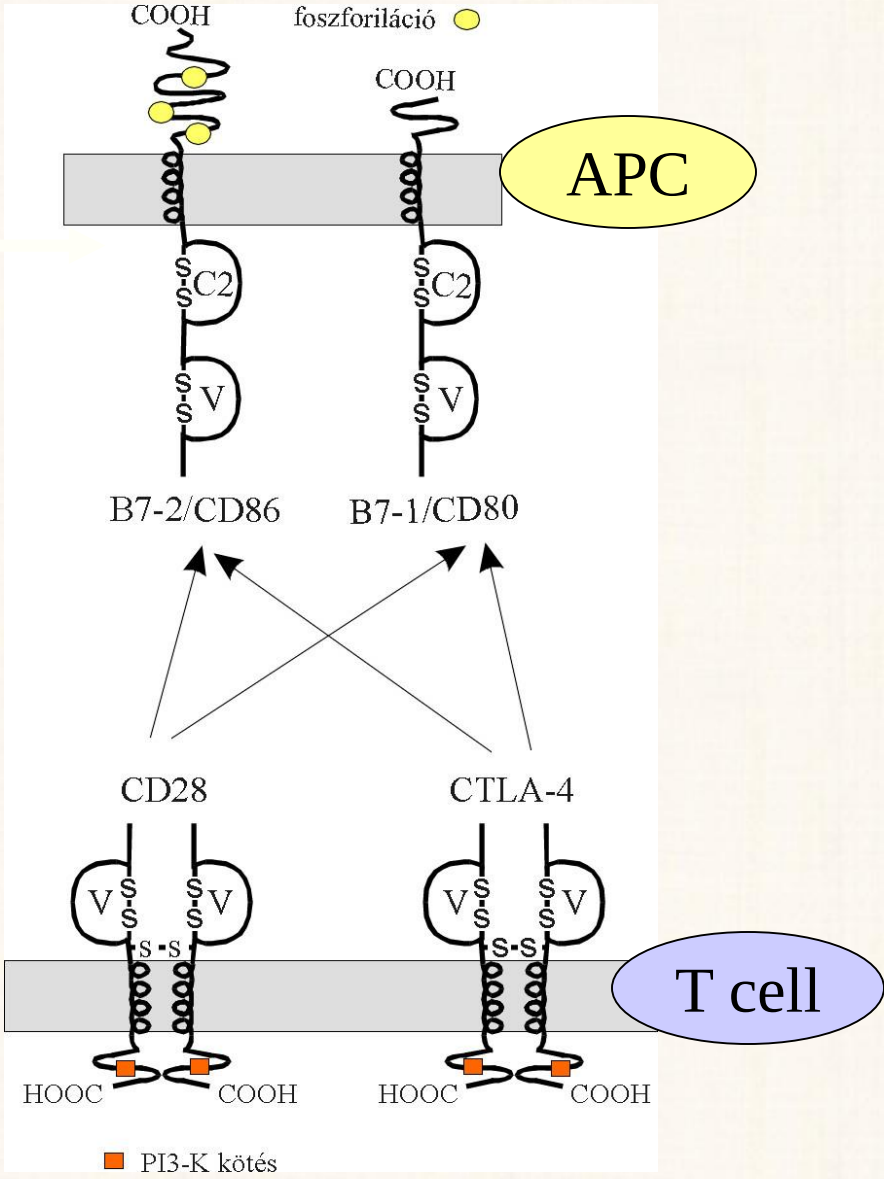


B7 (CD80, CD86), CD28 and CTLA-4 molecules

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

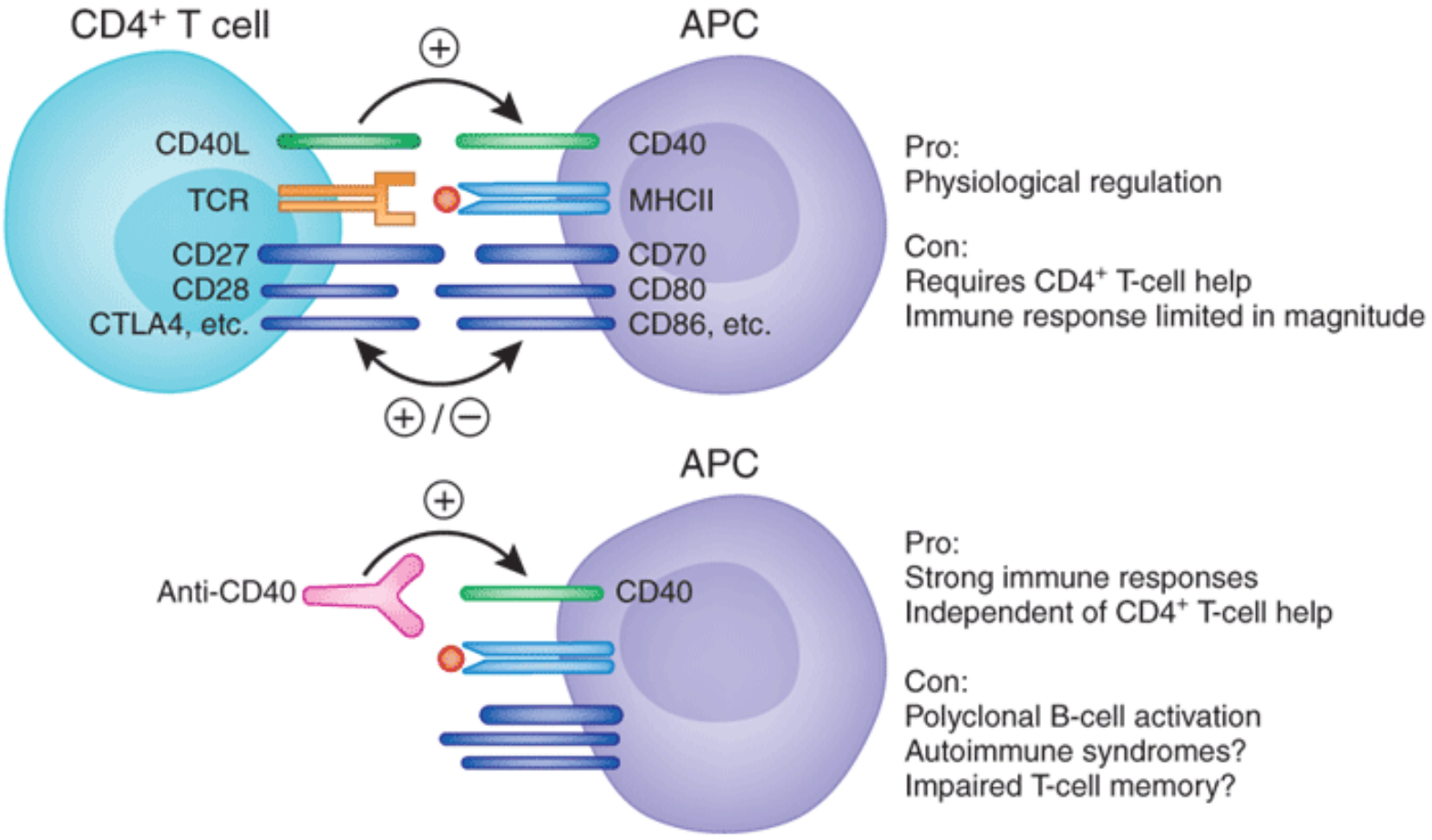
CD28: - co-stimulatory molecule in T cell activation
- Increases IL-2 and IL-2R expression,
- Induces T cell proliferation

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



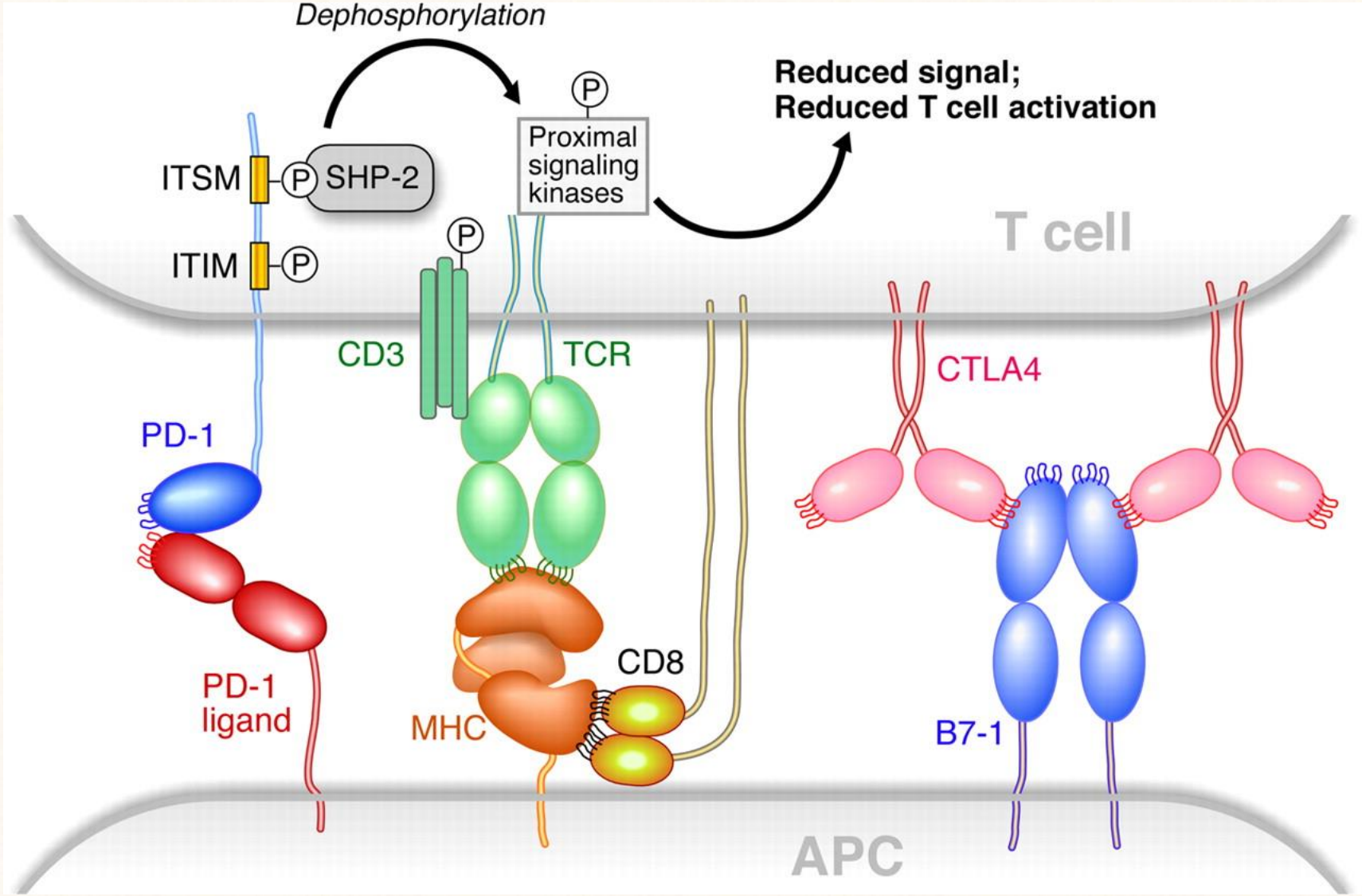
CTLA: **Cytolytic T lymphocyte associated Antigen**

CD40 and CD40L

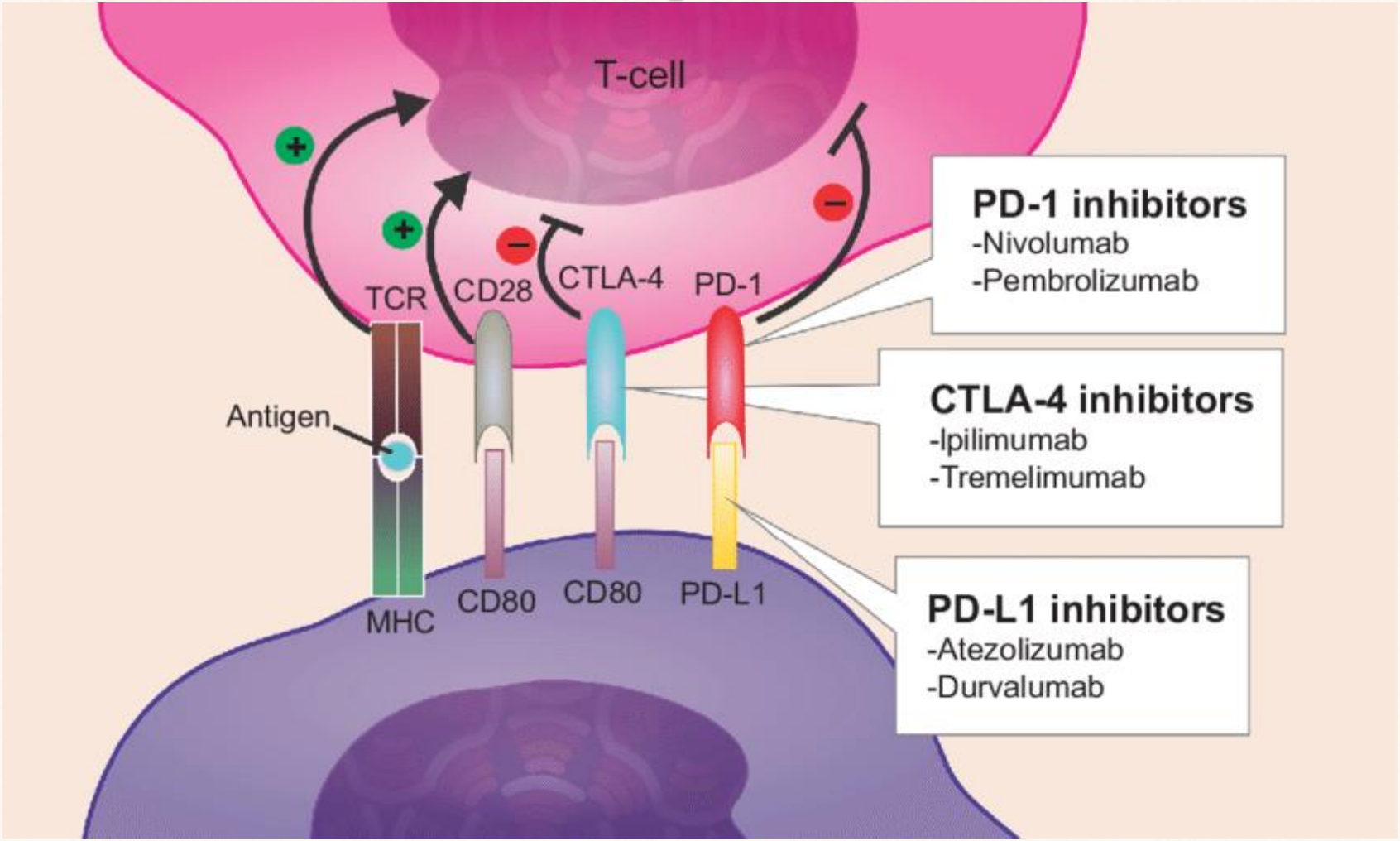


CD40 is a costimulatory protein found on antigen presenting cells and is required for their activation. The binding of CD154 (CD40L) on TH cells to CD40 activates antigen presenting cells and induces a variety of downstream effects

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



Immune checkpoint inhibitors



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

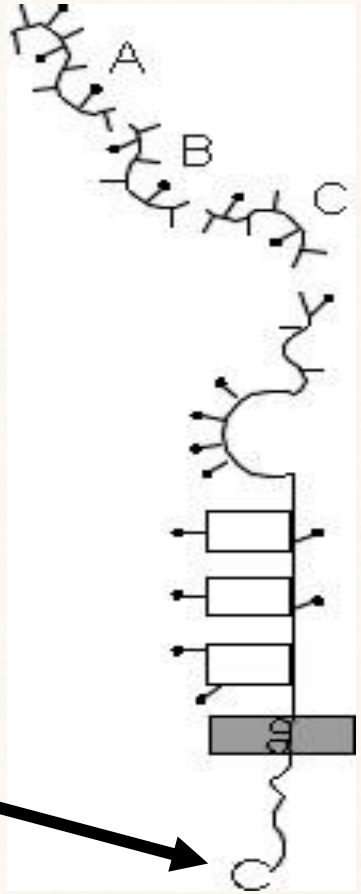
2018 Nobel Prize: use of immune checkpoint inhibitors to treat cancer.

„OTHER” accessory molecules

CD45

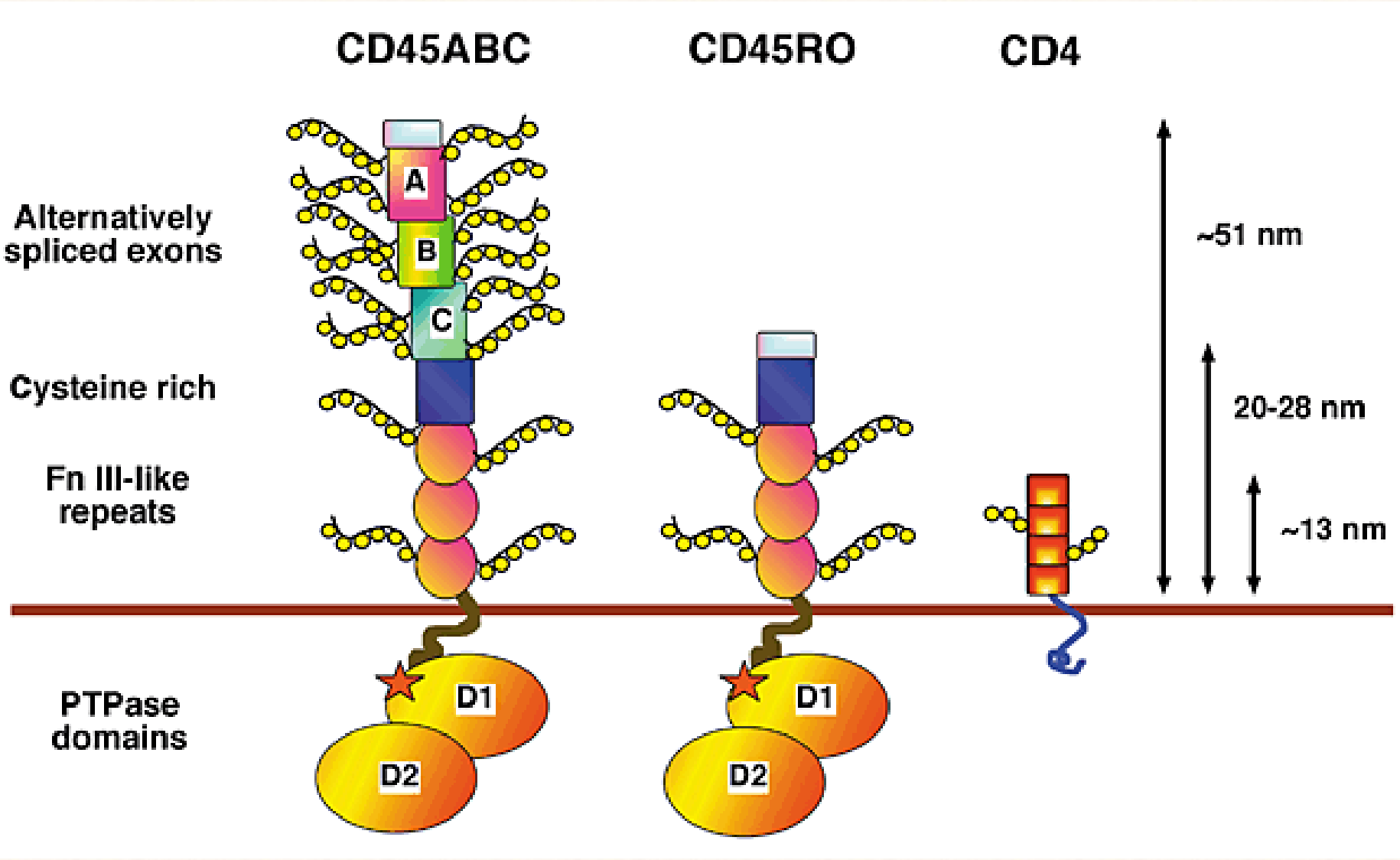
Expressed on every leukocyte
“pan-leukocyte marker”
- Highly glycosylated,
- More isoforms (180, 190, 200, 205, 220 kDa)
- alternate splicing

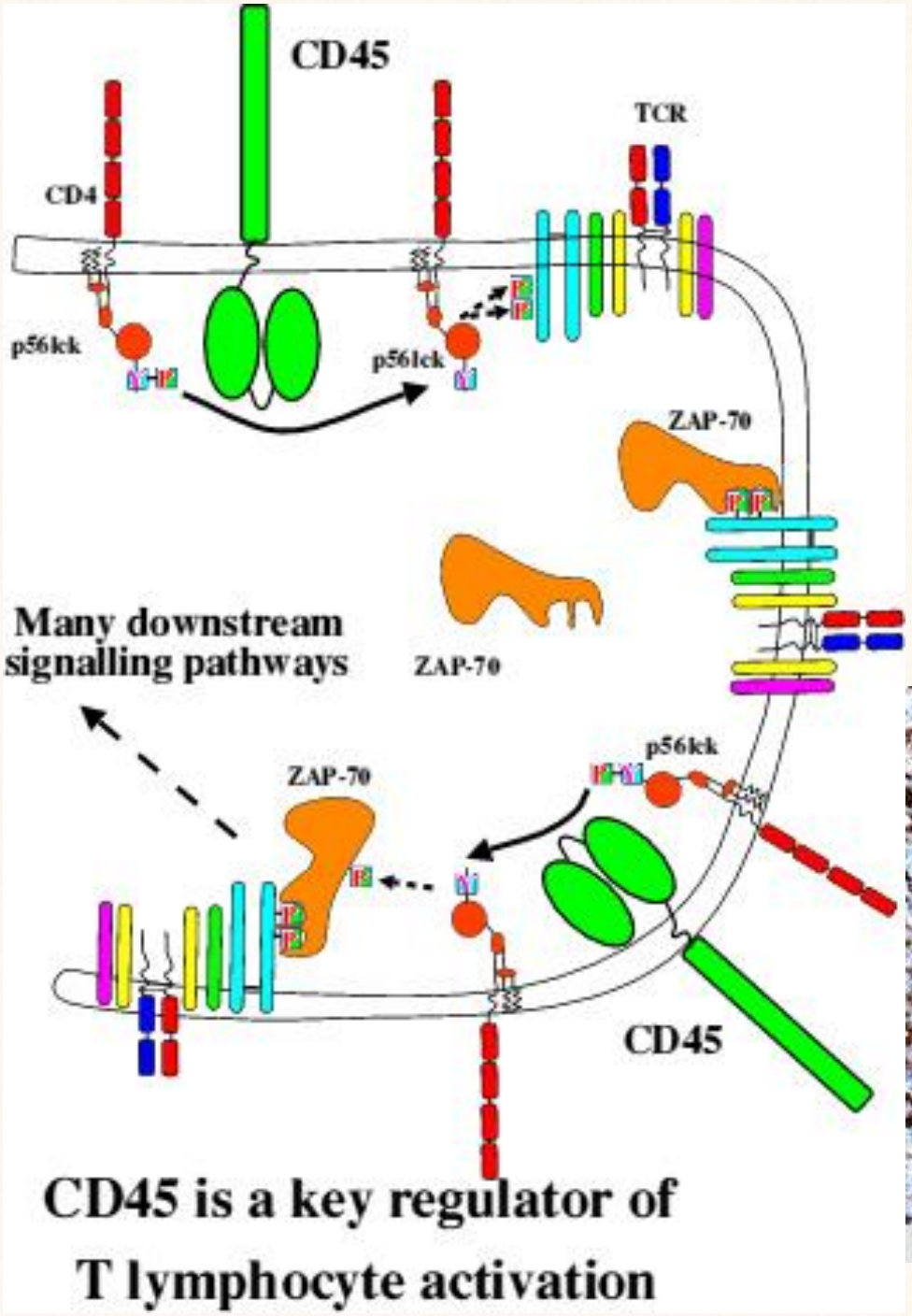
Plays important role in cell activation and in regulation of signal transduction
- ***protein-tyrosine-phosphatase domain: dephosphorylation***



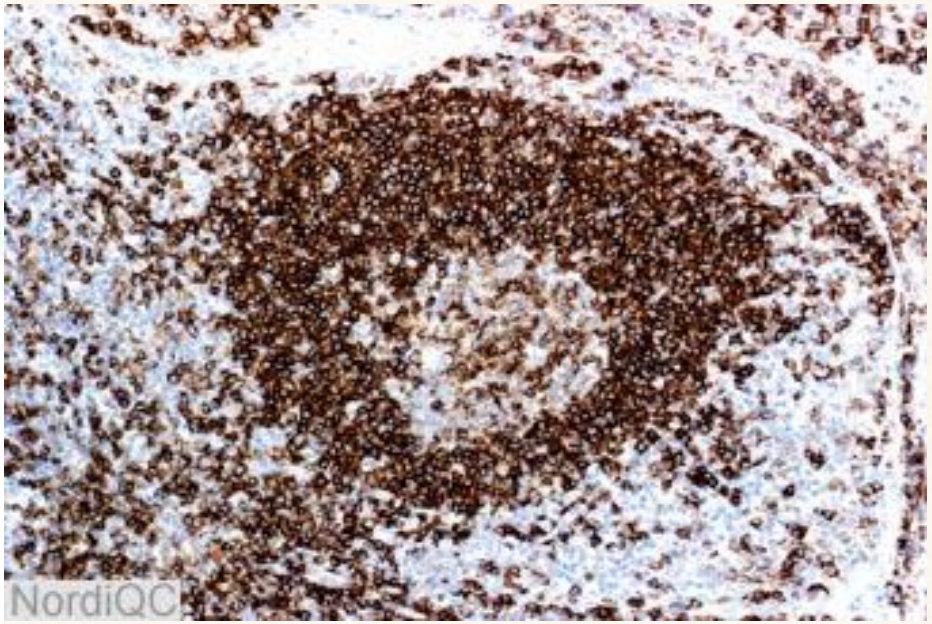
CD45

CD45 isoforms




CD45
TCR
CD4
p56lck
p561ck
ZAP-70
Many downstream
signalling pathways
ZAP-70
p56lck
ZAP-70
CD45
CD45 is a key regulator of
T lymphocyte activation

CD45


NordiQC

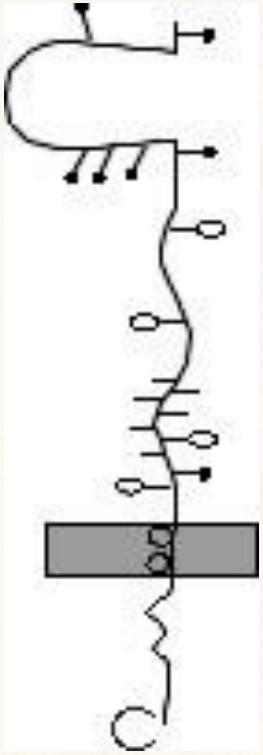
„OTHER” accessory molecules

CD44

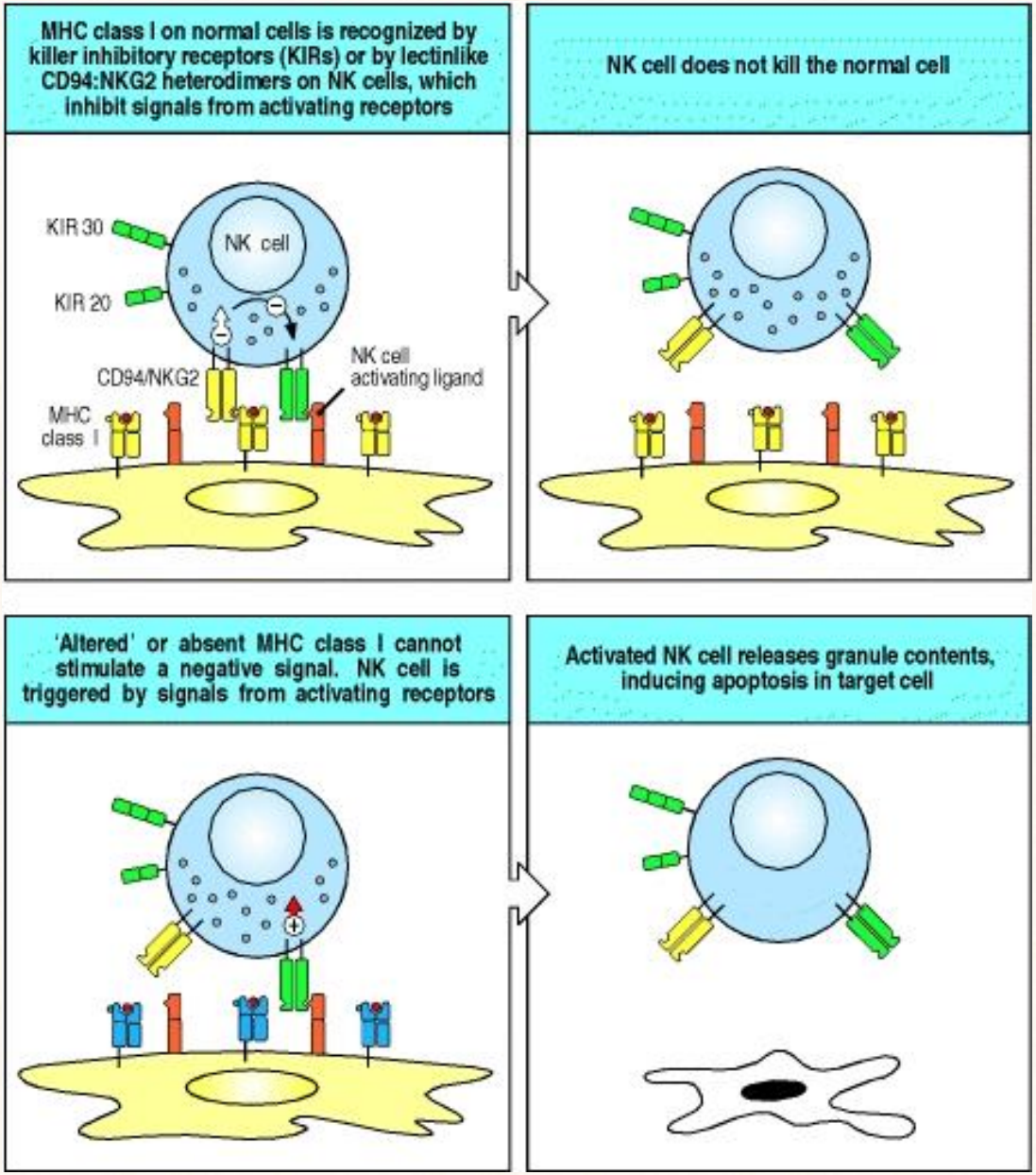
Expressed on activated and memory T- and B-cells, phagocytes, fibroblasts, neuronal cells and tumor cells.

More isoforms - *alternate splicing*

Important in migration of cells including „homing” of leukocytes

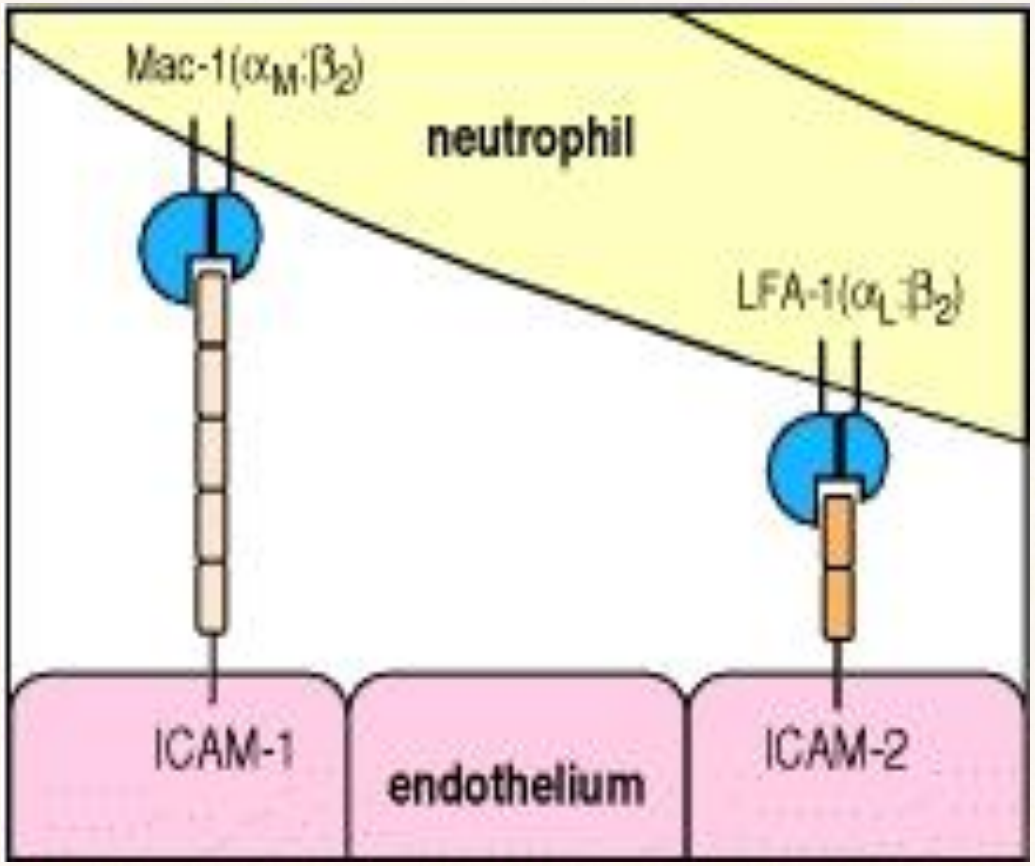


CD44



POSSIBLE MECHANISMS BY WHICH NK CELLS DISTINGUISH INFECTED FROM UNINFECTED CELLS

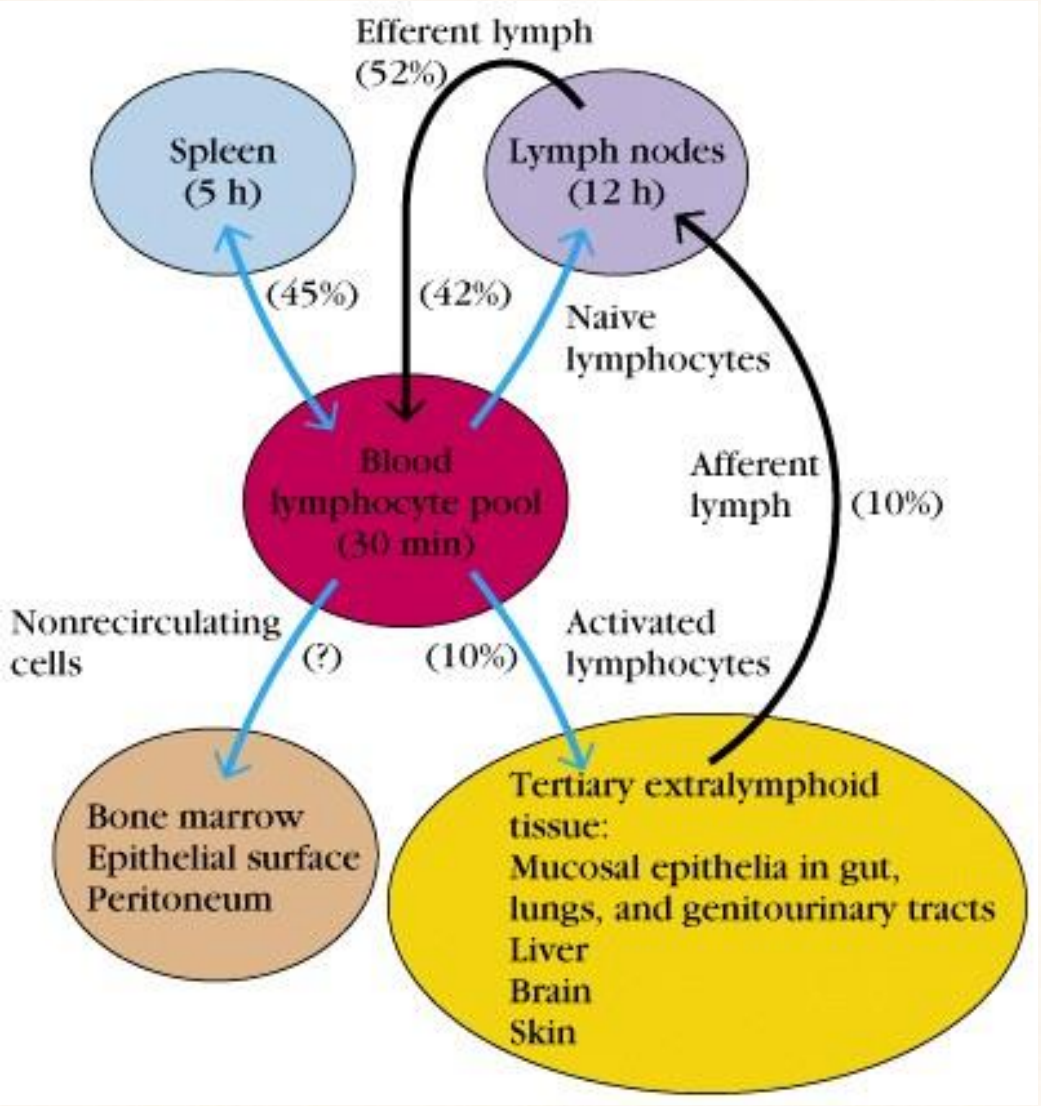
NK cells can use several different receptors that signal them to kill, including lectinlike activating receptors, or 'killer receptors,' that recognize carbohydrate on self cells. However, another set of receptors, called Ly49 in the mouse and killer inhibitory receptors (KIRs) in the human, recognize 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 immuno-globulin superfamily for KIRs. The KIRs are made in two forms, p58 and p70, which differ by the presence of one immunoglobulin domain.



PHAGOCYTE ADHESION TO VASCULAR ENDOTHELIUM IS MEDIATED BY INTEGRINS

Vascular endothelium, when it is activated by inflammatory mediators, expresses two adhesion molecules—ICAM-1 and ICAM-2. These are ligands for integrins expressed by phagocytes—αL:β2 (also called LFA-1 or CD11a: CD18) and αM:β2 (also called Mac-1, CR3, or CD11b:CD18).

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



Role:

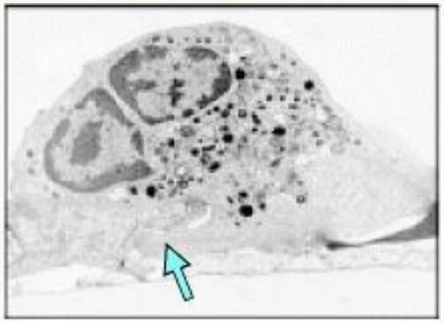
- Promots the antigen capturing

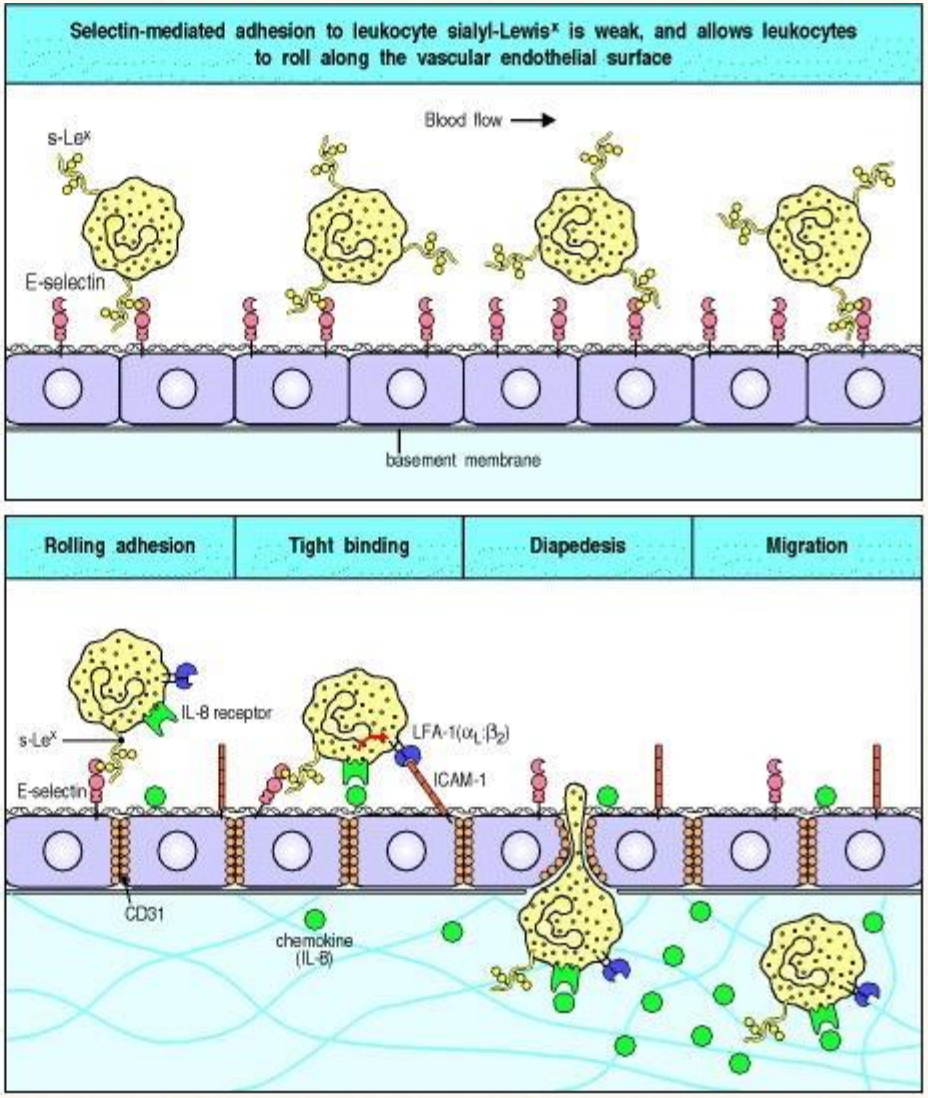
- Promots the development of inflammatory reactions

Mechanism:

-<u>Extravasation</u>: 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

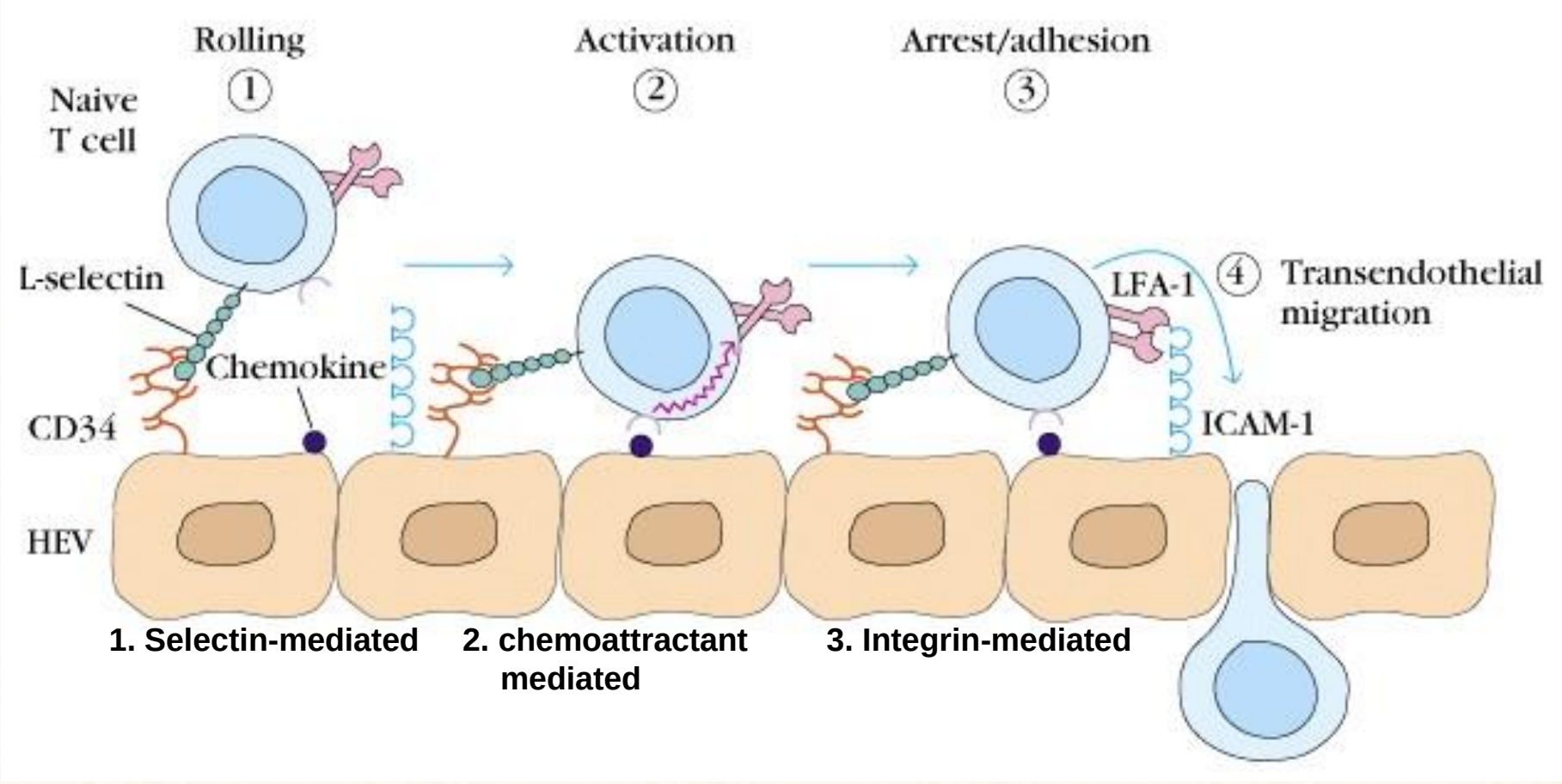




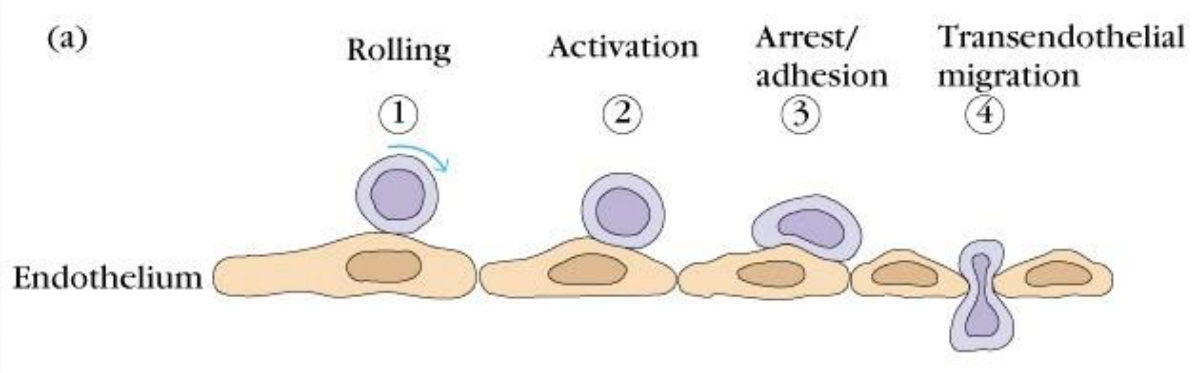
Neutrophils leave the blood and migrate to sites of infection in a multistep process mediated through adhesive interactions that are regulated by macrophage-derived cytokines and chemokines.

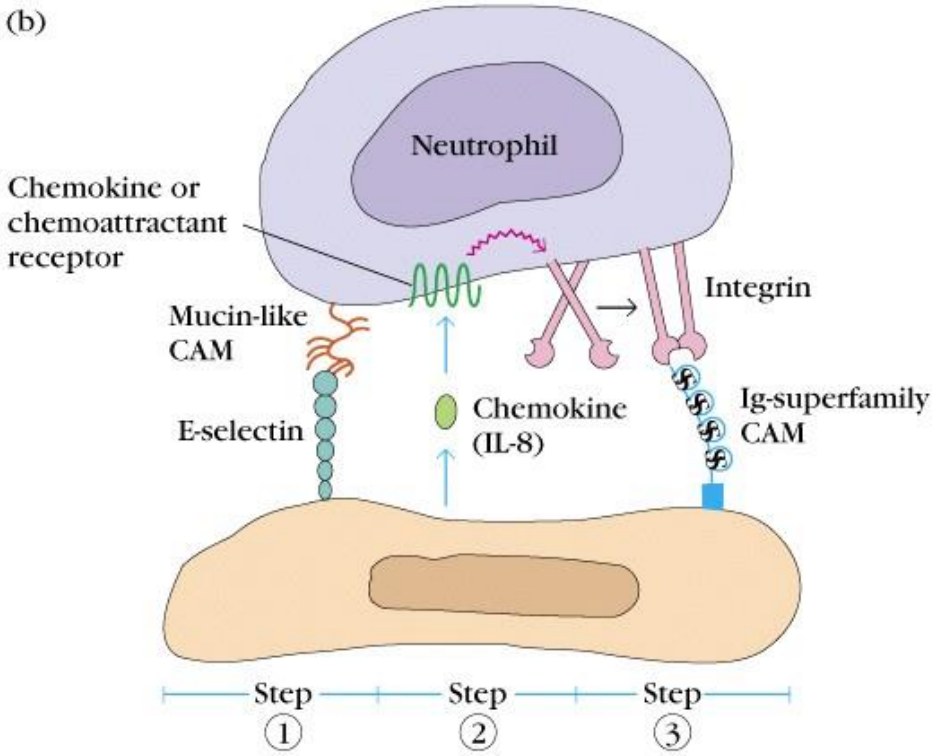
Naive lymphocytes migrating to the peripheral lymphatis tissues

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

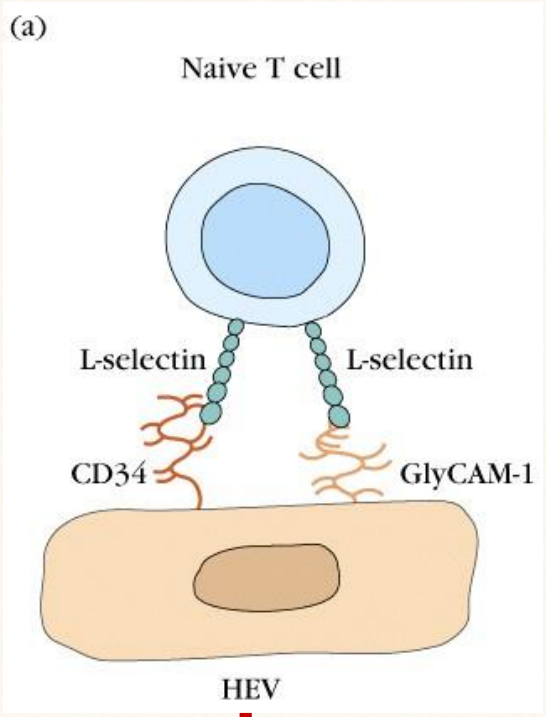


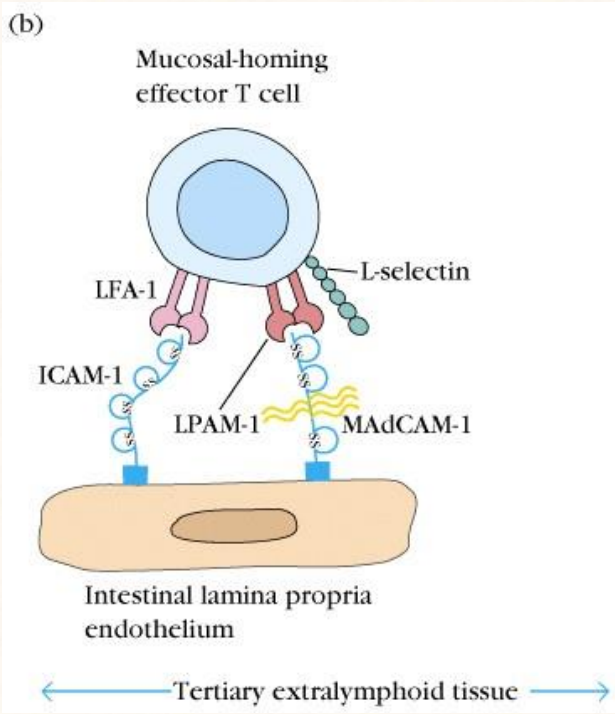
Migration of neutrophil granulocytes to the inflammed tissues throgh the endothel

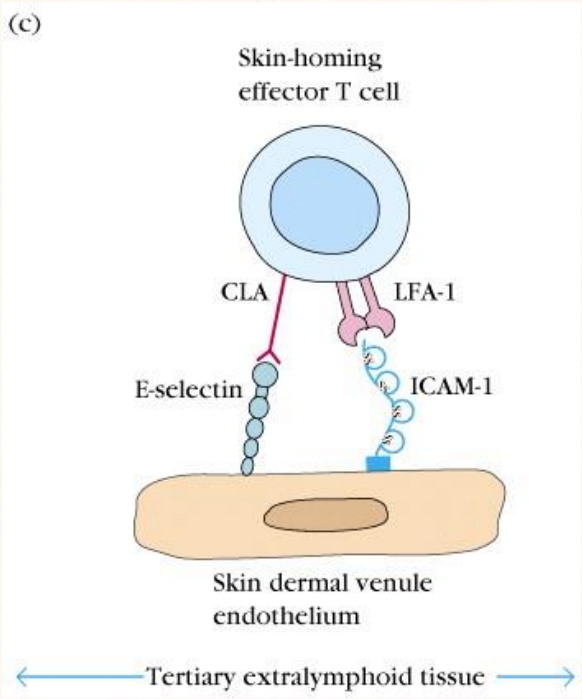




Different adhesion molecules determine the migration of naive and memory (effector) cells







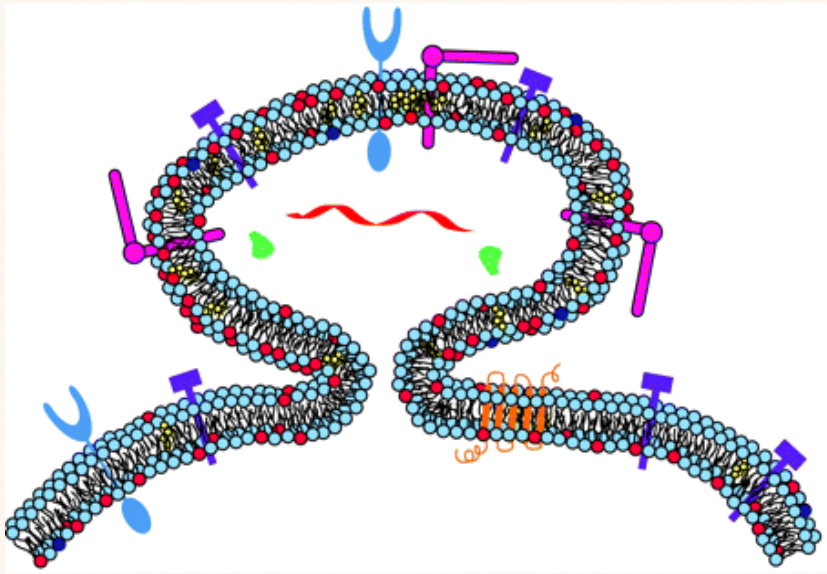
Peripheral lymphatic tissue

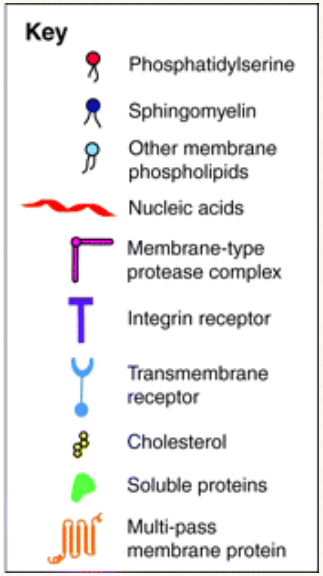
Inflammatory tissue

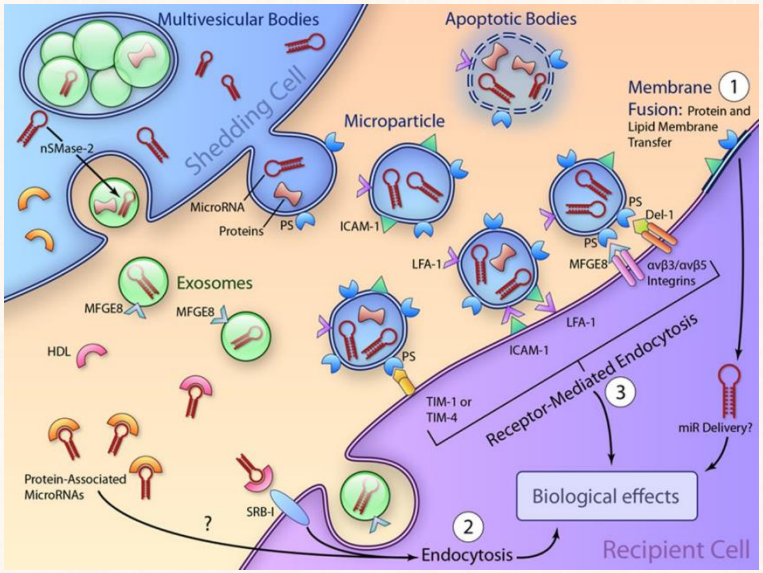
Some important accessory molecules

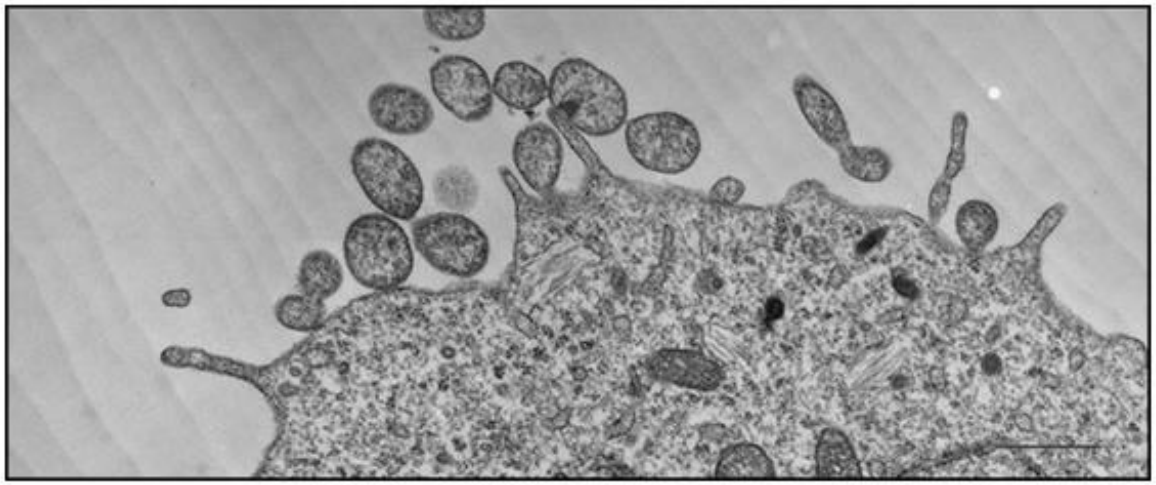
- CD3
- CD4 and CD8
- CD28
- CD80/86 (B7.1 and B7.2)
- CD152 (CTLA4)
- CD25 (IL-2 Receptor)
- CD45RA/RO
- CD154 (CD40 Ligand)

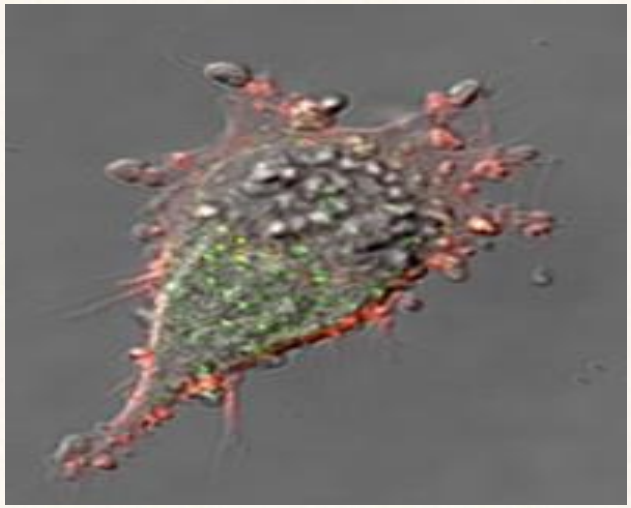
Microvesicles



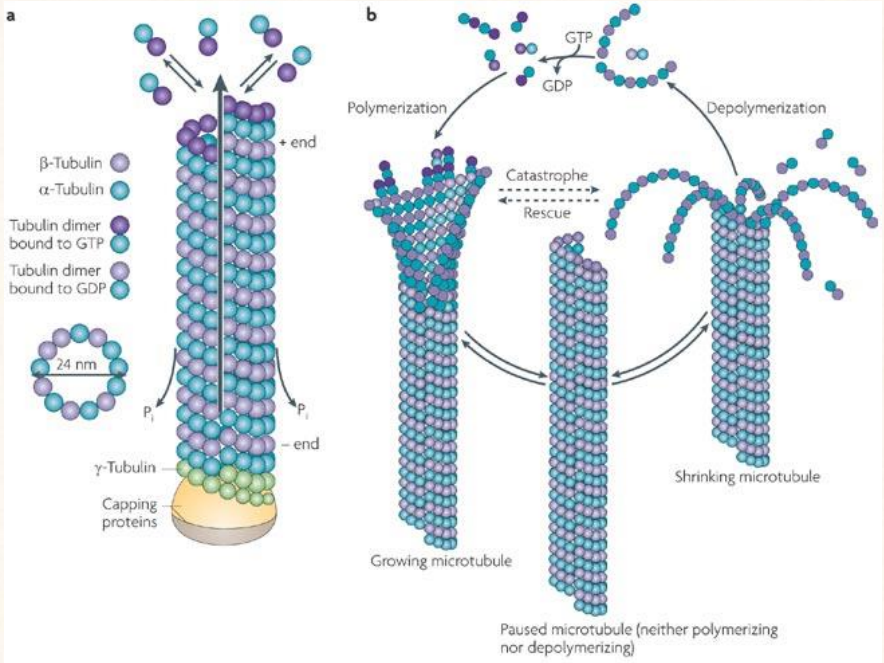








Mikrotububes



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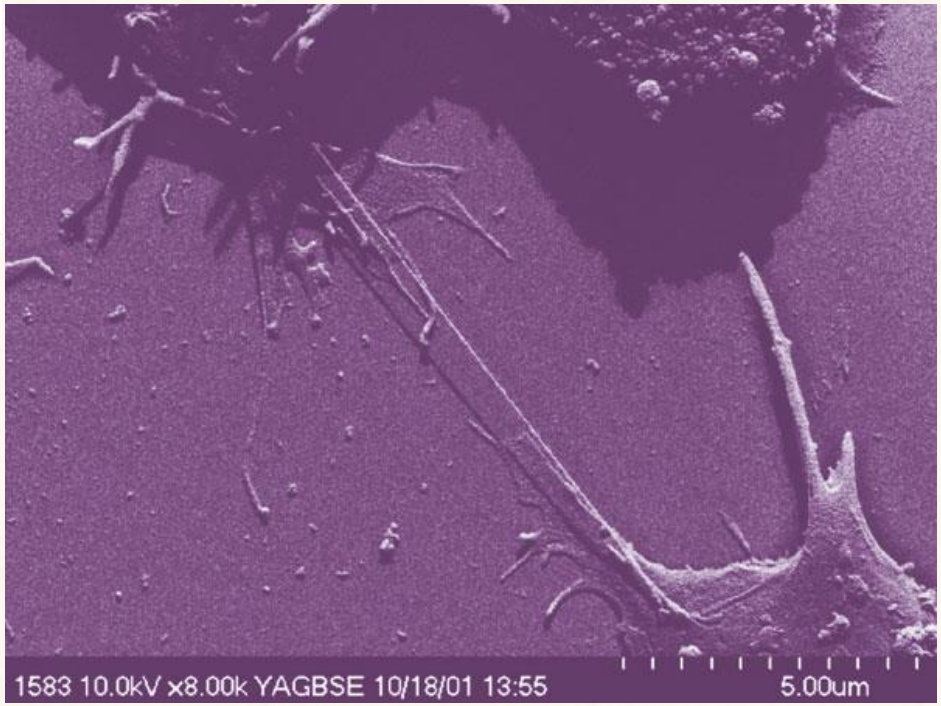
Direct cell-cell communication?



Cell-cell communication through cytokines and their receptors

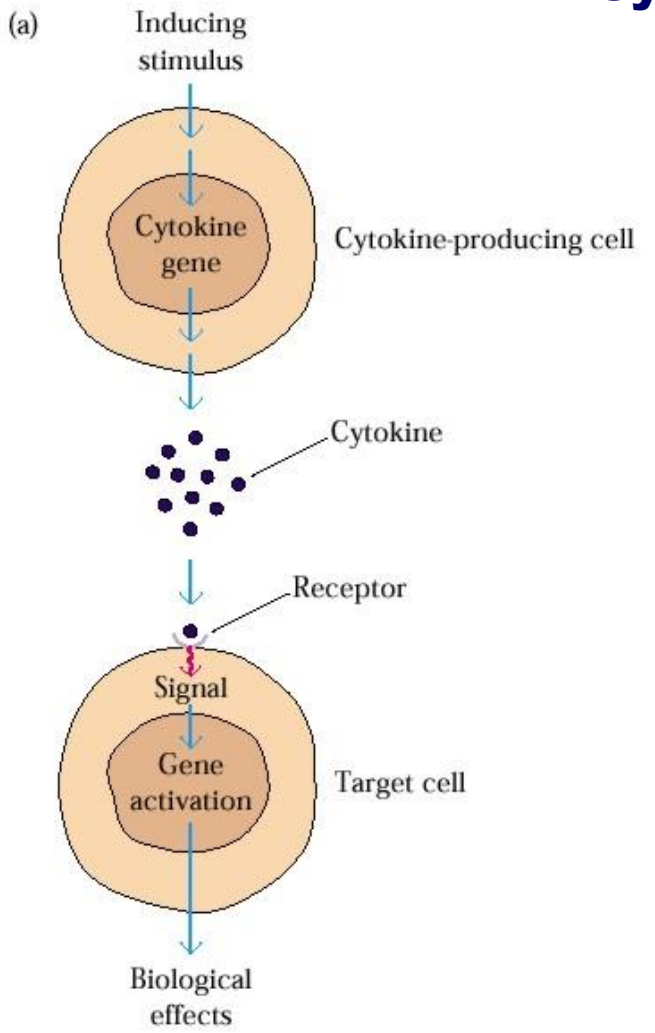
- Cytokines
- Chemokines
- Interferons
- Growth factors
- Tissue hormons

Basic characteristics of cytokies

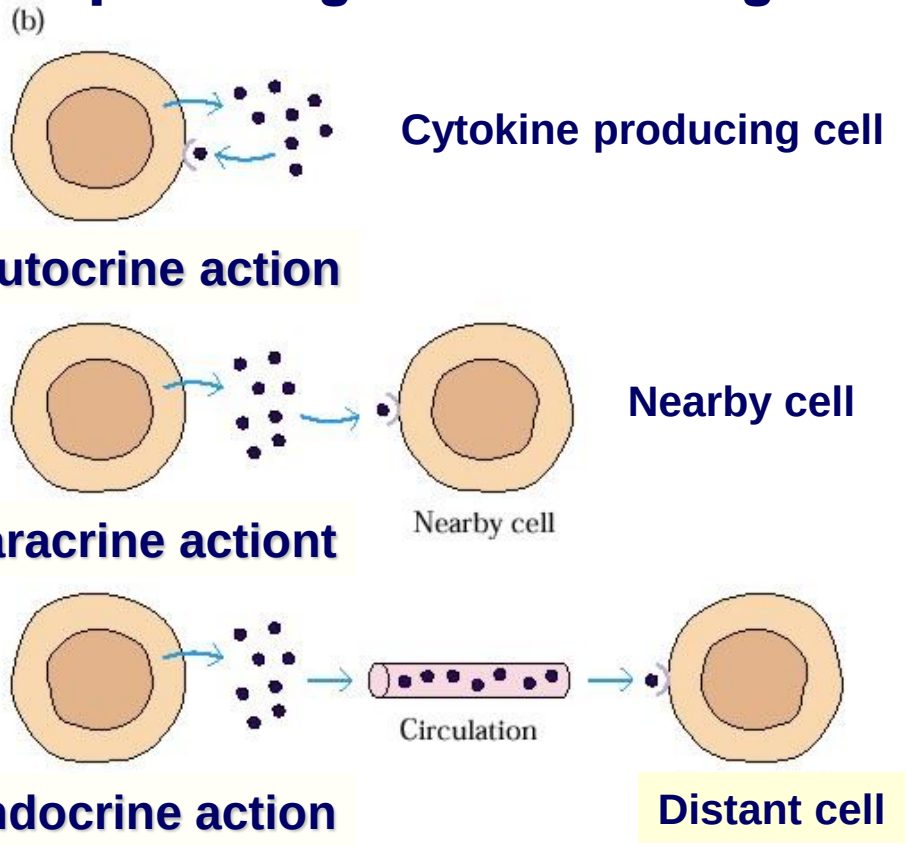
- Low molecular weight (10-40 kDa), and genetically well conserved glycoproteins
- Isolated cells secrete them, due to gene activation
- They mediate cell-cell interaction:
- - sending information
- - general regulation of biological homeostasis including immune response
- Mechanism of action:

  - 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:**



Mechanism of cytokine action II.

A cytokine induces different effects on different target cells

Pleiotropy

The action of more cytokine on the target cell is similar

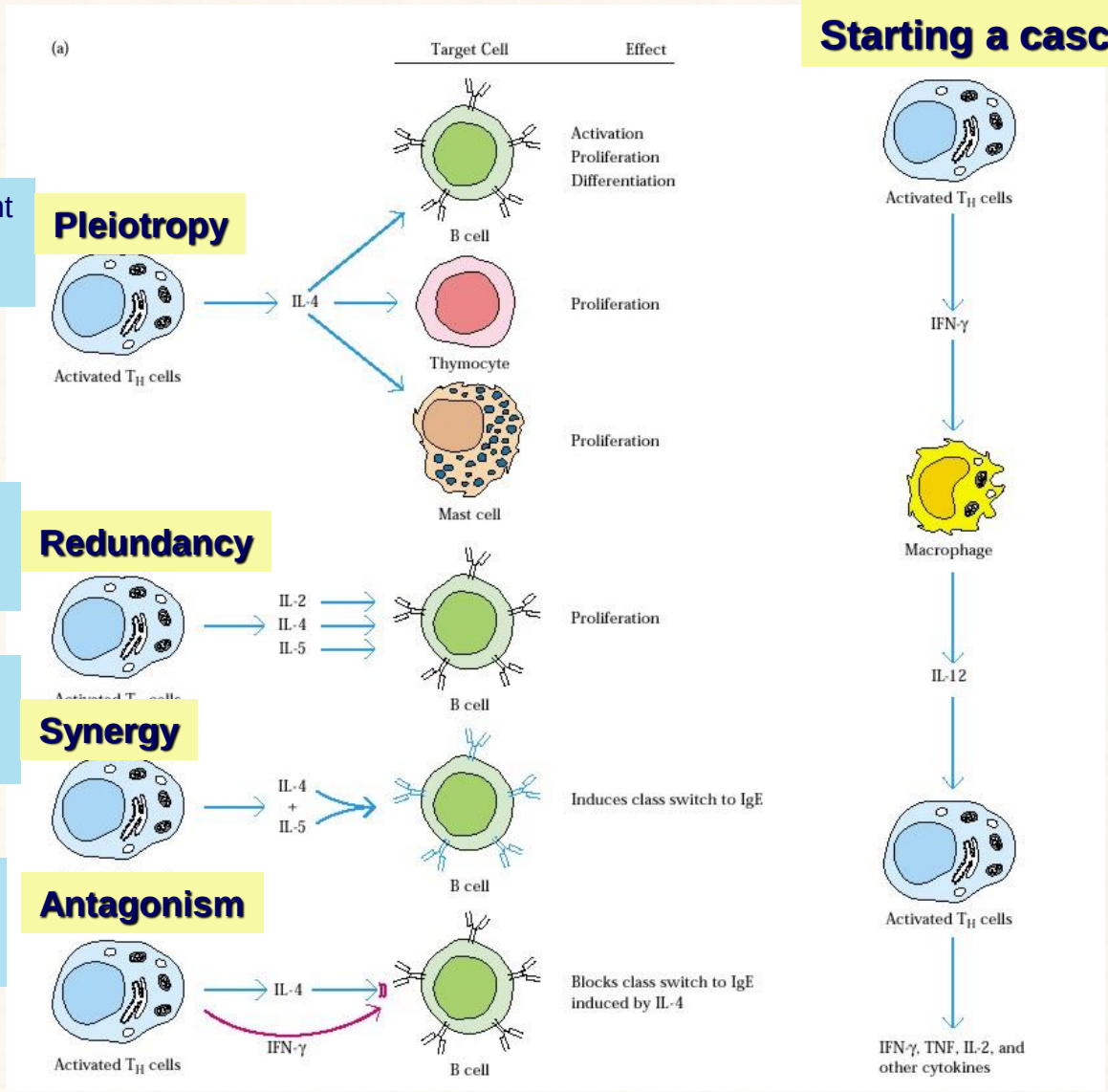
Redundancy

The effect of two cytokines is stronger than their additive effects

Synergy

One cytokine inhibits the effects of another cytokine

Antagonism

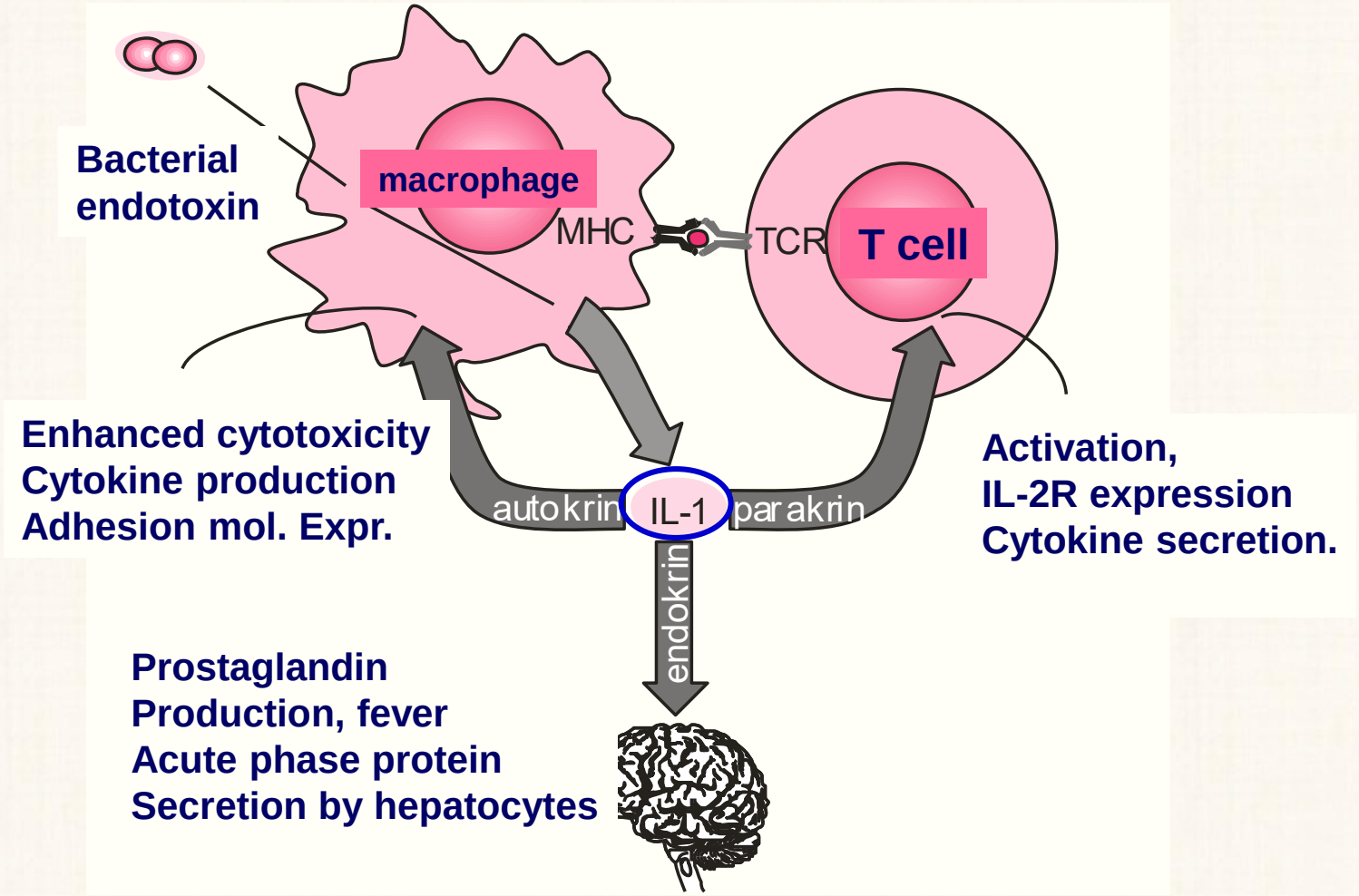


Starting a cascade

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**

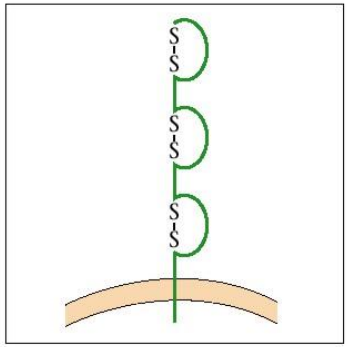
Autocrine, paracrine and endocrine action of IL-1



Cytokine receptors

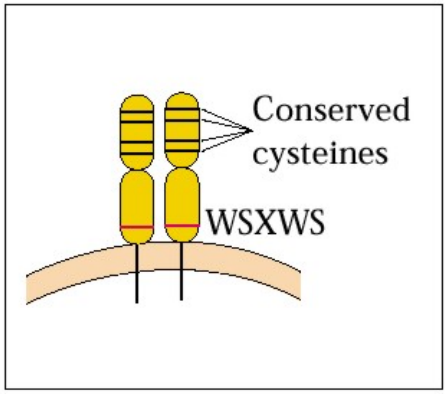
RECEPTOR FAMILY — LIGANDS

(a) Immunoglobulin superfamily receptors



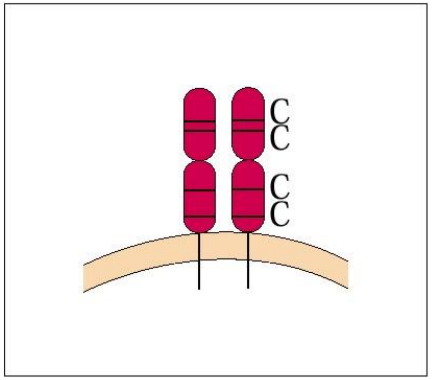
IL-1
M-CSF
C-Kit

(b) Class I cytokine receptors (hematopoietin)



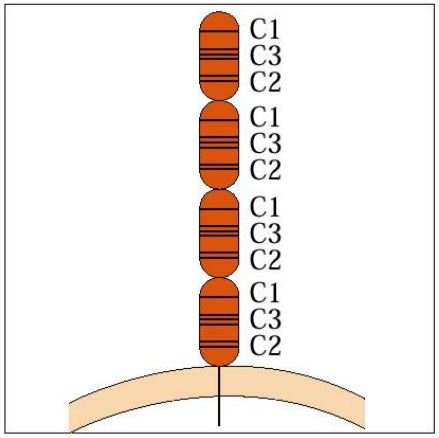
IL-2
IL-3
IL-4
IL-5
IL-6
IL-7
IL-9
IL-11
IL-12
IL-13
IL-15
GM-CSF
G-CSF
OSM
LIF
CNTF
Growth hormone
Prolactin

(c) Class II cytokine receptors (interferon)



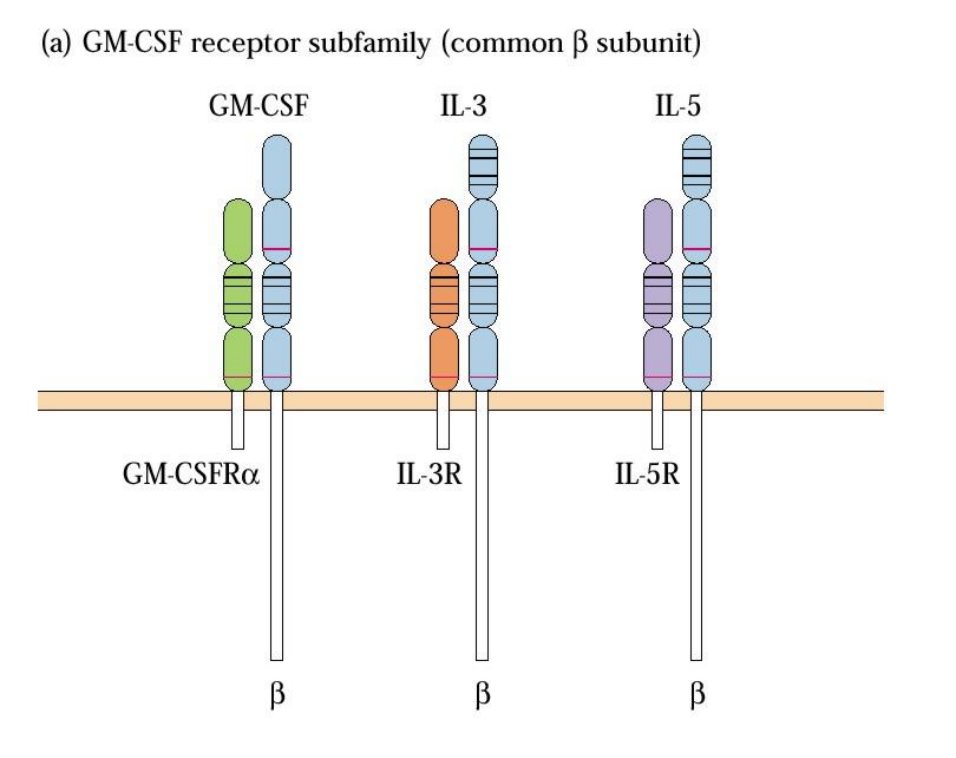
IFN-α
IFN-β
IFN-γ
IL-10

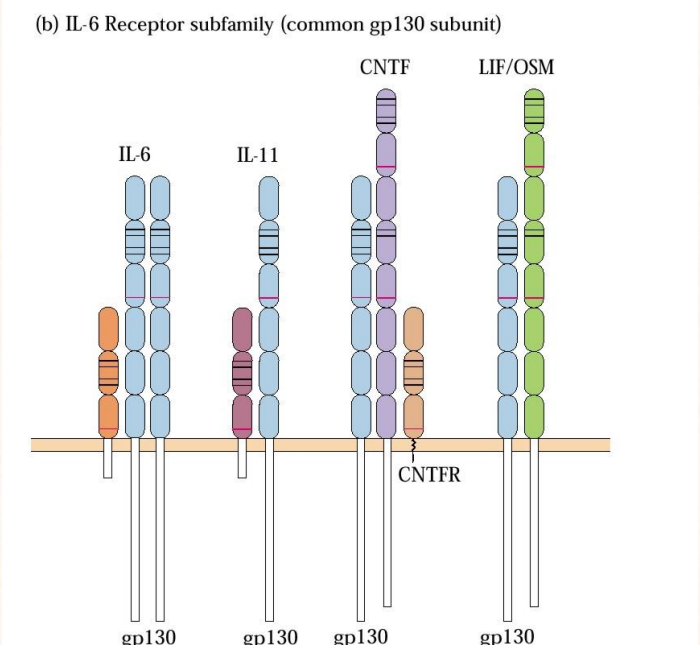
(d) TNF receptors

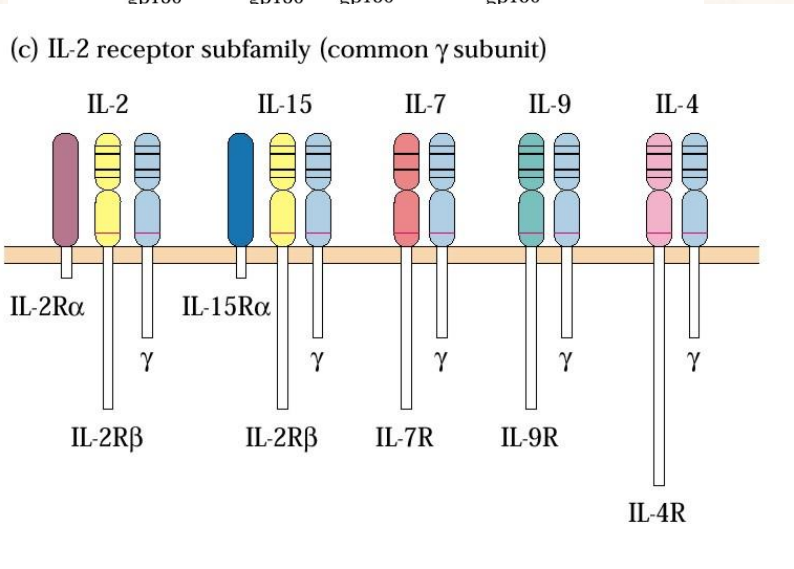


TNF-α
TNF-β
CD40
Nerve growth factor (NGF)
FAS

Characteristics of multichain cytokine receptors







Chemokines

- 90-130 aa. Polypeptides
- Receptorial action
- Produced by lymhatic 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