INNATE IMMUNITY

When you were born, you brought with you several mechanisms to prevent illness. This type of immunity is also called nonspecific immunity.

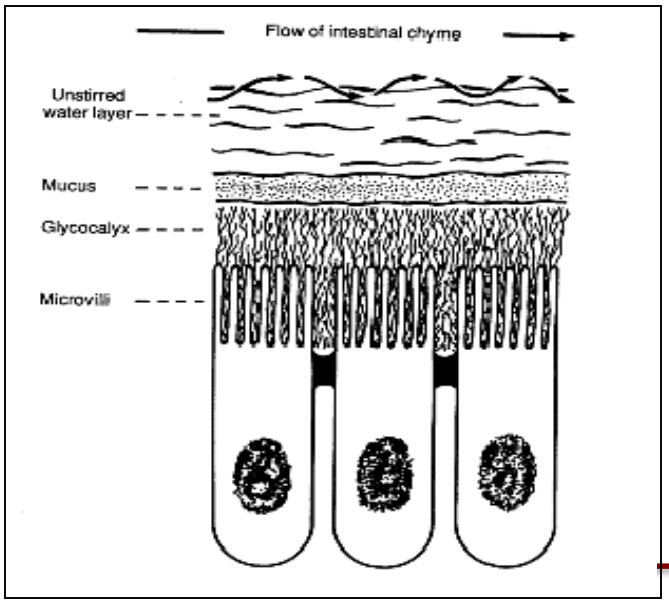
Innate immunity consists of:

- Barriers
- Cellular response
  - phagocytosis
  - inflammatory reaction
  - NK (natural killer) and mast cells
- Soluble factors

INNATE IMMUNITY
Cellular response

- nonspecific - the same response works against many pathogens
- this type of response is the same no matter how often it is triggered
- the types of cells involved are macrophages, neutrophils, natural killer cells, and mast cells
- a soluble factor, complement, is also involved

Innate barriers to infections…



1) **Anatomic**

skin -> epidermis w/ keratin

mucus memb. ->inner surfaces

2) **Physiological**

temperature, pH, soluble subst.

3) **Phagocytes**

blood monocytes, tissue MØ, and neutrophils

4) **Inflammatory response**

triggered by wound/foreign particle

4 Cardinal signs reflect 3 major events of inflam response:

-vasodilation

- >capillary permeability

-influx of phagocytes

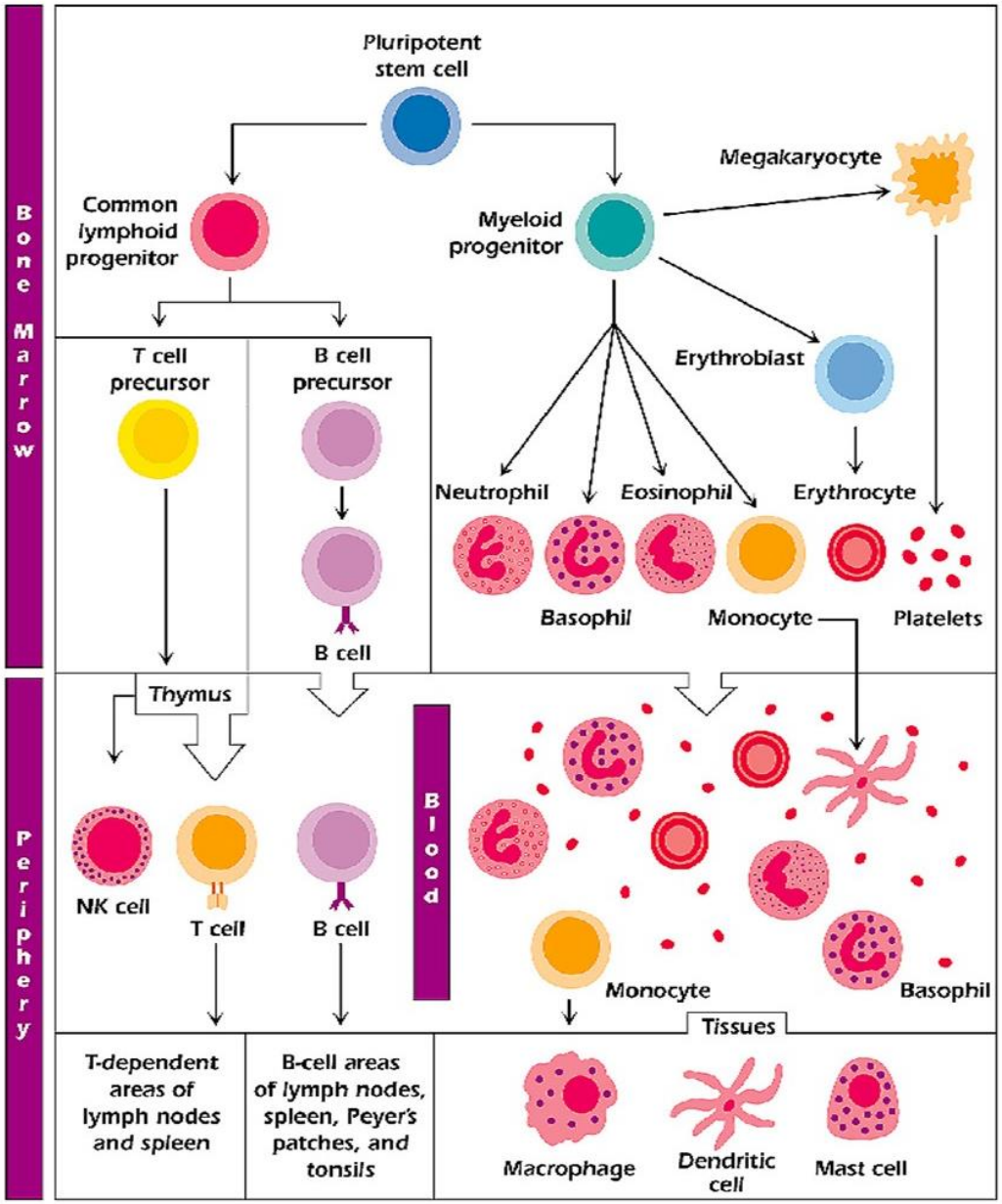


Figure 2.1. Developmental pathways of various hematopoietic cells from pluripotential bone marrow stem cells.

Polymorphonuclear Leukocytes (PMNs)

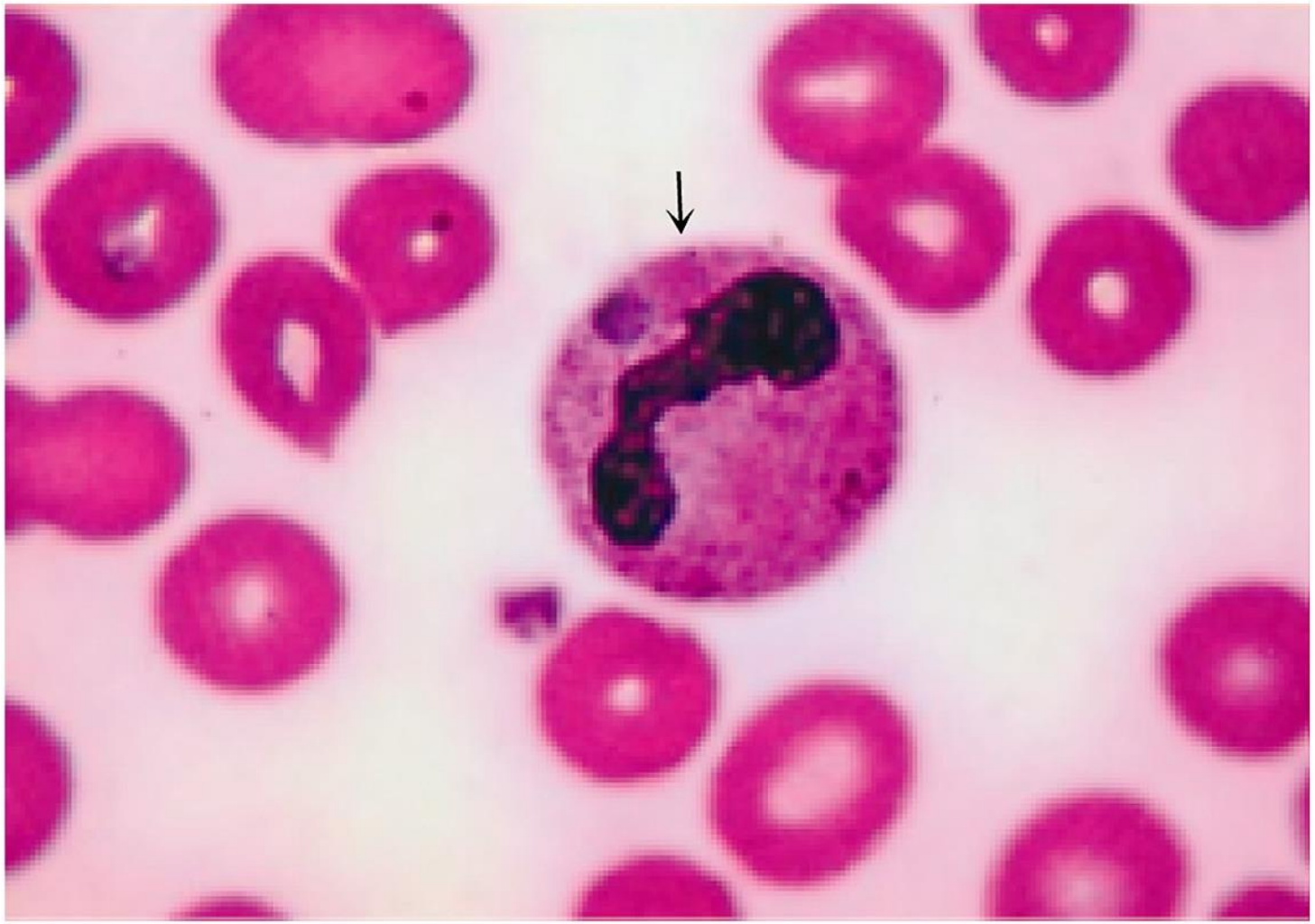
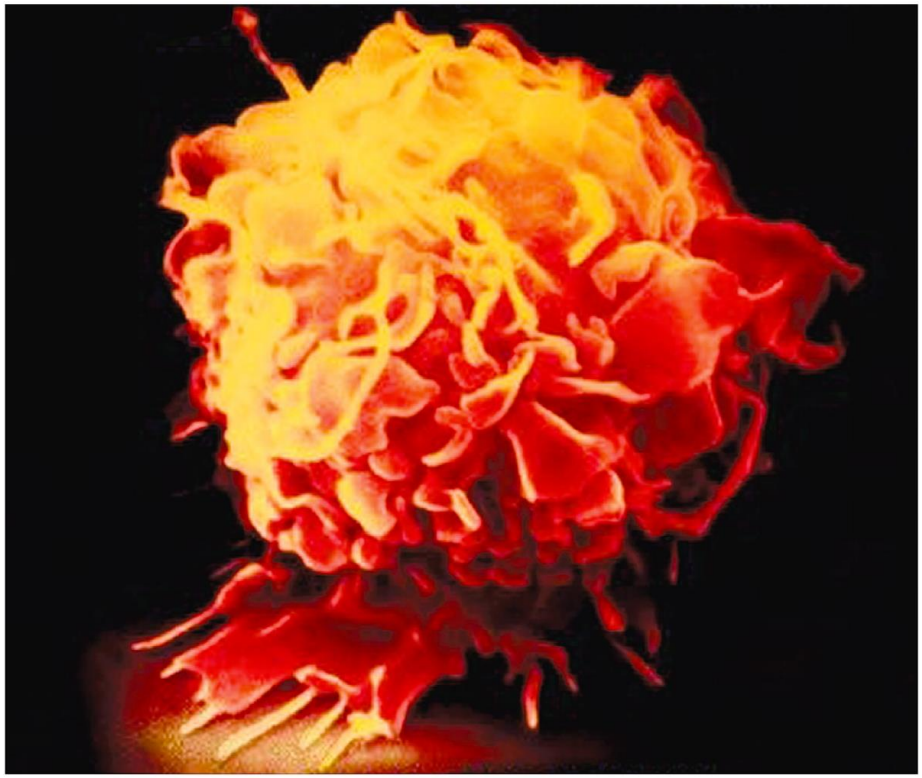
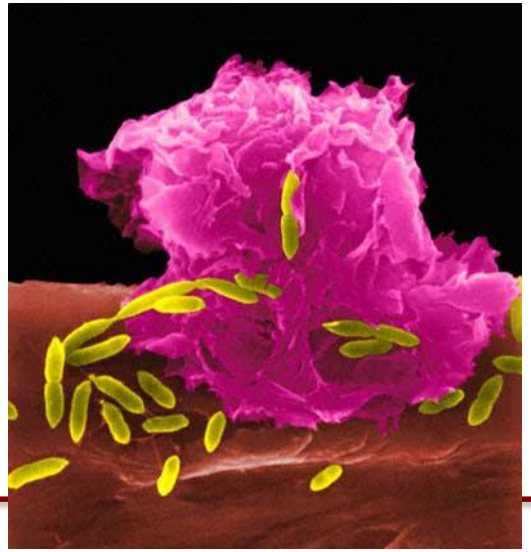


Figure 2.2. A PMN (surrounded by erythrocytes) with trilobed nucleus and cytoplasmic granules (×950). (Reproduced with permission from Olana and Walker, *Infect Med* 19: 318 [2007].)

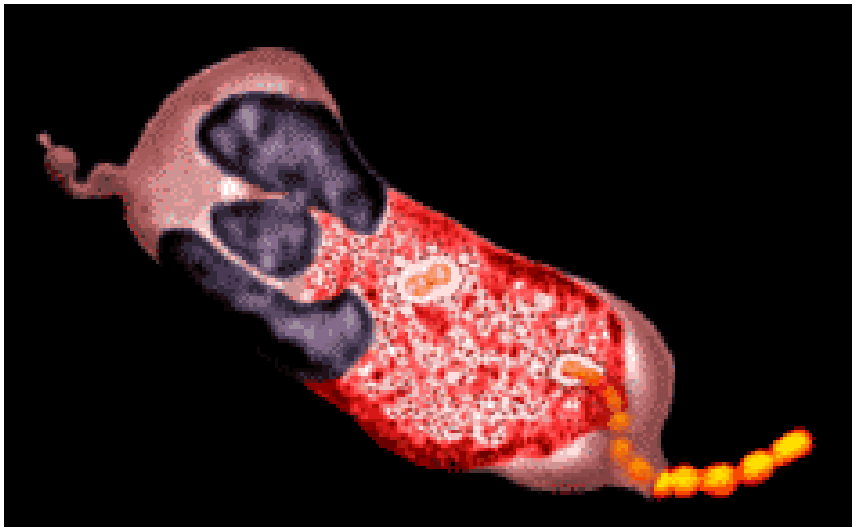
Macrophages

- WBCs that ingest bacteria, viruses, dead cells, dust
- most circulate in the blood, lymph and extracellular fluid
- they are attracted to the site of infection by chemicals given off by dying cells
- after ingesting a foreign invader, they “wear” pieces of it called antigens on their cell membrane receptors – this tells other types of immune system cells what to look for





Neutrophil phagocytosing *S. pyogenes,* the cause of strep throat



CELLS alive!

Human neutrophils are WBCs that arrive quickly at the site of a bacterial infection and whose primary function is to eat and kill bacteria. This neutrophil ingesting *Streptococcus pyogenes* was imaged in gray scale with phase contrast optics and colorized. neutrophils also release toxic chemicals that destroy everything in the area, including the neutrophils themselves

Natural killer cells (NK cells)

- instead of attacking the invaders, they attack the body's own cells that have become infected by viruses
- they also attack potential cancer cells, often before they form tumors
- they bind to cells using an antibody "bridge", then kill it by secreting a chemical (perforin) that makes holes in the cell membrane of the target cell. With enough holes, the cell will die, because water rushing inside the cell will induce osmotic swelling, and an influx of calcium may trigger apoptosis.

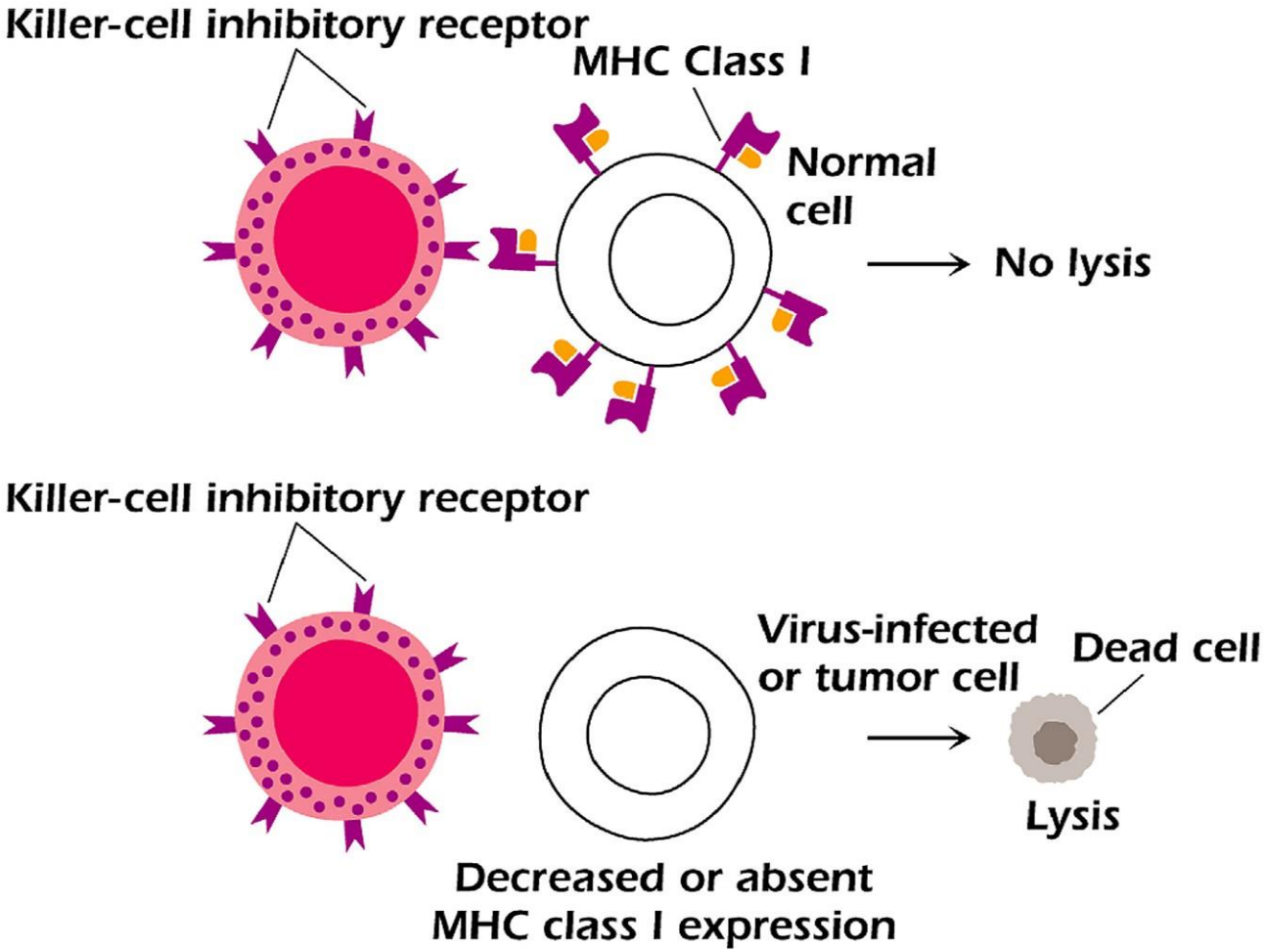


Figure 2.4. NK-cell inhibitory receptors and killing.

Natural killer T cells (NKT cells)

- TCRs with restricted variability
- Recognize Gram – and + bacterial cell wall comp.
- Secrete IL-4 and interferony

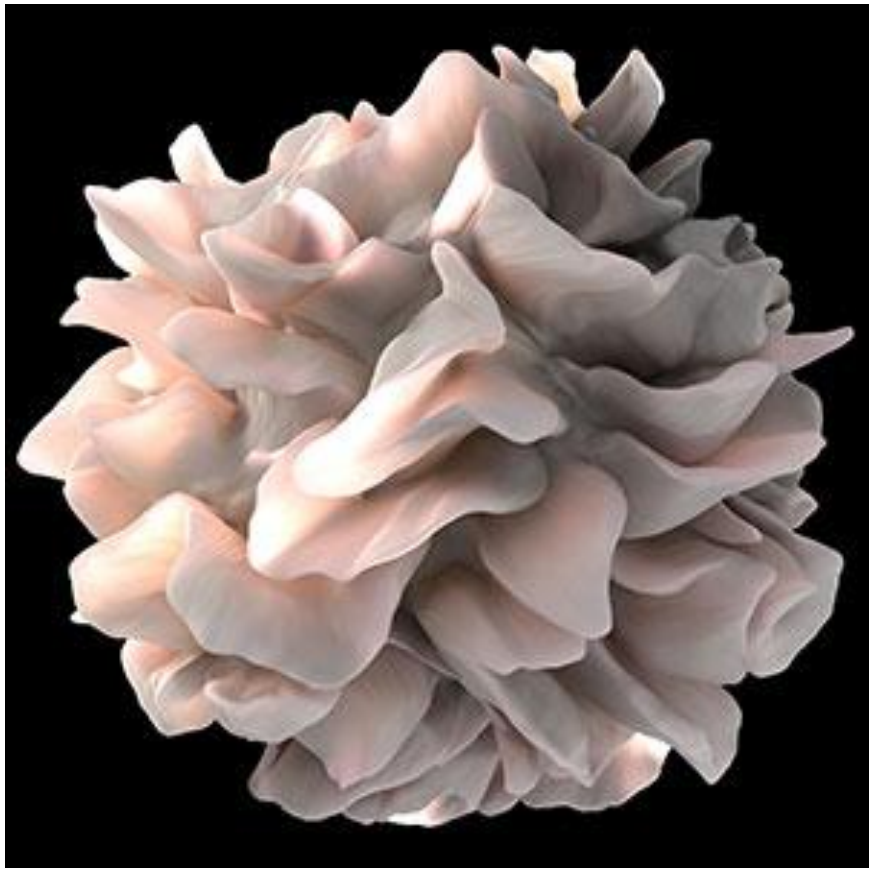
Fas/Fas Ligand Interactions Promote Activation-Induced Cell Death of NK T Lymphocytes

Maria C. Leite-de-Moraes, André Herbelin, Christine Gouarin, Yasuhiko Koezuka, Elke Schneider and Michel Dy

J Immunol 2000; 165:4367-4371; ;
doi: 10.4049/jimmunol.165.8.4367
http://www.jimmunol.org/content/165/8/4367

Dendritic Cells

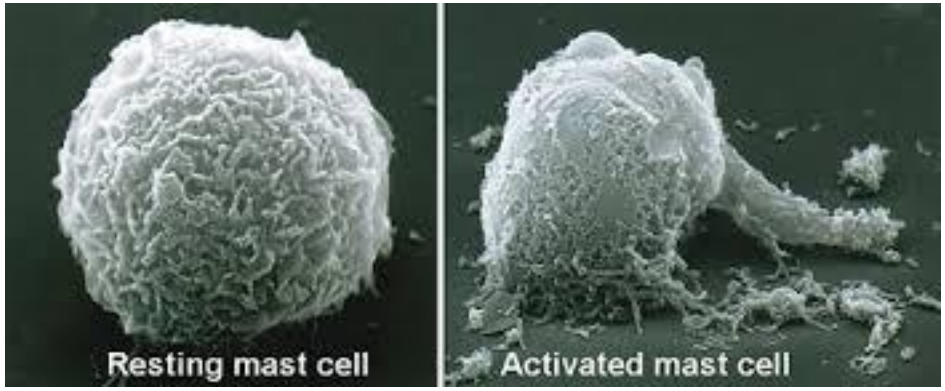
- APC
- Phagocytosis
  - Follicular DCs in thymus & spleen
  - Langerhans in skin and mucosa
  - Plasmacystoid DCs (noT myleoid but lymphoid) thus, secretes IFN-α/β



Innate Lympoid Cells (ILCs)

- Heteregenous populations of immune innate cells
  - Acute phase infection
  - Tissue remodeling-wound healing
  - Containment of good bacterial
  - Patrolling mucous barries (airways, gastrointestinal tracks)
- Sub-population of ILCs induce lymphoid cells → needs IL-12γ

Mast cells



- are found in tissues like the skin, near blood vessels.
- are activated after antigen binds to a specific type of antibody called IgE that is attached to receptors on the mast cell.
- activated mast cells release substances that contribute to inflammation, such as histamine.
- mast cells are important in allergic responses but are also part of the innate immune response, helping to protect from infection.

Pattern Recognition

	Innate immunity	Adaptive immunity
Specificity	For PAMPs: evolutionarily conserved structures shared by classes of microbes Different microbes Identical mannose receptors	For specific microbial molecules (antigens) Different microbes Distinct antibody molecules
Receptor types	PRRs encoded in germline, limited diversity Toll-like receptor *N*-formyl methionyl receptor Mannose receptor	Encoded by genes produced by somatic recombination of gene segments, greater diversity Ig TCR
Cellular distribution of receptors	Nonclonal: identical receptors on all cells of the same linage	Clonal: clones of lymphocytes with distinct specificities express different receptors

Figure 2.5. Comparison of specificity and cellular distribution of receptors used in innate and adaptive immunity.

Pattern Recognition Receptors (PRRs)
Toll-like receptors (TLRs)

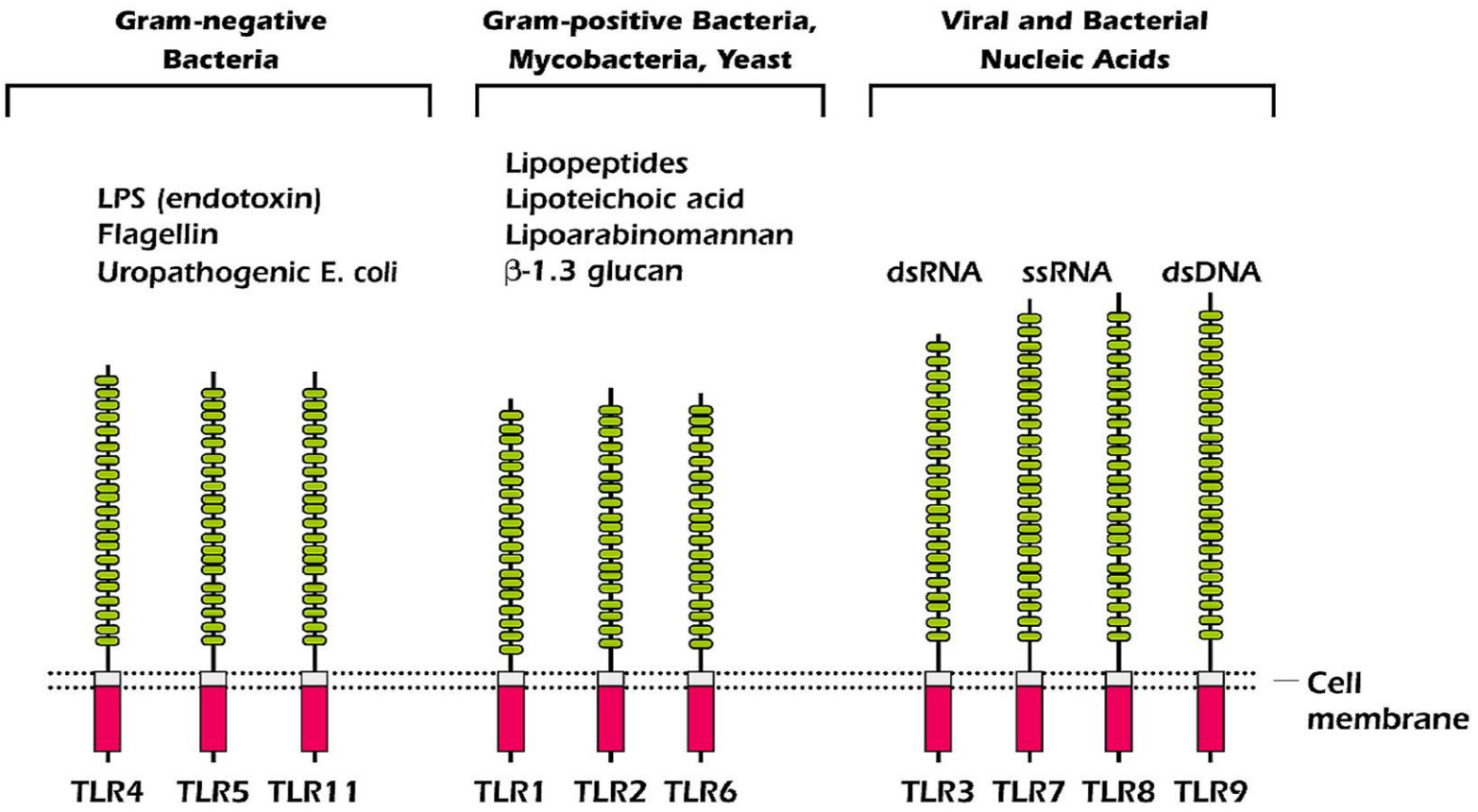
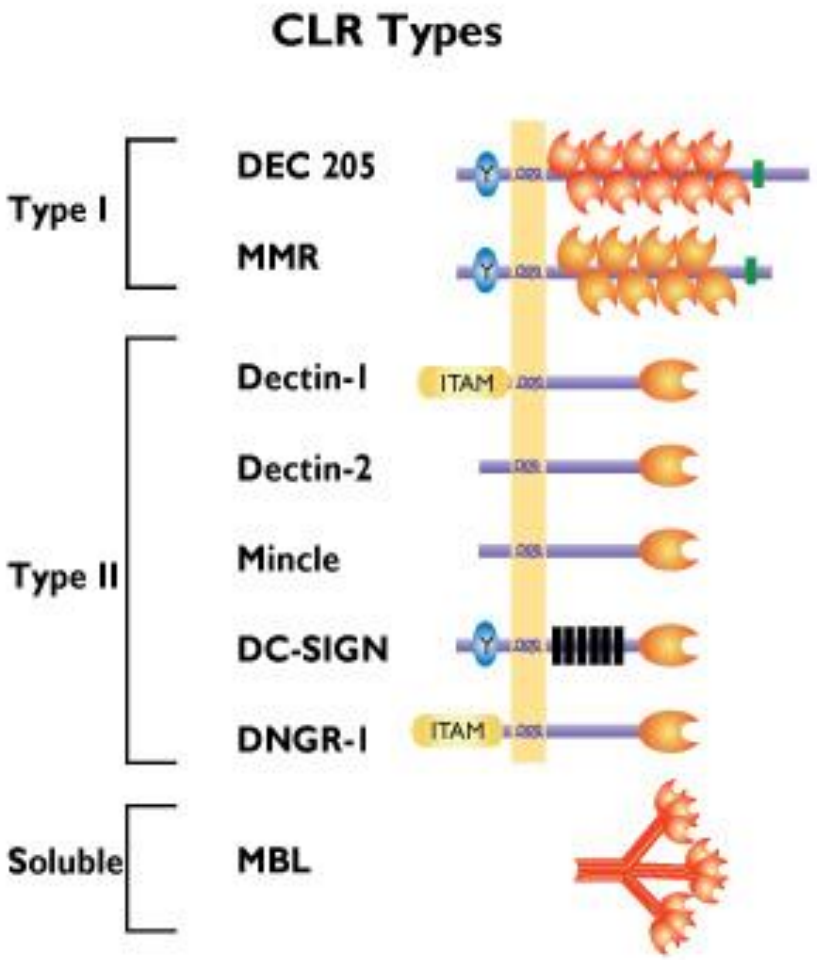


Figure 2.6. Pattern-recognition receptors called TLRs binding to molecules with specific pattern motifs expressed by various pathogens.

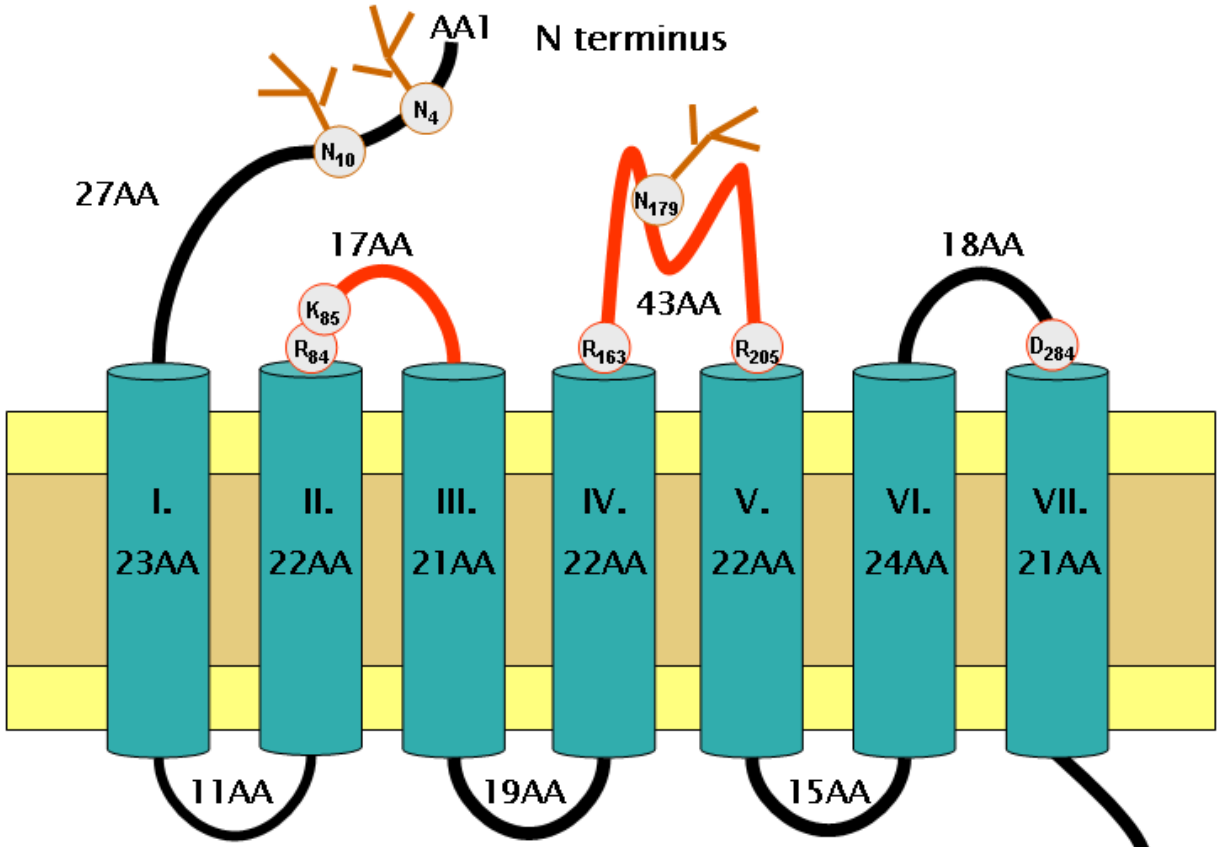
Pattern Recognition Receptors (PRRs)

C-type Lectin Receptors



Pattern Recognition Receptors (PRRs)

f-Met binding receptors



Intrareceptor interactions

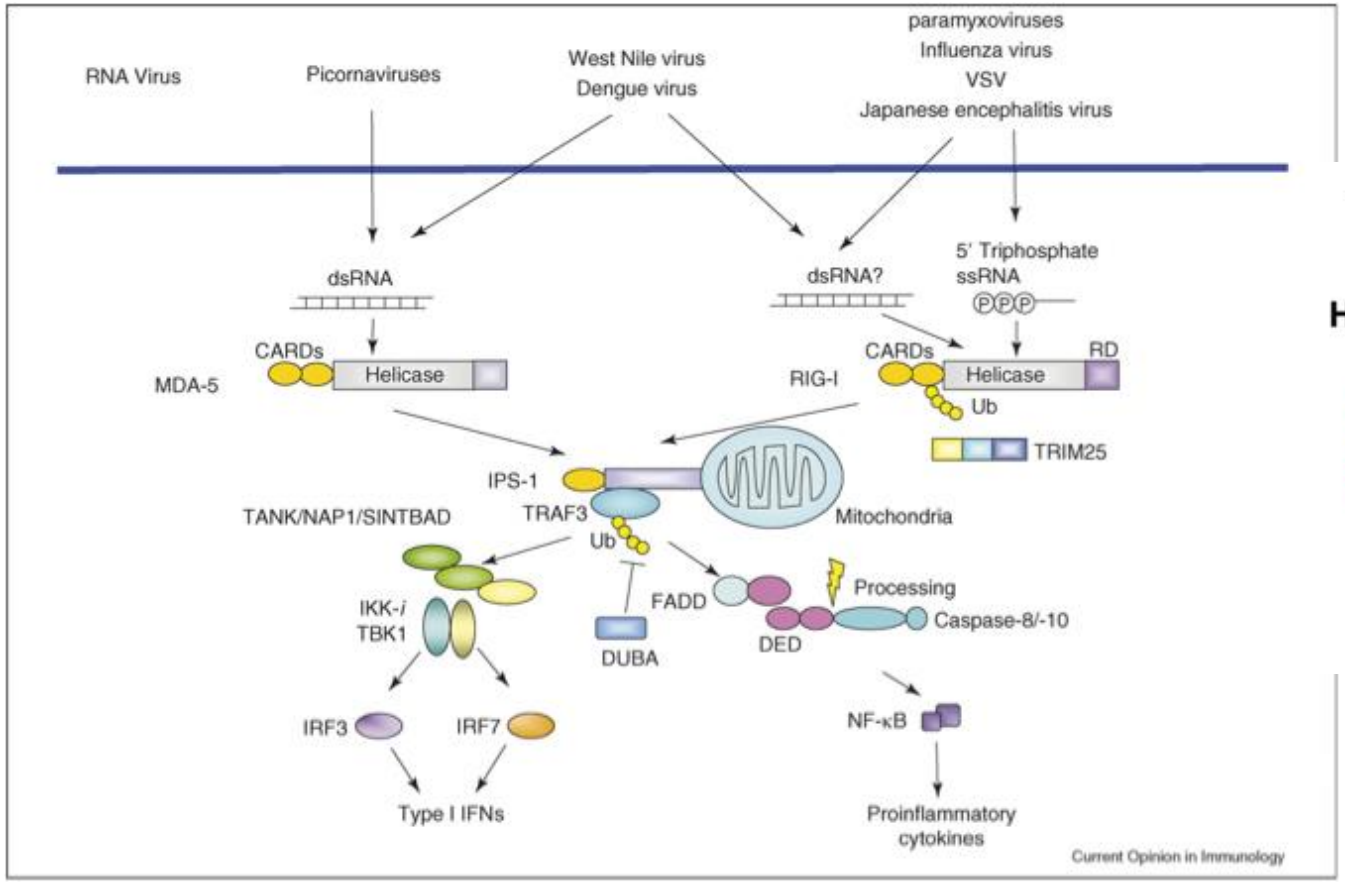
- Salt formation R_{84}–R_{205}, K_{85}–R_{205}, K_{85}–D_{284}
- Binding pocket determination R_{163}

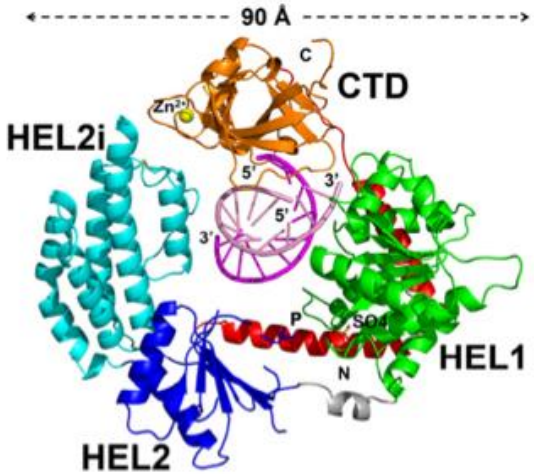
Ligand – receptor interactions

- H bond formation N-formyl group - R_{84}, R_{85}
- H bond formation fMLF peptide backbone - binding pocket
- Disulfeide bridges fMet and recepor Cys-s
- Interaction with fMLF - R_{163}

Pattern Recognition Receptors (PRRs)

Rig-I like receptors





Pattern Recognition Receptors (PRRs)

Nod-like receptors

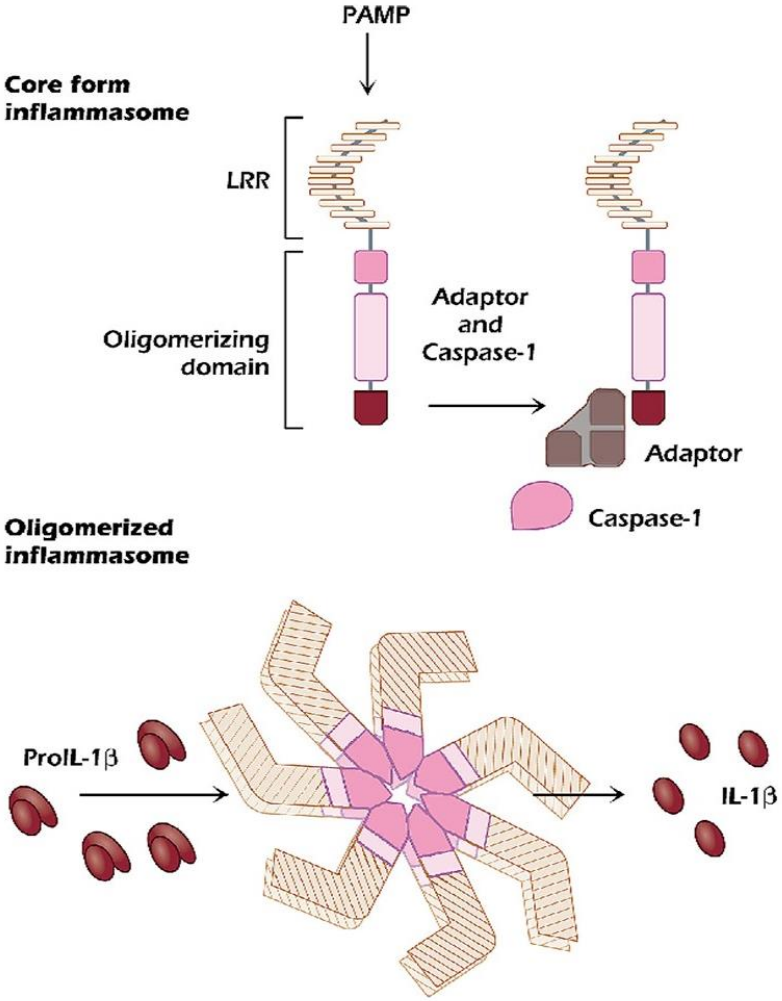


Figure 2.7. Binding of pathogen-associated molecular patterns (PAMPs) to the core form of an inflammasome. Binding of PAMPs to leucine-rich repeats (LRRs) on cytoplasmic inflammasomes causes the core form to bind to an adaptor protein and caspase-1. This is followed by oligomerization of the inflammasome, which enables it to catalyze the conversion of inactive IL-1 β to active IL-1β.

Complement

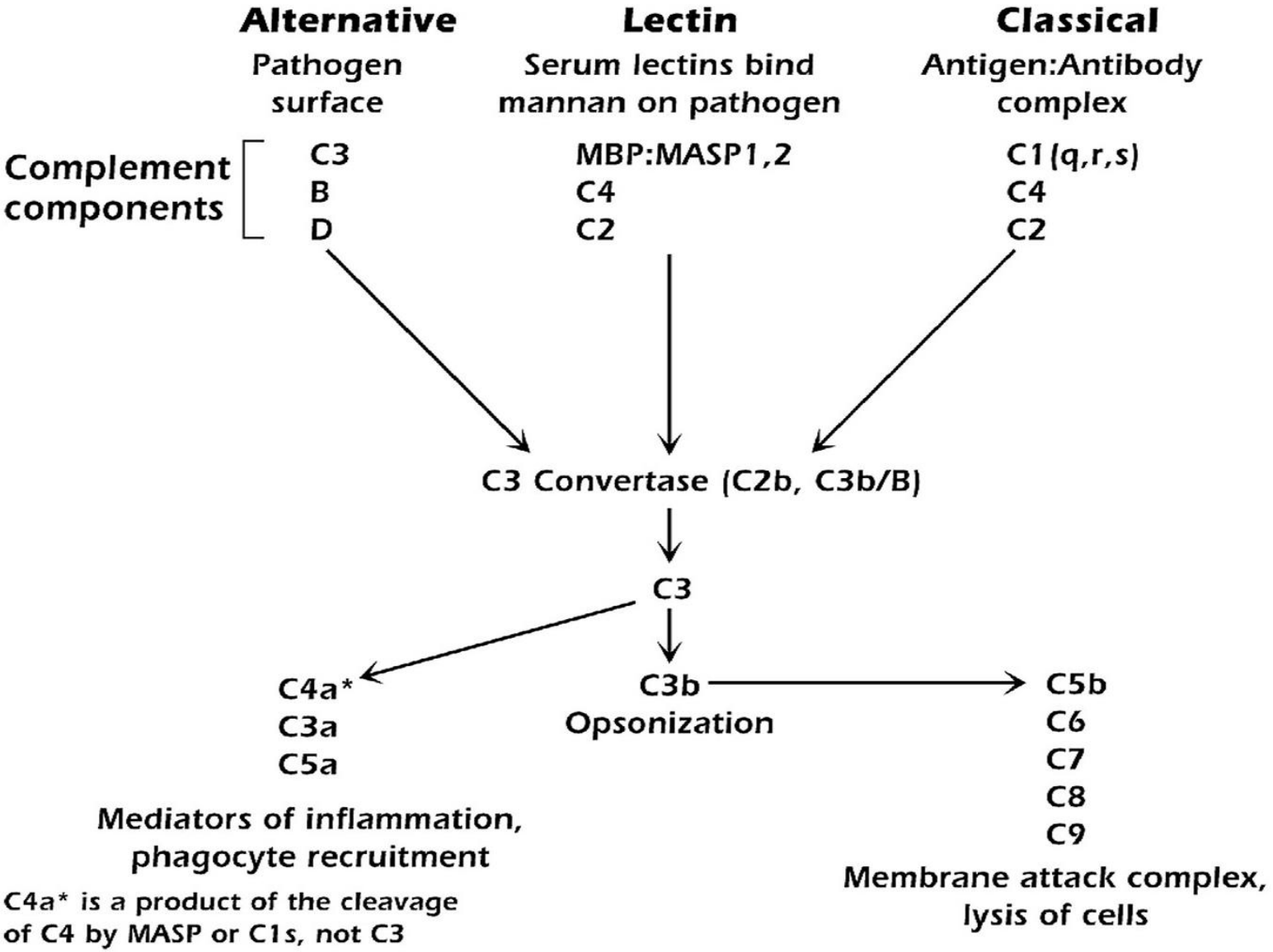
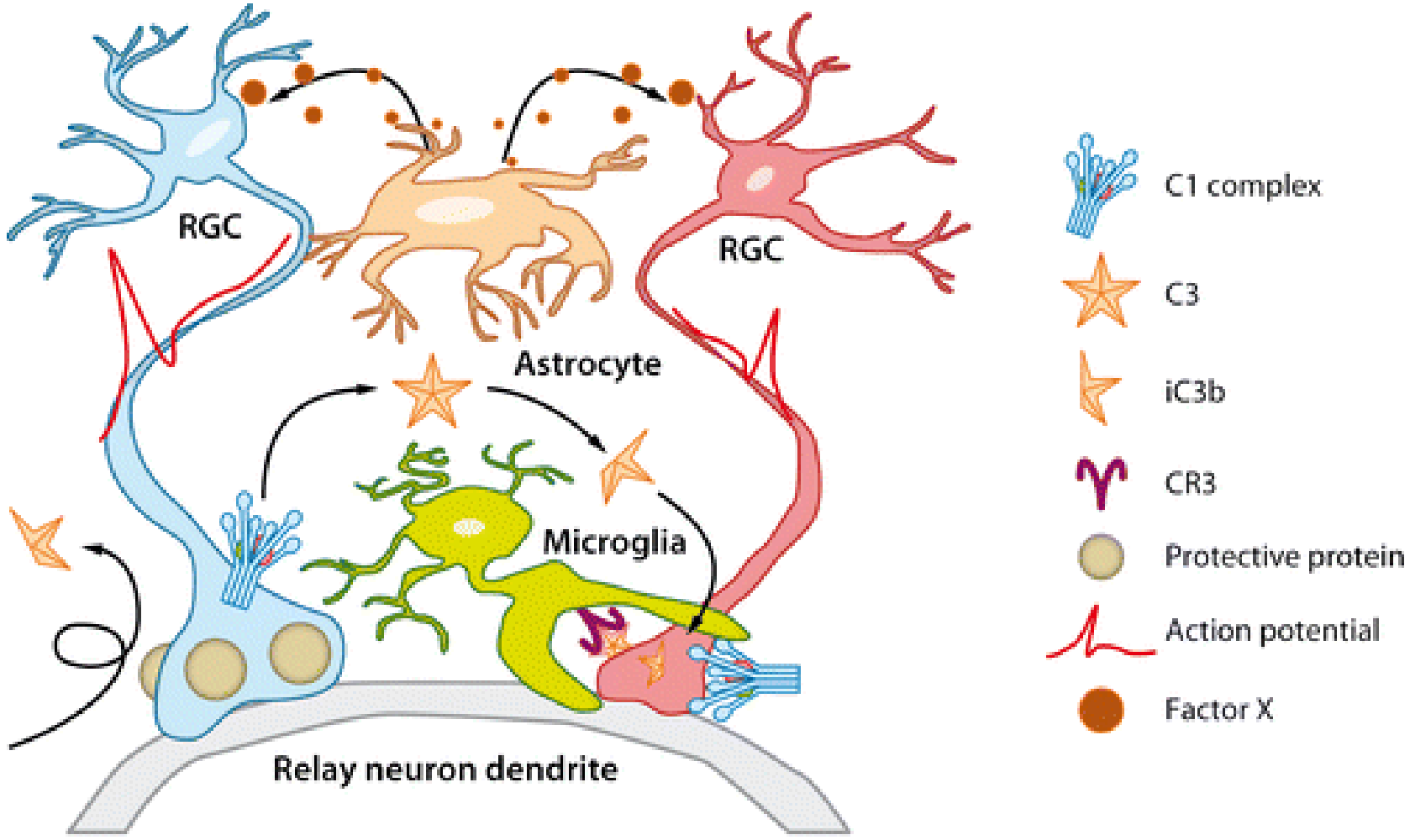


Figure 2.8. The three complement activation pathways: classical, alternative, and lectin.

Complement in development



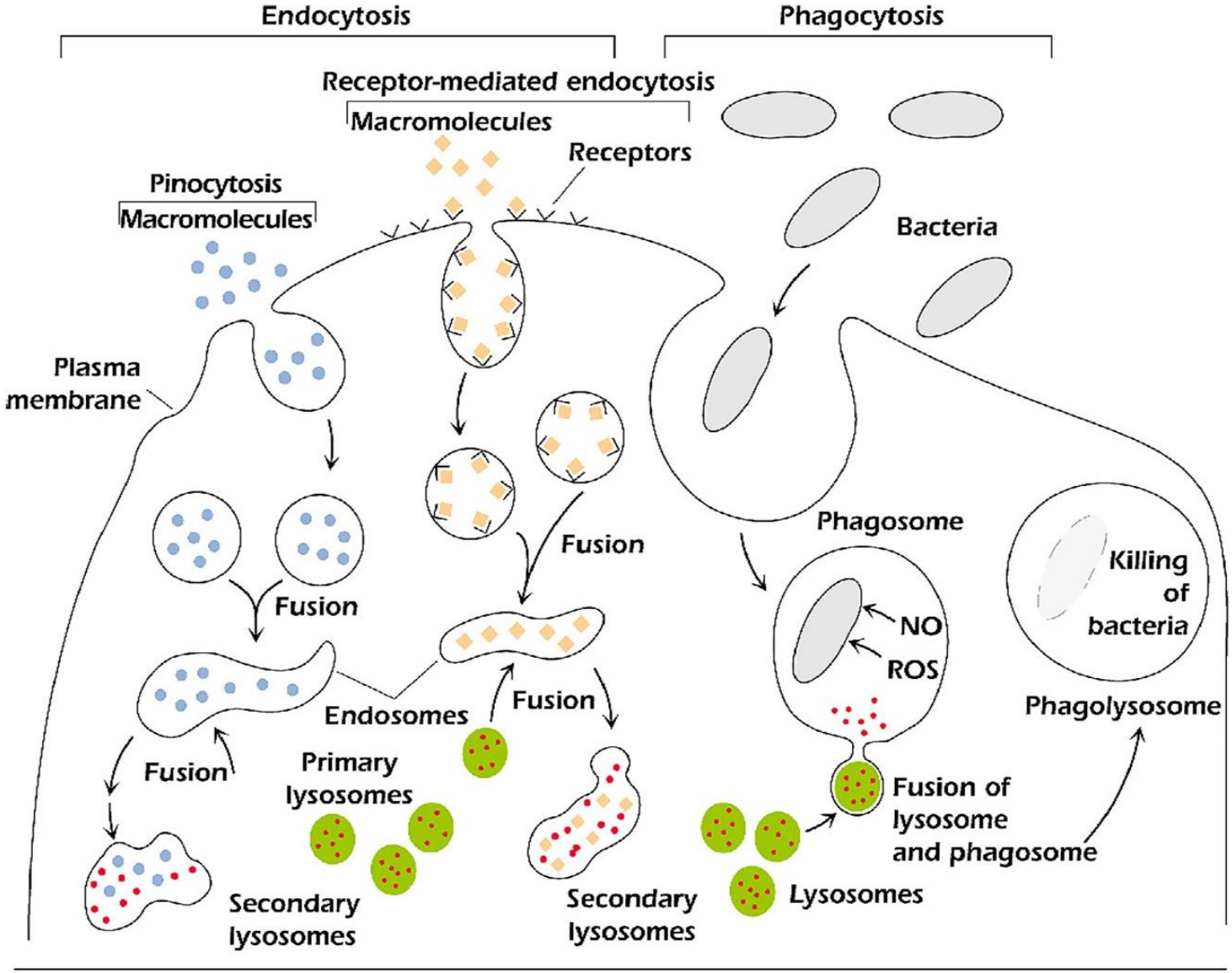


Figure 2.9. Endocytosis and phagocytosis by phagocytes.

INFLAMMATION

- A major component of the body's defense mechanisms →immunologic process to restore immune homeostasis (the injured →normal state)
    - Initiated by various types of damages
- Signs of inflammation
    - Pain (dolor), redness (ribor), swelling or pressure (tumor) and heat (calor)

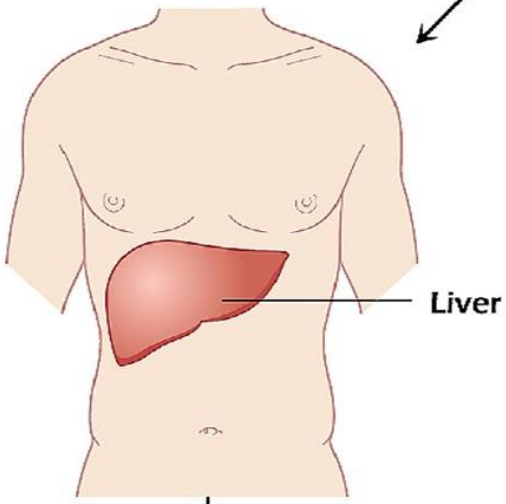
INNATE IMMUNITY –
Soluble factors

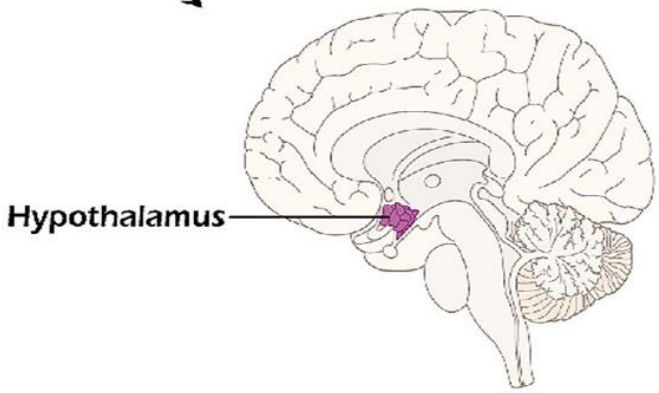
- Interferon
  - a chemical (cytokine) produced by virus-infected cells that contributes to their death by apoptosis
- PAMP and PRRs
  - Result in release of IL1, IL6 and TNF-α

- Acute phase proteins
  - proteins in the plasma that increase during infection and inflammation
  - can be used diagnostically to give an indication of acute inflammation

Acute phase response

Triggered by activated inflammatory cells that produce cytokines:
IL-1, IL-6, TNF-α





Induction of fever

Acute phase proteins:
C-reactive protein (CRP),
serum amyloid A,
C3, C4, haptoglobin,
fibrinogen, others

Increased plasma viscosity and consequently,
increased erythrocyte sedimentation rate (ESR)

Figure 2.10. The acute phase response stimulated by cytokines produced by innate immune cells.

INFLAMMATION

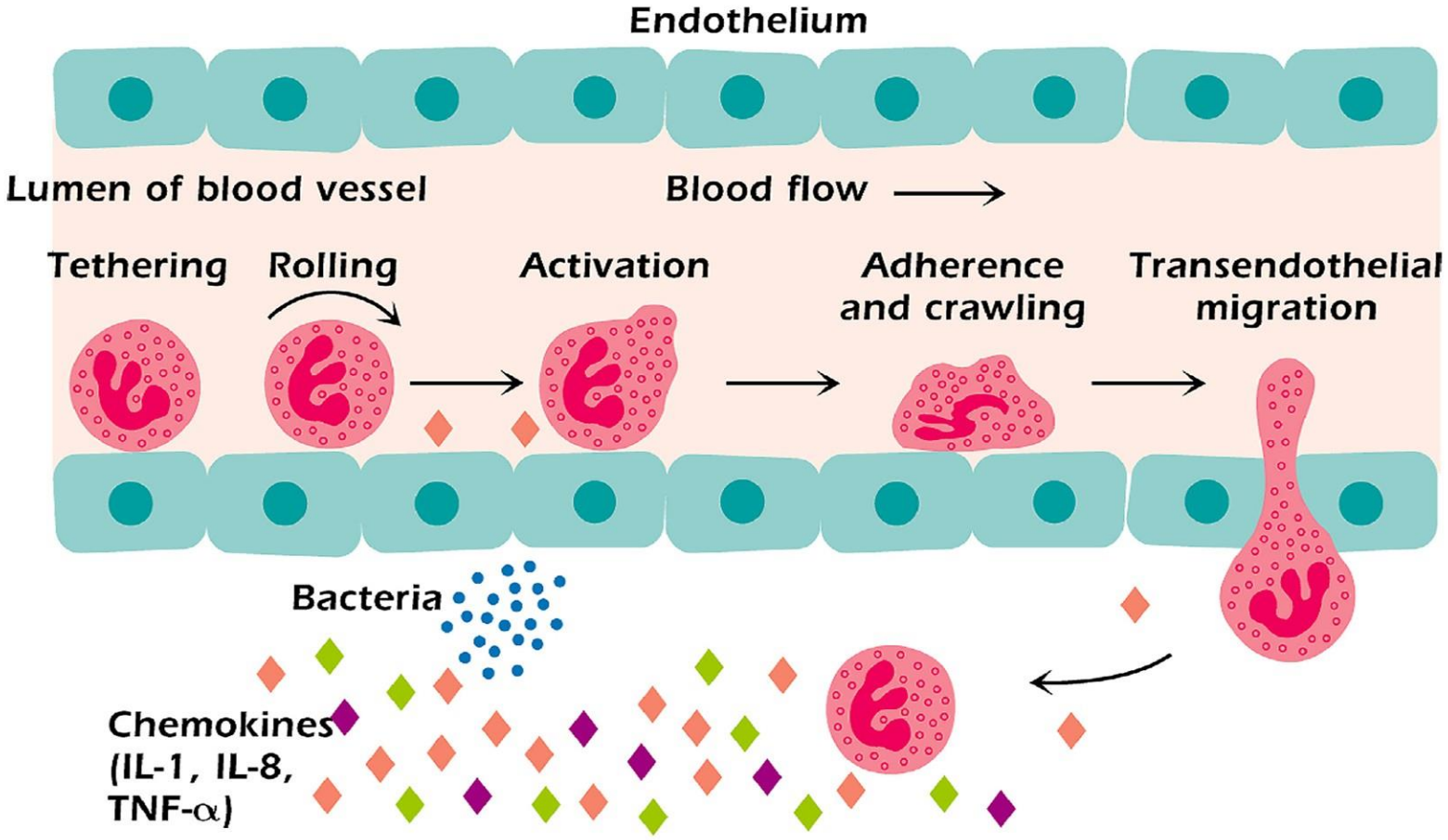


Figure 2.11. Leukocyte adhesion to endothelium leads to their adhesion, activation, and extravasation from the blood to tissue where they are needed to help destroy (e.g., phagocytize) pathogens such as bacteria that initiate this response.

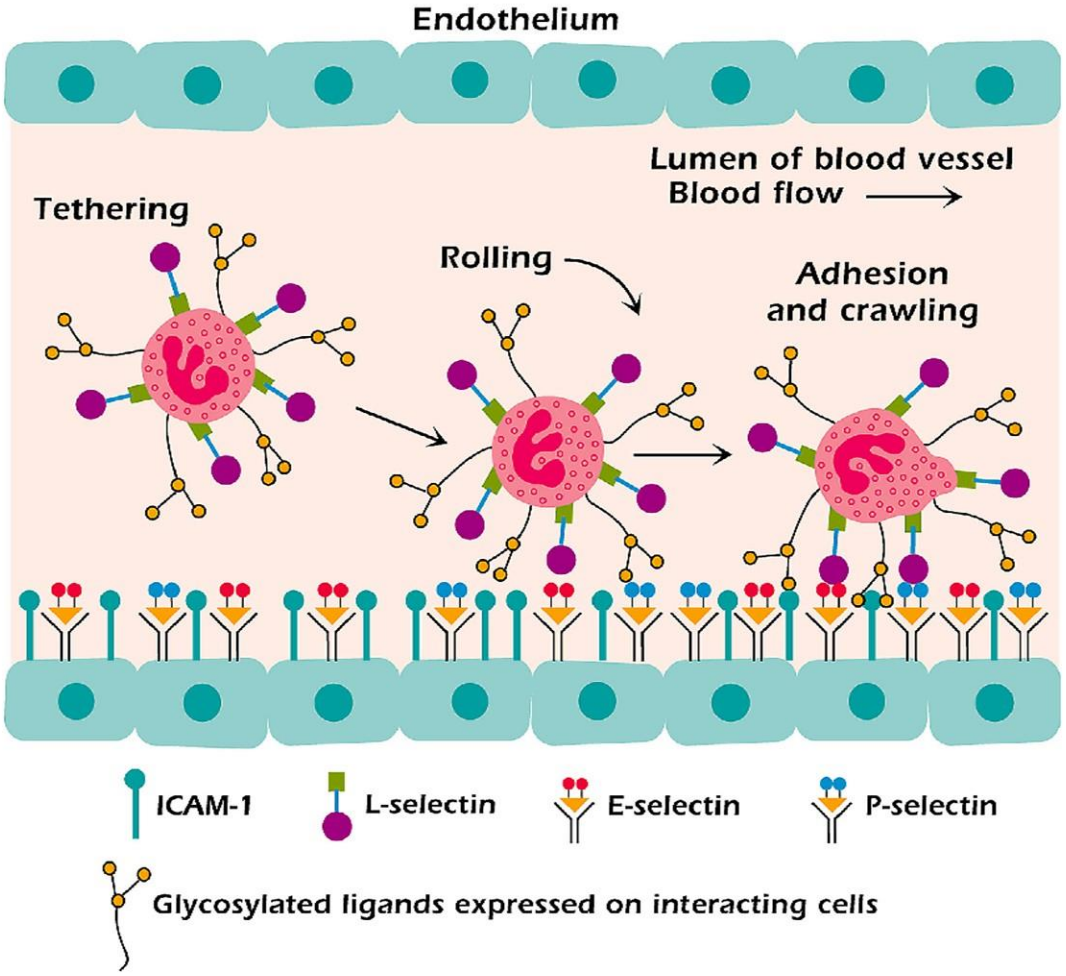
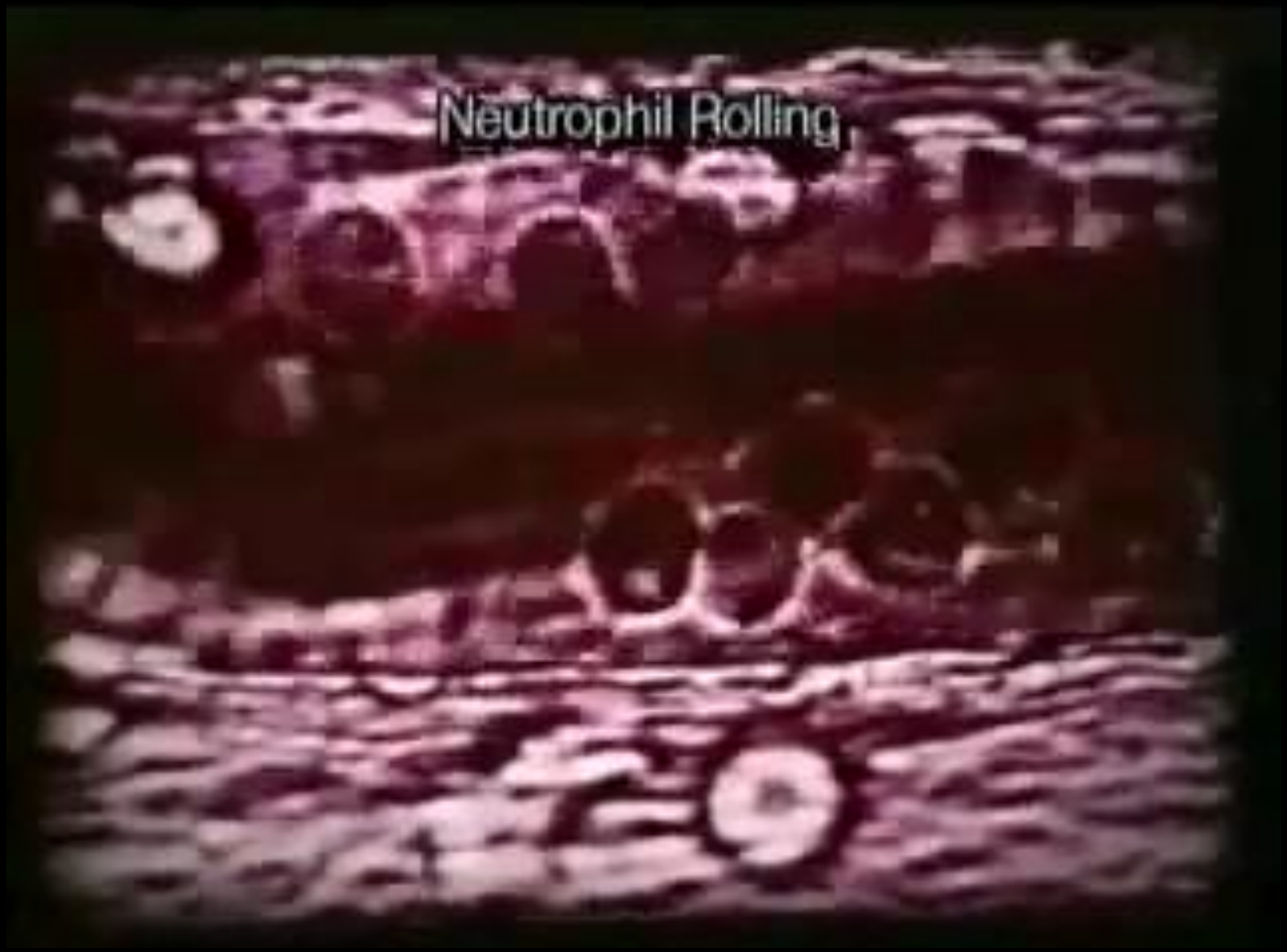
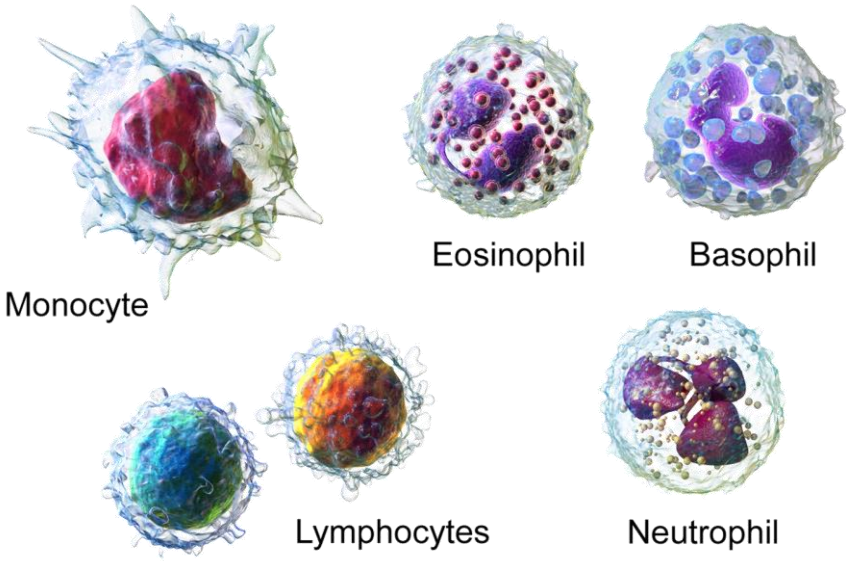
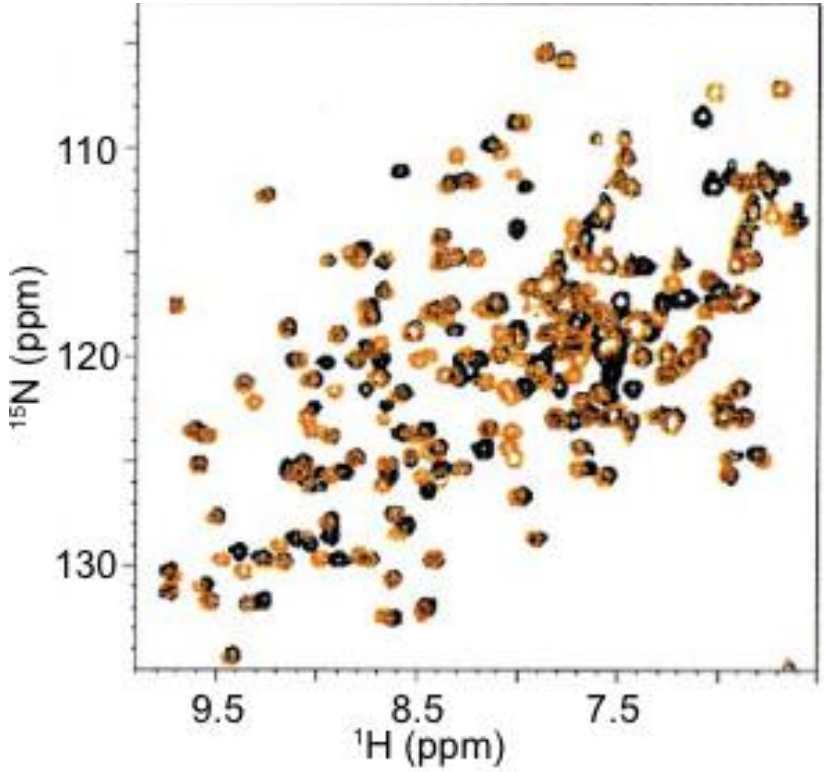


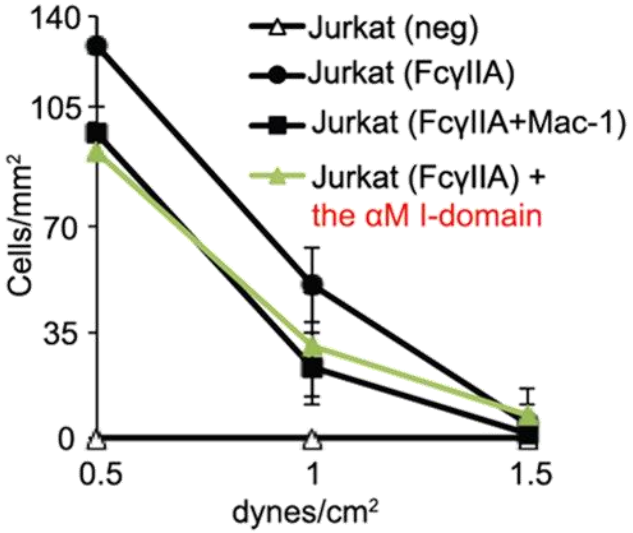
Figure 2.12. Adhesion molecules involved in leukocyte tethering, rolling, and adhesion to endothelium leading to transendothelial migration from blood to tissue.

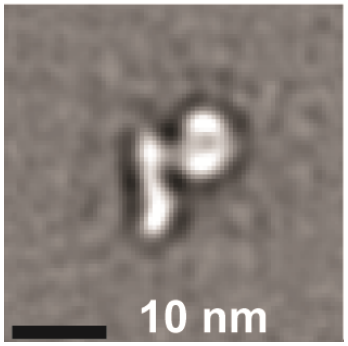
Cellular migration and receptors

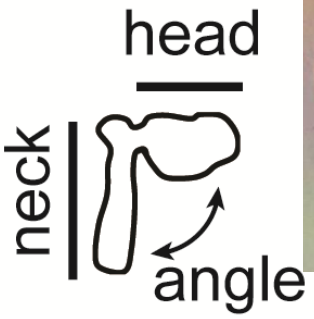


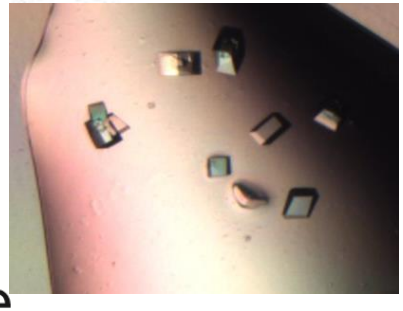

Monocyte
Eosinophil
Basophil
Lymphocytes
Neutrophil


110
120
130
^{15}N (ppm)
9.5
8.5
7.5
^{1}H (ppm)

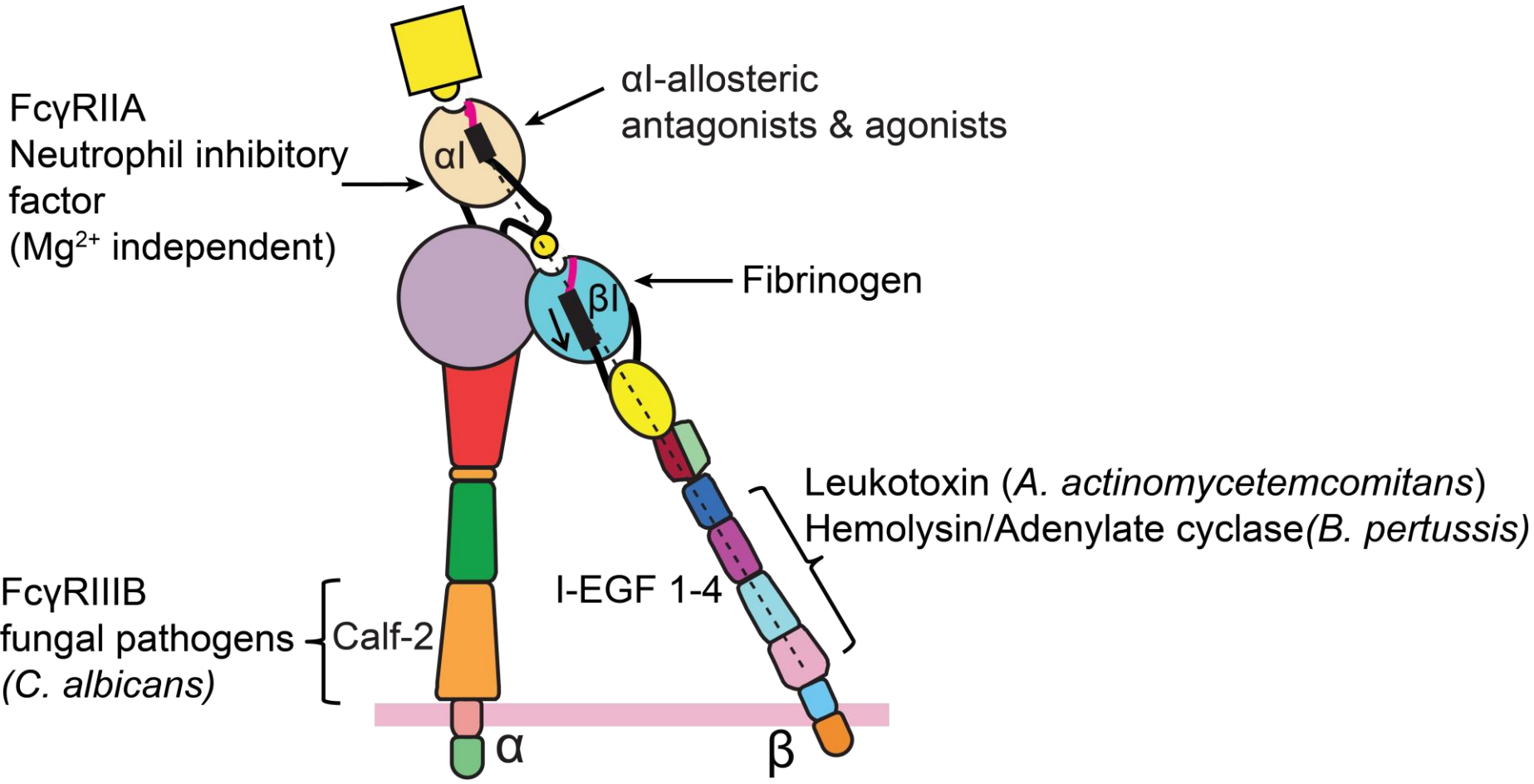

140
105
70
35
0
Cells/mm²
0.5
1
1.5
dynes/cm²
Jurkat (neg)
Jurkat (FcγIIA)
Jurkat (FcγIIA+Mac-1)
Jurkat (FcγIIA) +
the αM I-domain


10 nm

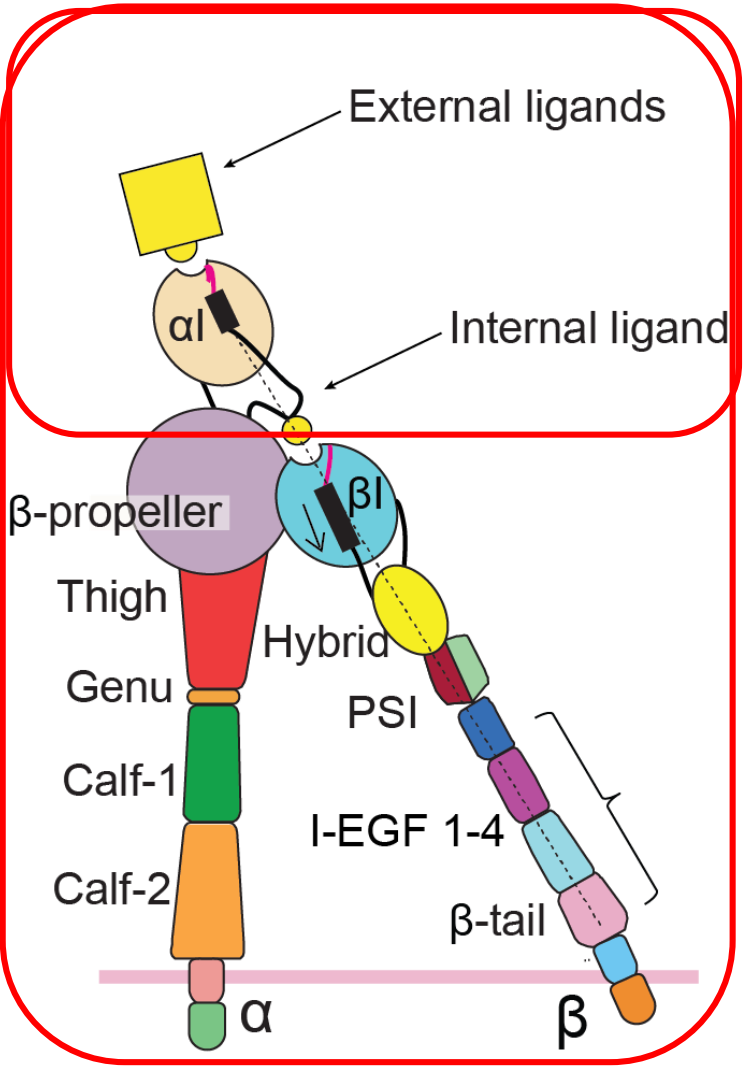

head
neck
angle

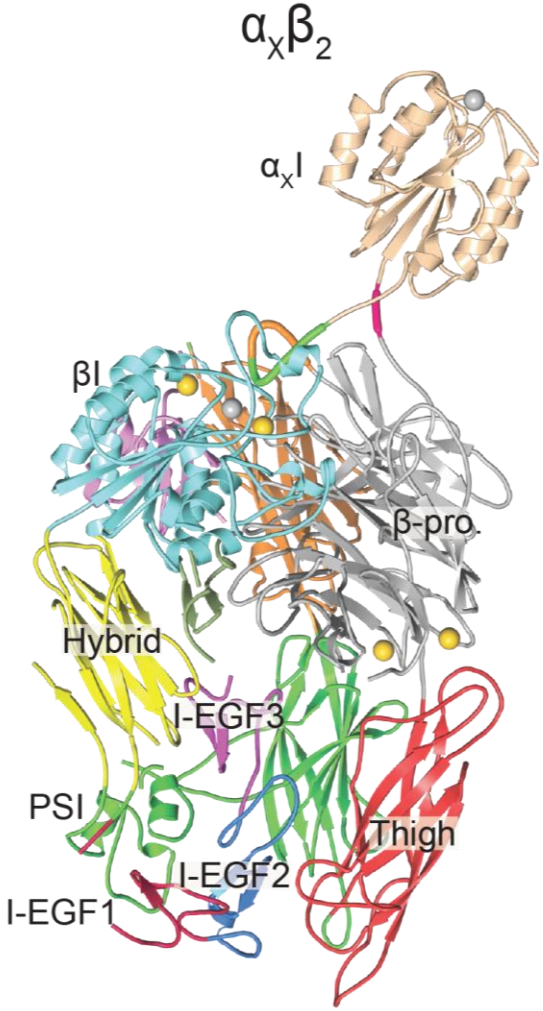


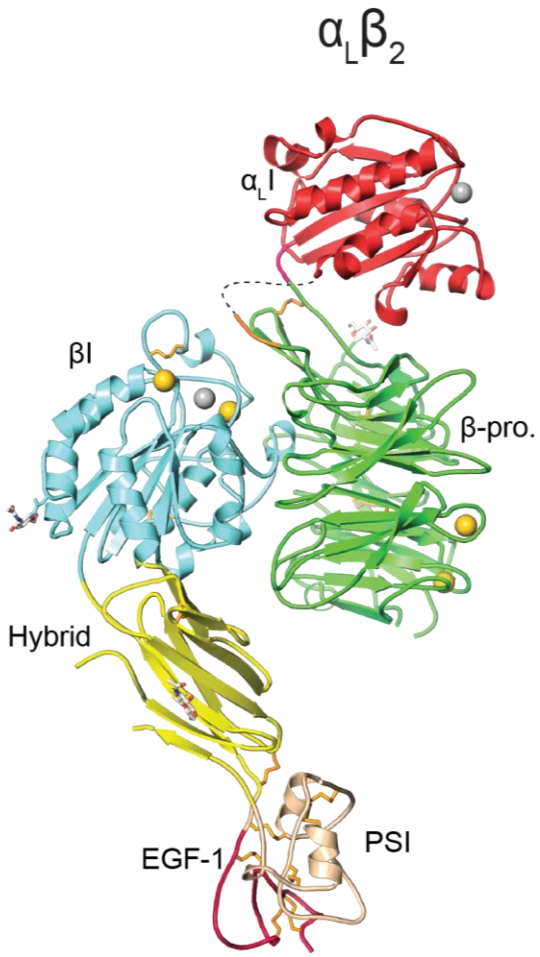
Interactions of leukocyte integrins



Structural Studies on αI- integrins are limited.

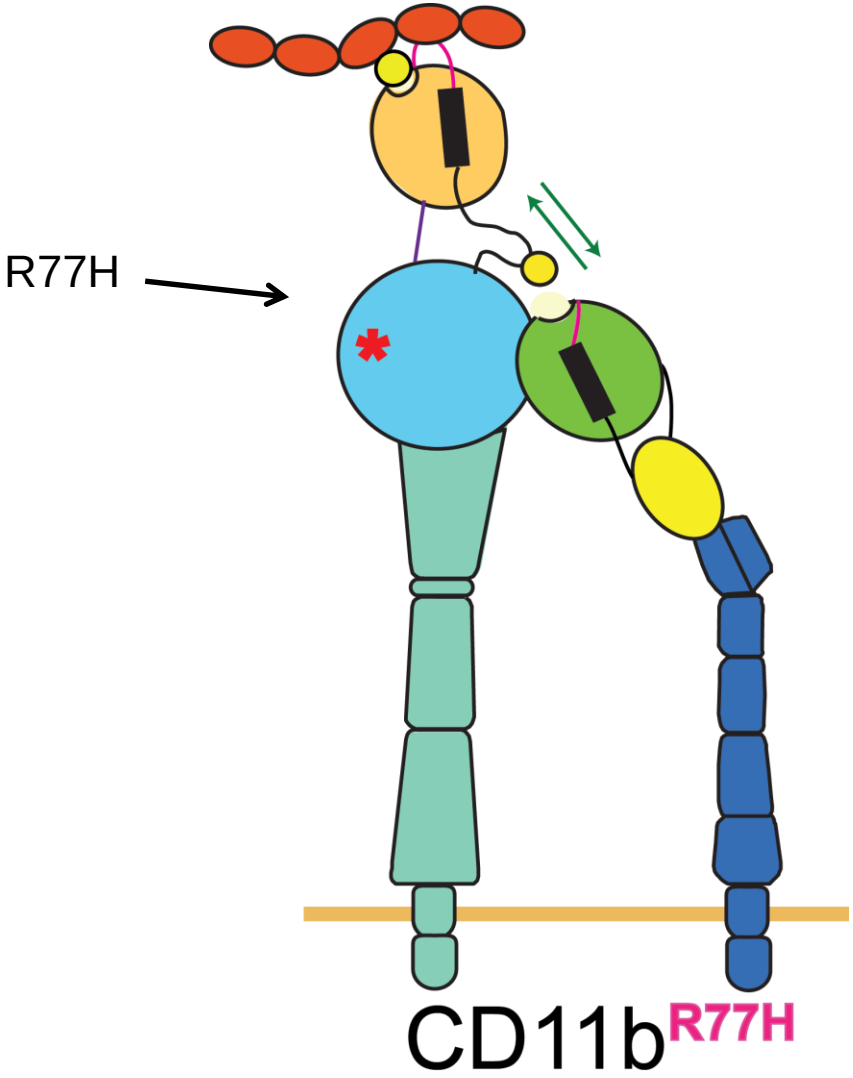


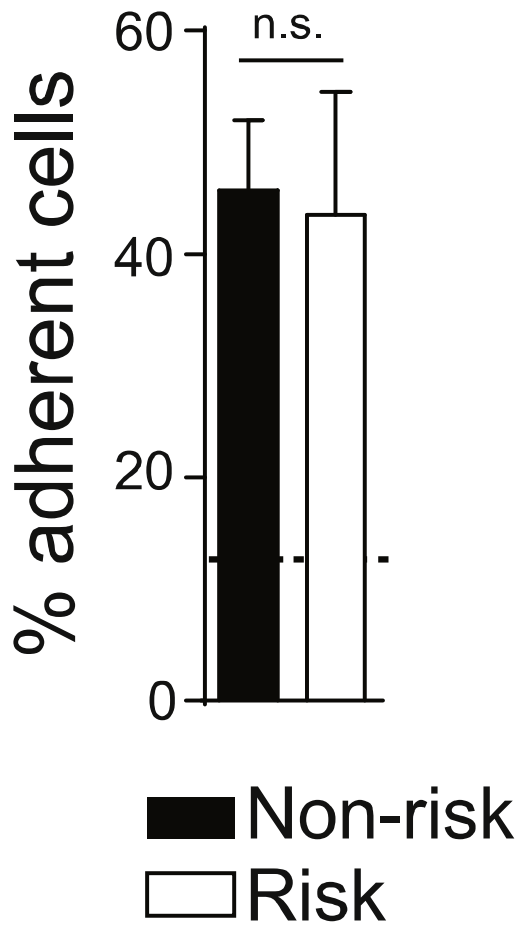




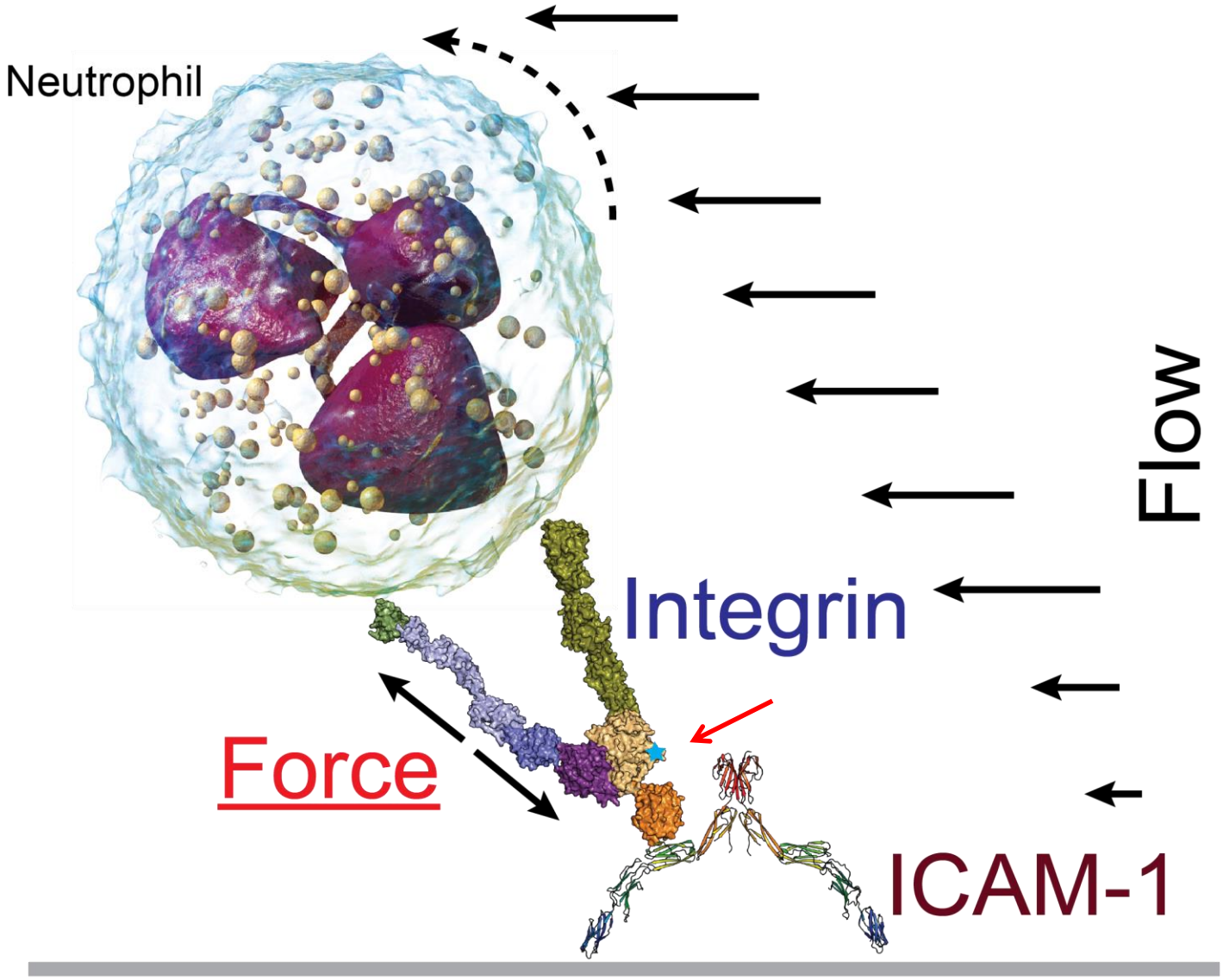
AN EXAMPLE

A lupus-associated integrin variant has an impaired binding under force

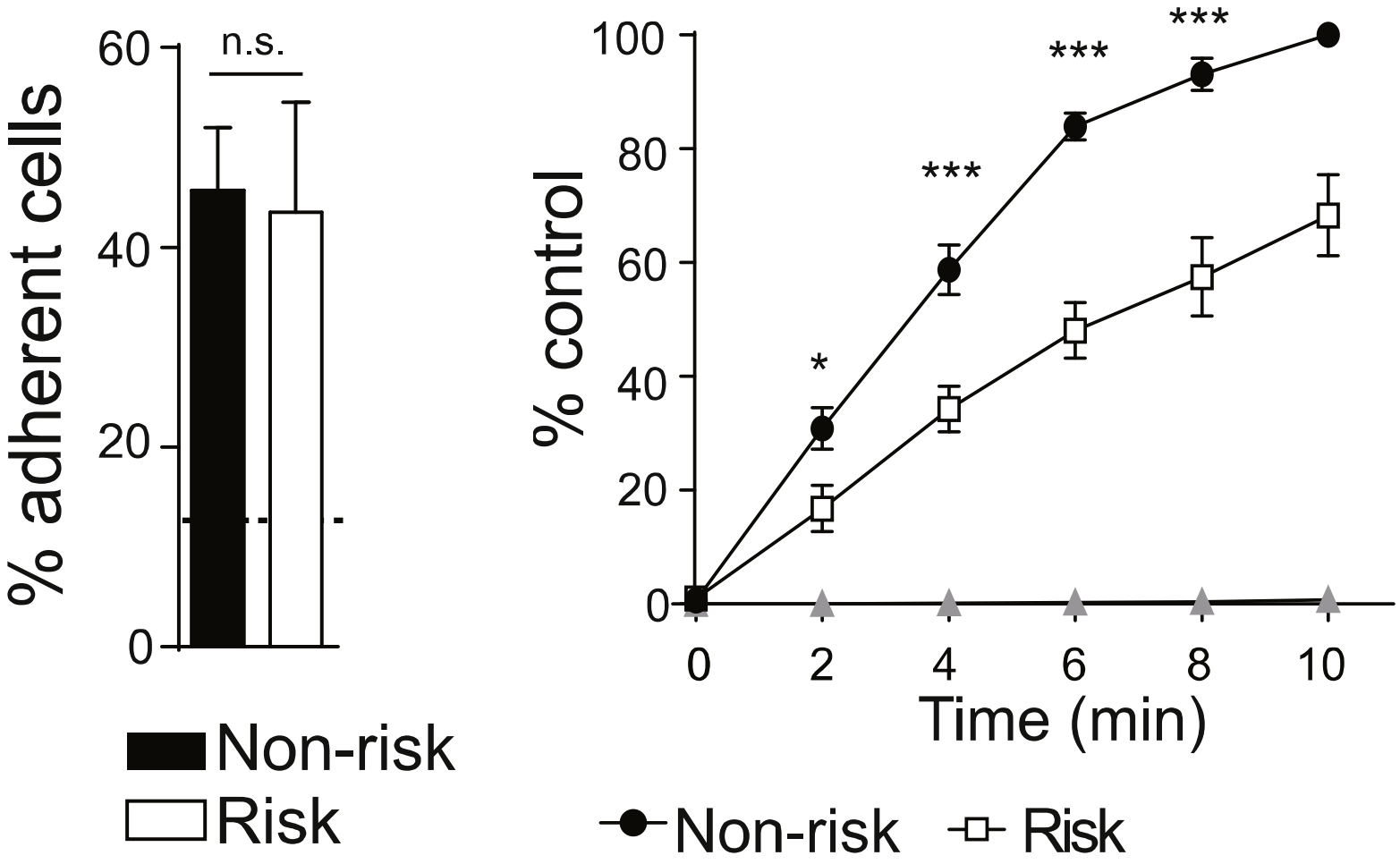




In reality, blood flow exerts a shear force



A lupus-associated integrin variant has an impaired binding under force



“The Force will be with you, always.” *Obi-Wan Kenobi*