Inflammation 2

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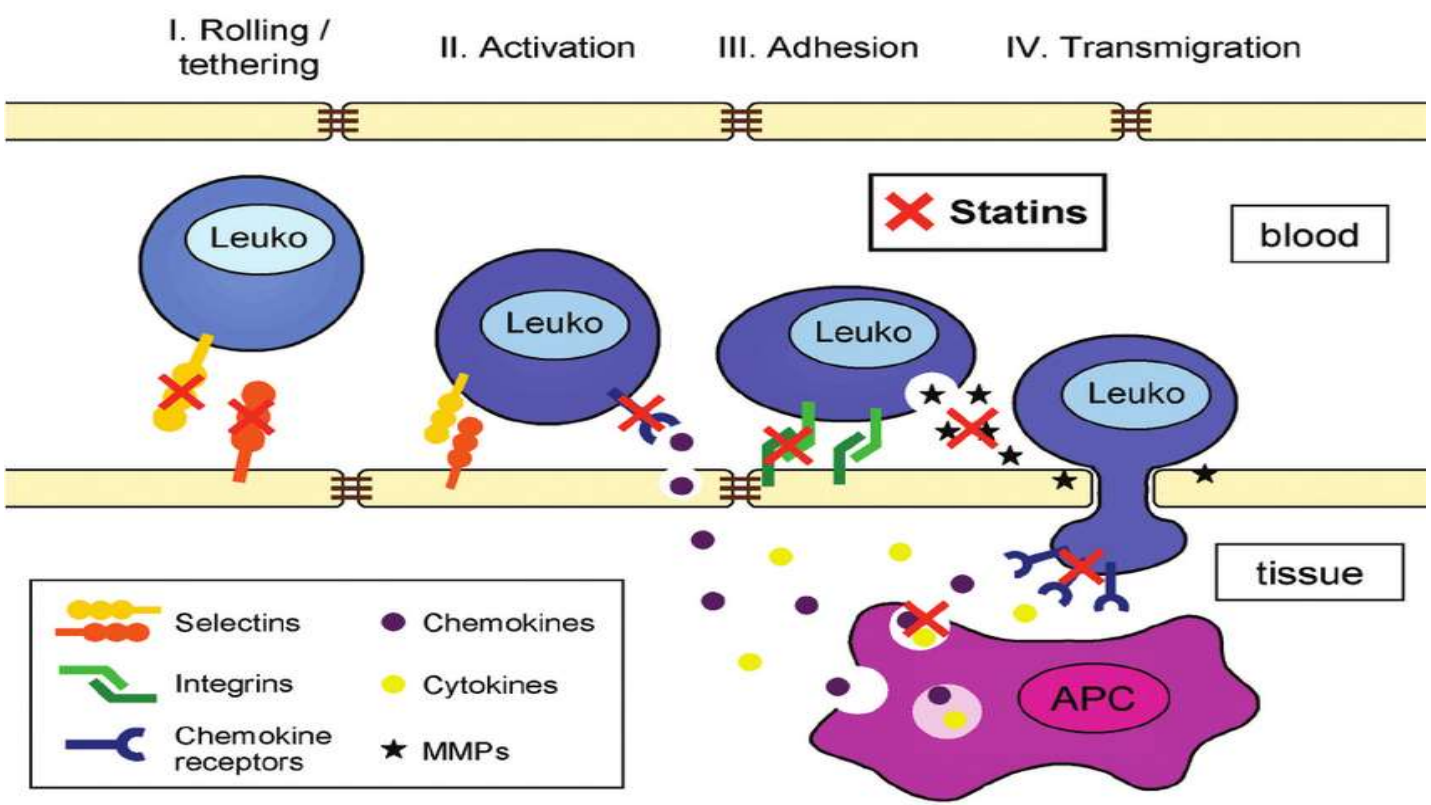
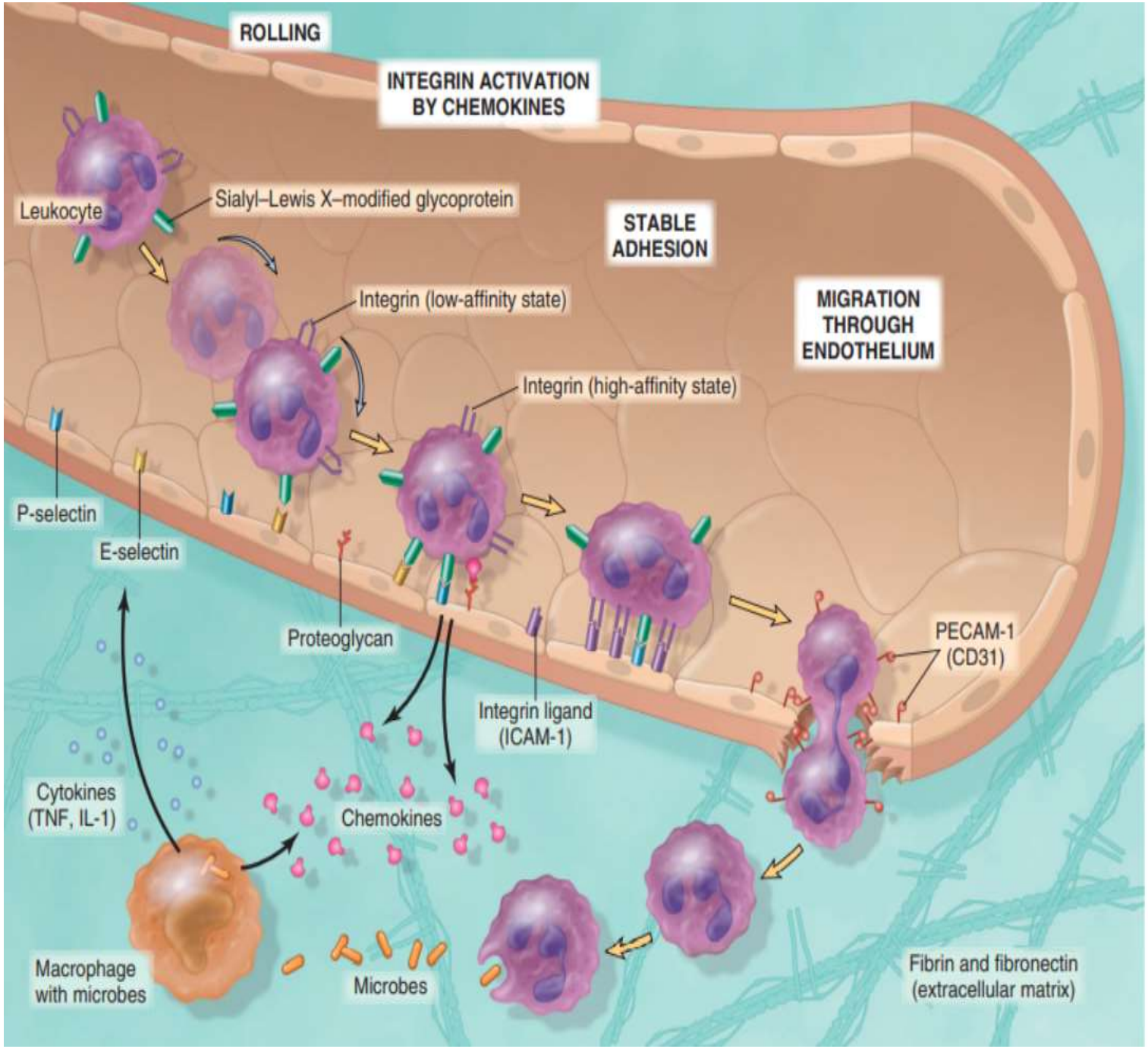


- The journey of leukocytes from the vessel lumen to the tissue is a multistep process that is mediated and controlled by adhesion molecules and cytokines, and consist of three phases:

- 1. Leukocyte Adhesion to Endothelium.
- 2. Leukocyte Migration Through Endothelium.
- 3. Movement of the cells toward the offending agent

I. Leukocyte Adhesion to Endothelium

- During blood stasis more white cells assume a peripheral position along the endothelial surface (margination.)
- Activated endothelial cells express adhesion molecules to which the leukocytes attach loosely, then bind and detach (rolling.)
- The cells finally come to rest at some point where they adhere firmly.
- The attachment of leukocytes to endothelial cells is mediated by complementary adhesion molecules on the two cell types whose expression is enhanced by cytokines, The two major families of molecules involved in leukocyte adhesion and migration are the selectins and integrins.


ROLLING
INTEGRIN ACTIVATION BY CHEMOKINES
Leukocyte
Sialyl–Lewis X–modified glycoprotein
STABLE ADHESION
Integrin (low-affinity state)
MIGRATION THROUGH ENDOTHELIUM
Integrin (high-affinity state)
P-selectin
E-selectin
Proteoglycan
PECAM-1 (CD31)
Integrin ligand (ICAM-1)
Cytokines (TNF, IL-1)
Chemokines
Macrophage with microbes
Microbes
Fibrin and fibronectin (extracellular matrix)

1. Selectins

- Mediate the initial weak interactions between leukocytes and endothelium.

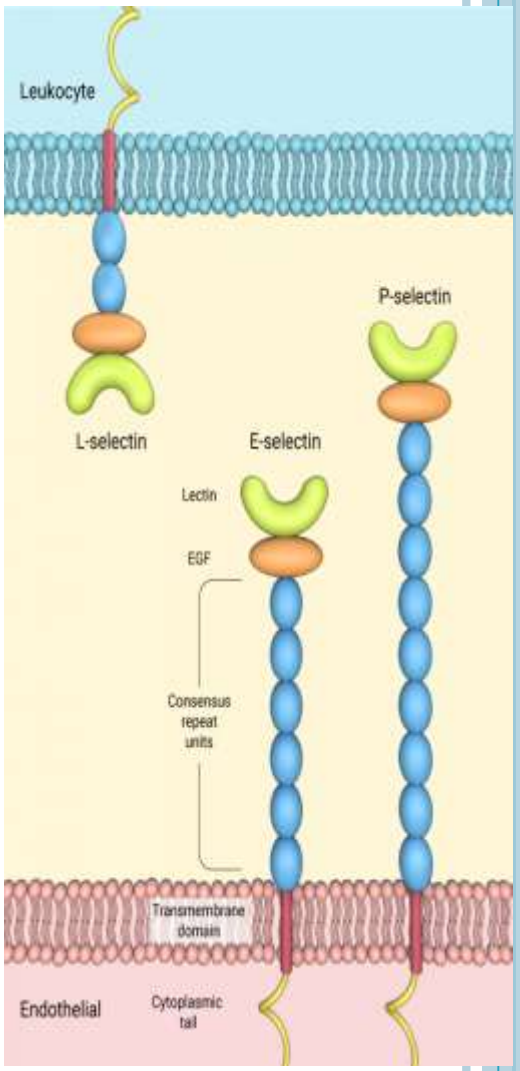
- Selectins are receptors expressed on leukocytes and endothelium that contain an extracellular domain that binds sugars (hence the lectin part of the name).

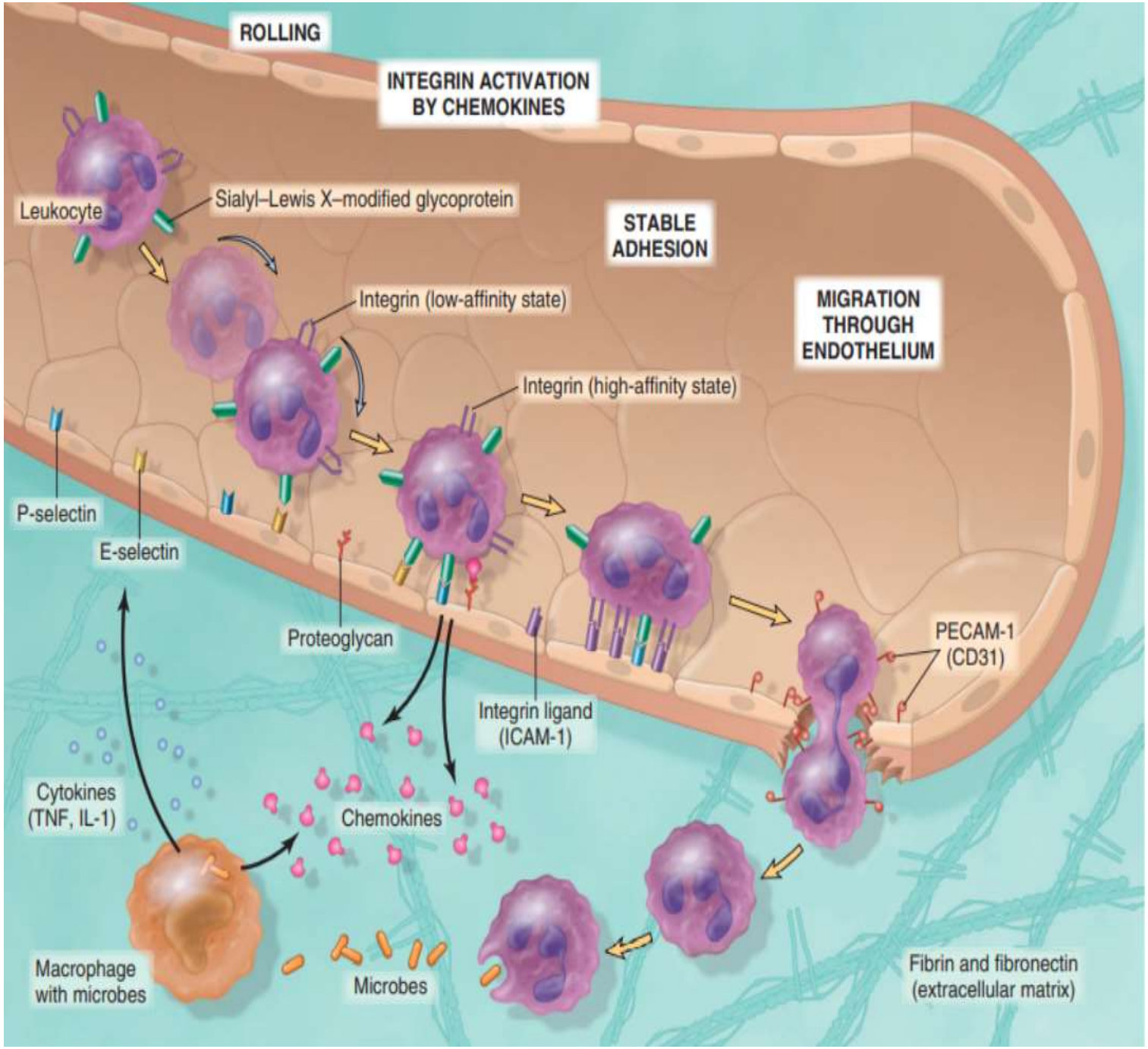
- The three members of this family are:
- E-selectin (also called CD62E), expressed on endothelial cells.
- P-selectin (CD62P), present on platelets and endothelium.
- L-selectin (CD62L), found on the surface of most leukocytes.

- The endothelial selectins are expressed at low levels on unactivated endothelium, they are upregulated after stimulation by cytokines and other mediators.

- Therefore, binding of leukocytes is largely restricted to the endothelium at sites of infection or tissue injury (where the mediators are produced).

- These weak selectin-mediated rolling interactions slow down the leukocytes and give them the chance to recognize additional adhesion molecules on the endothelium.

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2.INTEGRINS

- a family of leukocyte surface proteins that mediate the adhesion of leukocytes to endothelium and of various cells to the extracellular matrix.

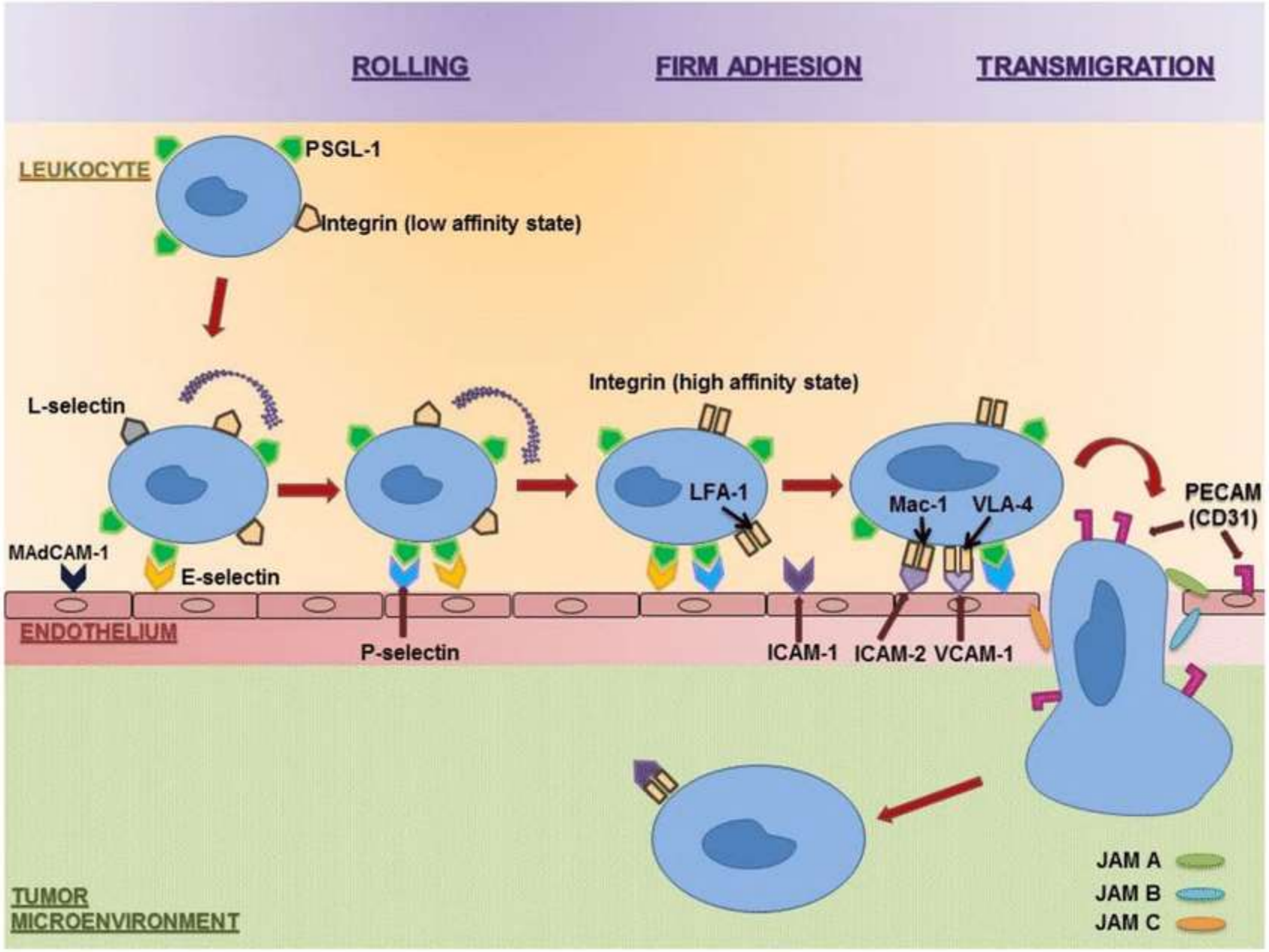
- They are normally expressed on leukocyte plasma membranes in a low-affinity form and do not adhere to their specific ligands until the leukocytes are activated by chemokines.

- When the rolling leukocytes activated their integrins undergo conformational changes and cluster together, thus converting to a high-affinity form.

- TNF and IL-1, activate endothelial cells to increase their expression of ligands for integrins.

Integrin with their ligands:

- intercellular adhesion molecule-1 (ICAM-1), which binds to the integrins (LFA-1)
- macrophage-1 antigen (Mac-1): ICAM-2.
- VCAM-1 which binds to the integrin : VLA-4.
- The leukocytes stop rolling, and engagement of integrins by their ligands delivers signals leading to cytoskeletal changes that arrest the leukocytes and firmly attach them to the endothelium


ROLLING
FIRM ADHESION
TRANSMIGRATION
LEUKOCYTE
PSGL-1
Integrin (low affinity state)
L-selectin
Integrin (high affinity state)
LFA-1
Mac-1
VLA-4
PECAM (CD31)
MAdCAM-1
E-selectin
ENDOTHELIUM
P-selectin
ICAM-1
ICAM-2
VCAM-1
JAM A
JAM B
JAM C
TUMOR MICROENVIRONMENT

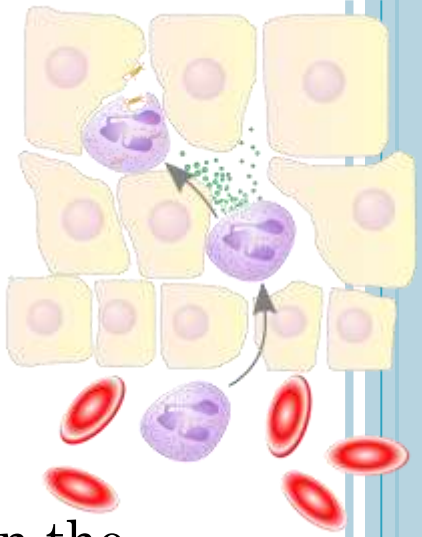
II. Leukocyte Migration Through Endothelium

- leukocytes migrate through the vessel wall primarily by:

  - driven by chemokines produced in extravascular tissues
  - squeezing between cells at intercellular junctions.
  - platelet endothelial cell adhesion molecule-1 (PECAM-1)*

- After traversing the endothelium, leukocytes pierce the basement membrane, probably by secreting collagenases, and they enter the extravascular tissue.

Chemotaxis of Leukocytes

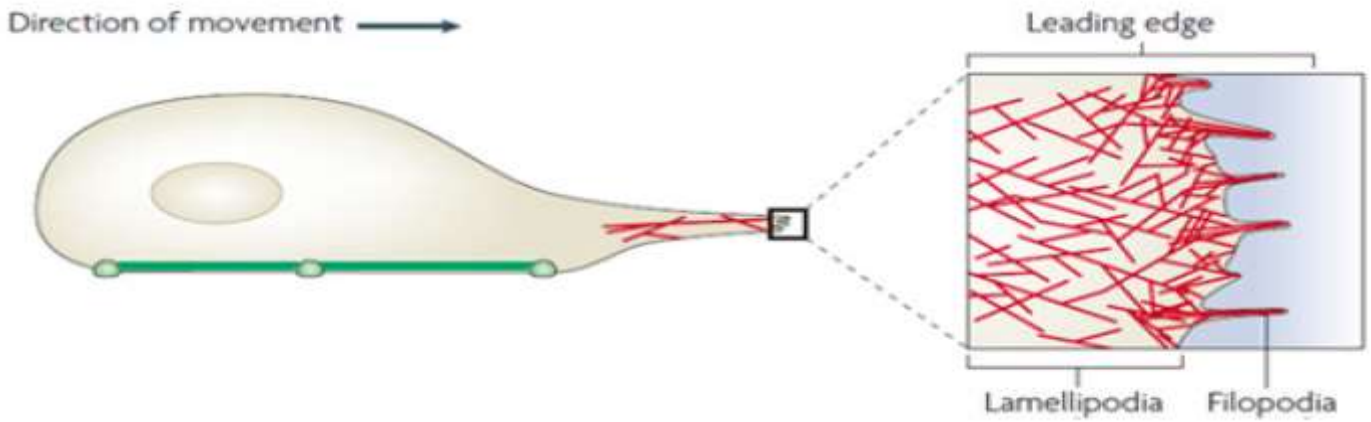


- after leaving the circulation , movement of leukocytes in the tissues, toward the site of injury occurs along a chemical gradient.

- Exogenous and endogenous substances can act as chemoattractants, including the following:

  - Bacterial products.
  - Cytokines, especially those of the chemokine family.
  - Components of the complement system, particularly C5a .
  - Products of the lipoxygenase pathway of arachidonic acid (AA) metabolism, particularly leukotriene B4 (LTB4)

- The leukocyte moves by extending filopodia that pull the back of the cell in the direction of extension, much like the front wheels

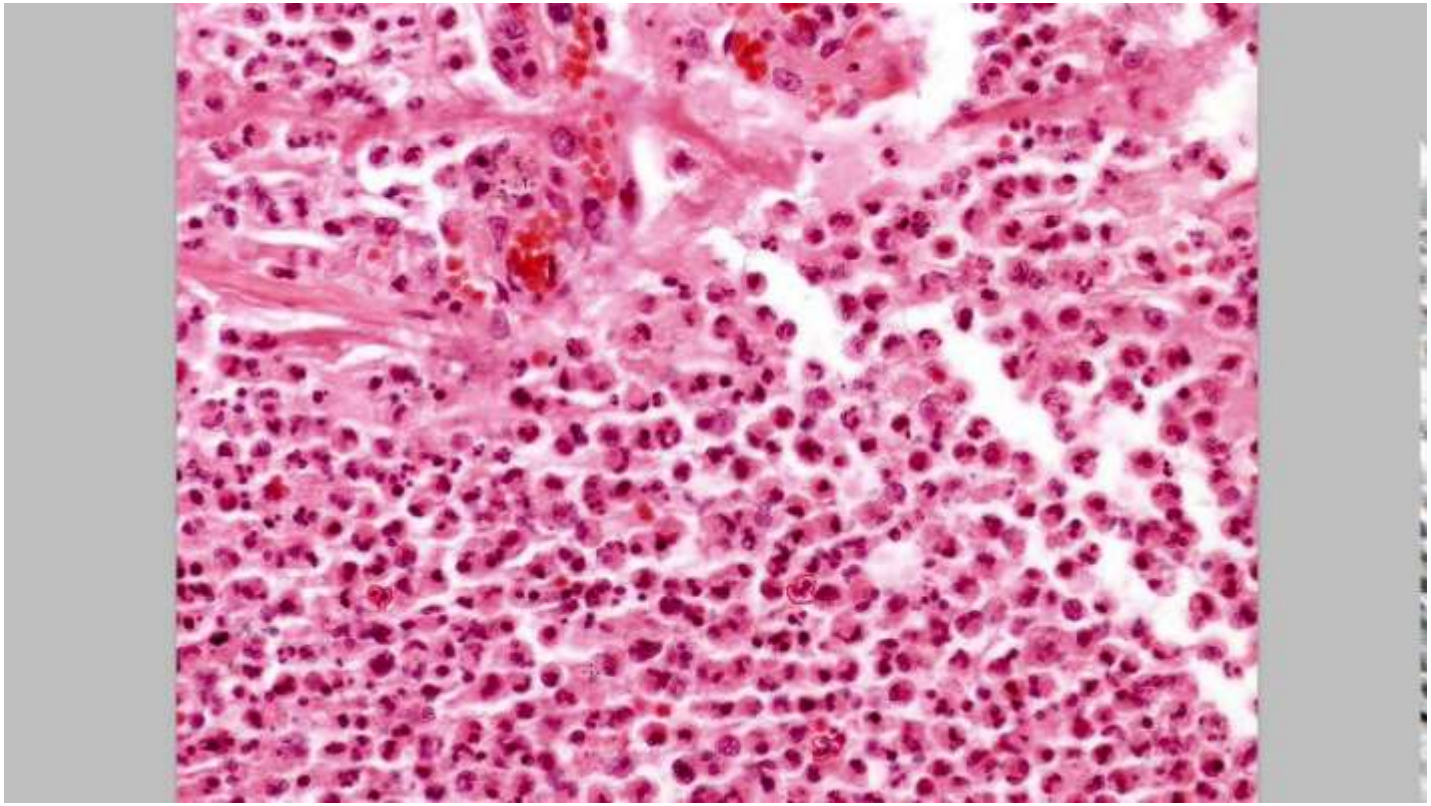


Type of inflammatory cells during inflammation:

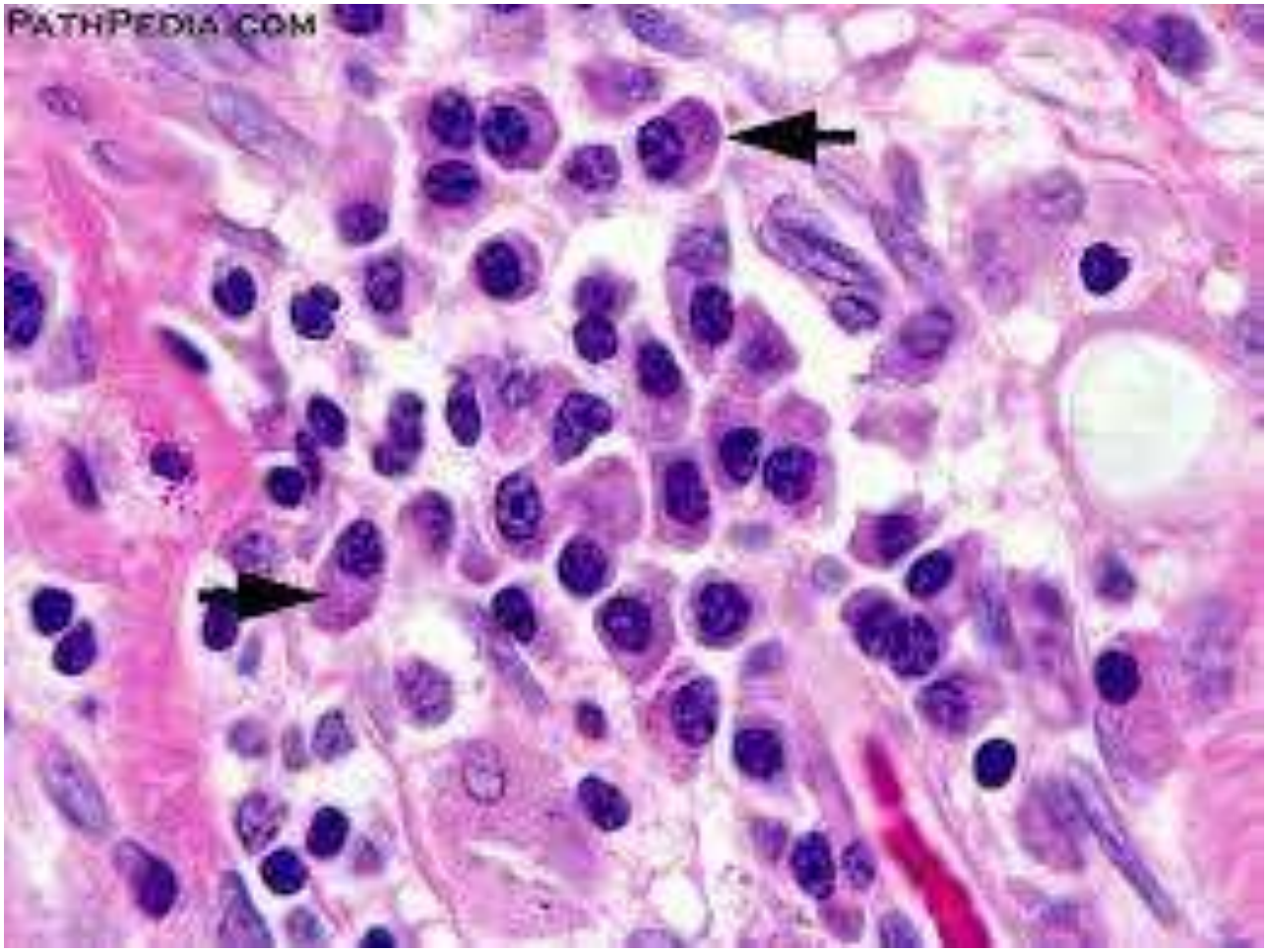
- In most forms of acute inflammation:

- Neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours.
- Monocyte-derived macrophages over 24 to 48 hours.

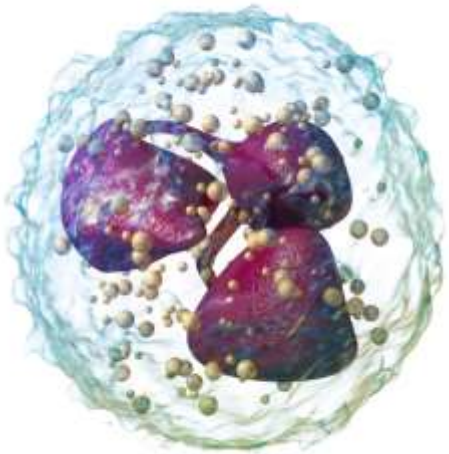
Acute inflammation



Chronic inflammation



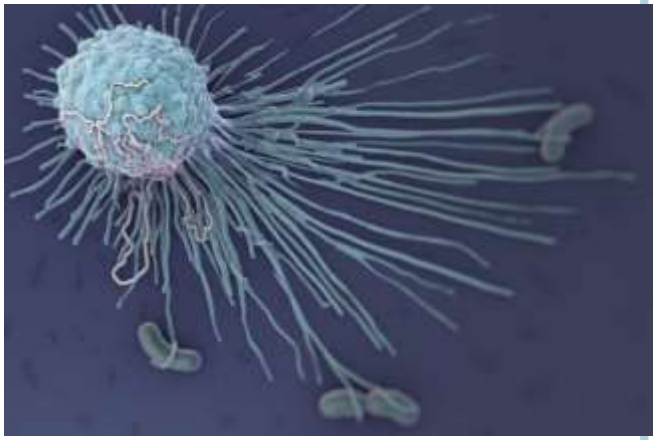
Neutrophils, why in acute?



- More numerous in the blood than other leukocytes.
- They respond more rapidly to chemokines.
- They may attach more firmly to the adhesion molecules that are rapidly induced on endothelial cells, such as P- and E-selectins.

- After entering tissues, neutrophils are short-lived; they undergo apoptosis and disappear within 24 to 48 hours.

Macrophages



- Survive longer .
- May proliferate in the tissues, and thus they become the dominant population in prolonged inflammatory reactions.

Exceptions are present?

- Infection with Pseudomonas bacteria, the cellular infiltrate is dominated by neutrophils for several days.
- In viral infections, lymphocytes may be the first cells to arrive.
- In allergic reactions, eosinophils may be a prominent cell type.

LEUKOCYTE ACTIVATION

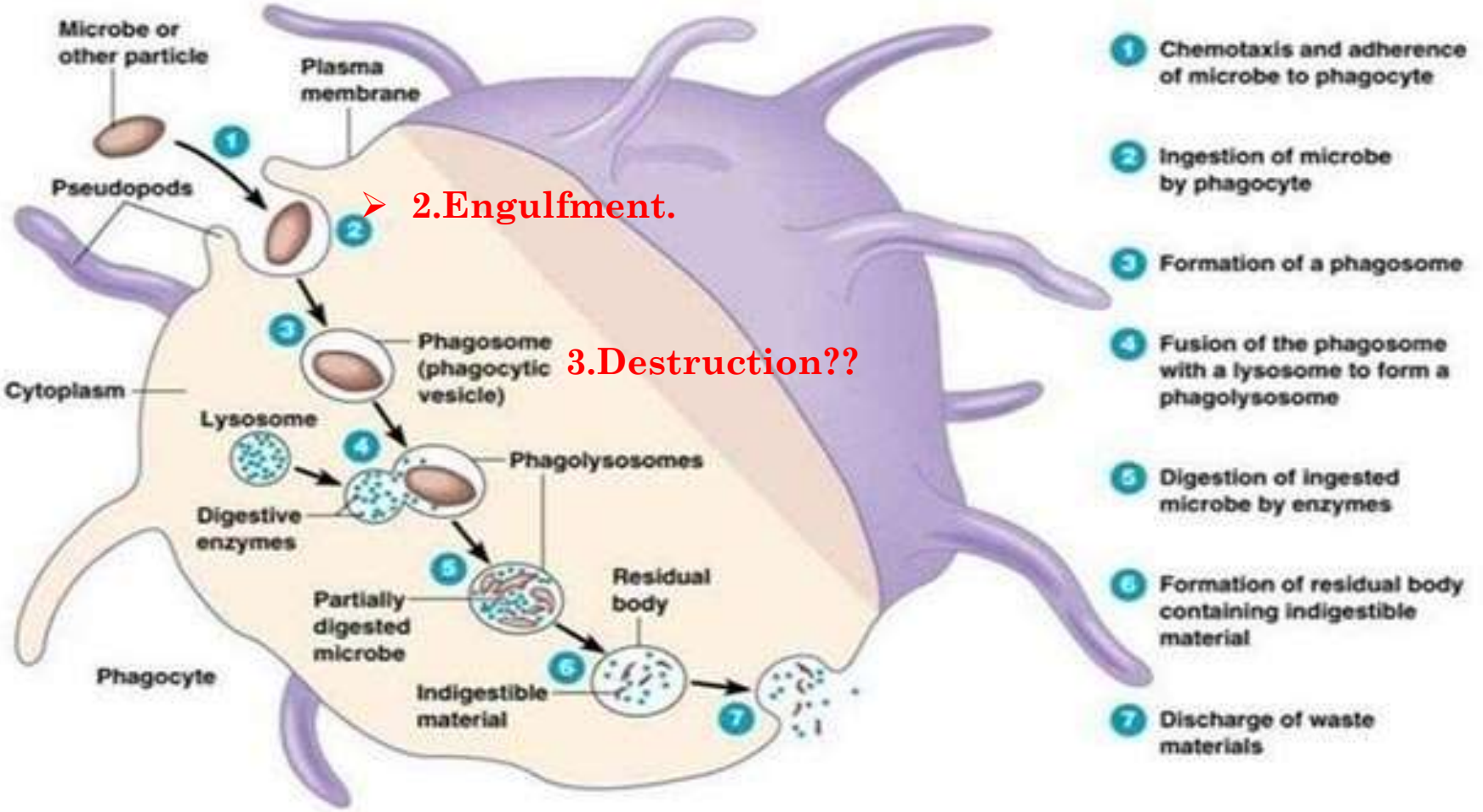
- After leukocytes (particularly neutrophils and monocytes) have been recruited to a site of infection or tissue injury they must be activated to perform their functions.

- The functional responses that are most important for destruction of microbes and other offenders are :
- Phagocytosis.
- Intracellular killing

1. Phagocytosis

- Phagocytosis involves three sequential steps:
- (1) recognition and attachment of the particle to be ingested by the leukocyte.
- (2) engulfment, with subsequent formation of a phagocytic vacuole.
- (3) killing or degradation of the ingested material

- **Recognesion:**
- **Mannose receptors.**
- **Scavenger receptors**



- **2.Engulfment.**

3.Destruction??

Destructive mechanisms:

- 1. respiratory burst :
- Is the rapid release of the reactive oxygen species (ROS), superoxide anion (O2) and hydrogen peroxide (H2O2).

- 2. Nitric Oxide:
- Endothelial (eNOS): maintain vascular tone
- Neuronal (nNOS): acts as neurotransmitter.
- Inducible (iNOS): involved in microbial killing, expressed when macrophages are activated by cytokines (e.g., IFN-γ) or microbial products.

- 3. Granule Enzymes: Neutrophils contain granules packed with enzymes and anti-microbial proteins

Azurophilic (also known as primary) granules
HBP, neutrohil elastase, Cathepsin G, Protease 3, azurocidin, myeloperoxidase

Secondary granules
Lysozyme, Alkaline phosphatase, Collagenase, Vit B12 binding protein, Lactoferrin

Tertiary granules
Gelatinase, Cathepsin B, Cathepsin D, β-d-Glucuronidase, α-Mannosidase, Plasminogen activator, MMP-9

- These harmful proteases, however, are normally controlled by a system of anti-proteases in the serum and tissue fluids.

- For most among these is α1-anti-trypsin, which is the major inhibitor of neutrophil elastase.

- A deficiency of these inhibitors may lead to sustained action of leukocyte proteases, as is the case in patients with α1-anti-trypsin deficiency

Leukocyte-Mediated Tissue Injury

- Leukocytes are important mediators of injury to normal cells and tissues under several circumstances:

- As part of a normal defense reaction against infectious microbes, in some infections that are difficult to eradicate, such as TB, hepatitis.

- In certain autoimmune diseases.

- In allergic diseases, including asthma

Termination of the Acute Inflammatory Response

- 1. Degradation of mediators.
- 2. Neutrophils apoptosis.
- 3. Stop signals :

- a switch in the type of arachidonic acid metabolite produced, from proinflammatory leukotrienes to anti-inflammatory lipoxins.
- liberation of anti-inflammatory cytokines, including transforming growth factor-β (TGF-β) and IL-10, from macrophages

Any question????