Inflammation

Inflammation is a response of vascularized tissues to infections and tissue damage that brings cells and molecules of host defense from the circulation to the sites where they are needed, to eliminate the offending agents .

- It serves to rid the host from both the initial cause of cell injury (e.g., microbes , toxins) and the consequences of such injury (e.g., necrotic cells and tissues).

- Inflammation is induced by chemical mediators that are produced by host cells in response to injurious stimuli .

- Without inflammation, infections would go unchecked and wounds would never heal.

The typical inflammatory reaction develops through a series of sequential steps :

- The offending agent, which is located in extravascular tissues, is recognized by host cells and molecules .
- Leukocytes and plasma proteins are recruited from the circulation to the site where the offending agent is located.
- The leukocytes and proteins are activated and work together to destroy and eliminate the offending substance.
- The reaction is controlled and terminated .
- The damaged tissue is repaired .

External manifestations of inflammation (cardinal signs of inflammation)

1- Rubor (redness).

2-Tumor (swelling).

3-Calor (heat).

4-Dolor (pain).

5-Functio laesa (loss of function).

Types of inflammation

1- Acute inflammation :- The initial, rapid response to infections and tissue damage .

It typically develops within minutes or hours and is of short duration, lasting for several hours or a few days, Its main characteristics are the exudation of fluid and plasma proteins (edema) and the emigration of leukocytes, predominantly neutrophils (also called polymorphonuclear leukocytes).

But if the initial response fails to clear the stimulus, the reaction progresses to a protracted type of inflammation that is called **chronic inflammation**

2- Chronic inflammation:- may follow acute inflammation its longer duration (days to years), and is associated with more tissue destruction , the presence of lymphocytes and macrophages, the proliferation of blood vessels, and fibrosis.

Causes of Inflammation

Inflammatory reactions may be triggered by a variety of stimuli.

1-Infections (bacterial, viral, fungal, parasitic) and microbial toxins are among the most common and medically important causes of inflammation .

2-Trauma (blunt and penetrating) .

3- *physical and chemical injury* *(e.g., thermal injury, as in burns or frostbite; irradiation; exposure to some environmental chemicals).*

4-Tissue necrosis elicits inflammation regardless of the cause of cell death, which may include ischemia (reduced blood flow, the cause of myocardial infarction) . Several molecules released from necrotic cells are known to trigger inflammation.

5-Foreign bodies (splinters, dirt, sutures).

6-Immune reactions (also called hypersensitivity reactions) immune responses against environmental substances or (autoimmune diseases) immune responses against self antigen.

Acute inflammation has two major components:-

1- *Vascular changes*:

- dilation of small vessels, leading to an increase in blood flow (***vasodilation***)

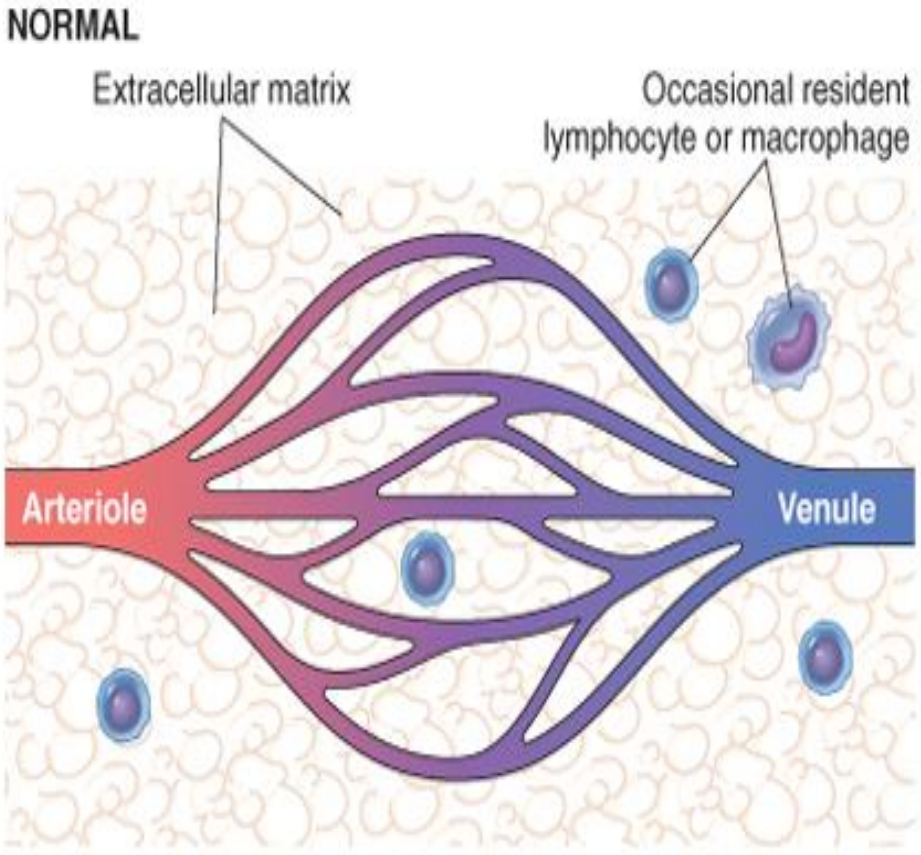
- increased permeability of the microvasculature, enabling plasma proteins and leukocytes to leave the circulation . (***increased vascular permeability***).

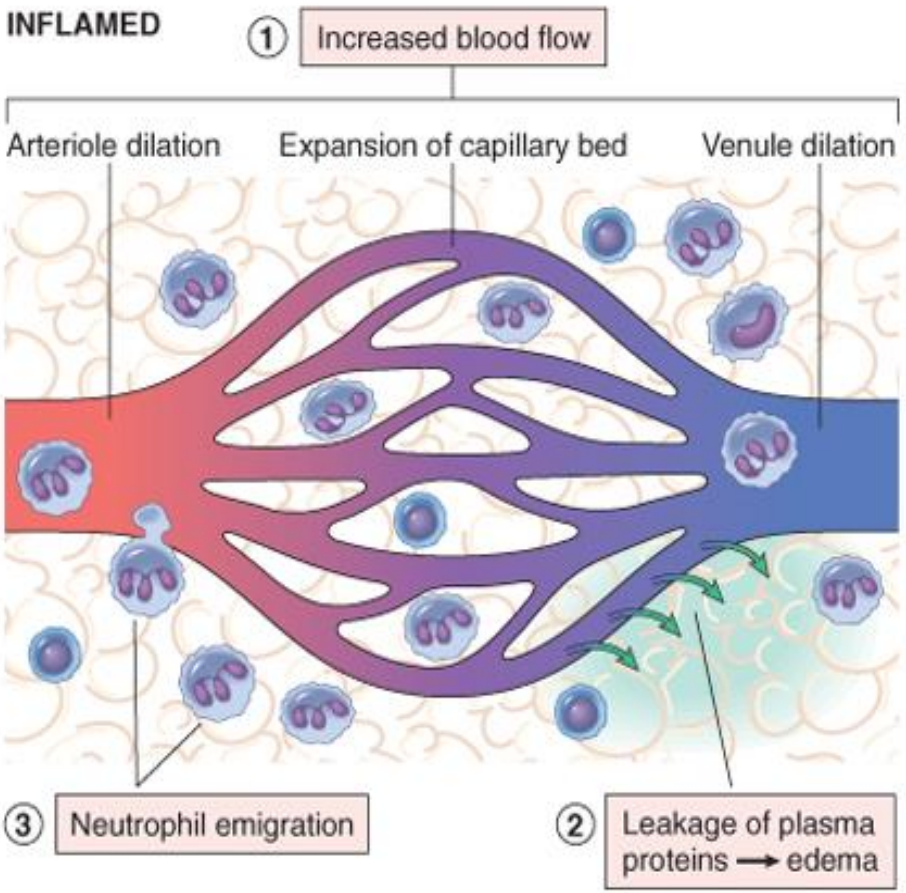
2- *Cellular changes* : -

-Emigration of the leukocytes from the microcirculation and accumulation of them in the site of injury (**cellular recruitment**) , followed by

-**Activation of the leukocytes**, enabling them to eliminate the offending agent (**cellular activation**) .

The principal leukocytes in acute inflammation are **neutrophils (polymorphonuclear leukocytes)**.





The major local manifestations of acute inflammation, compared to normal. (1) Vascular dilation and increased blood flow (causing erythema and warmth), (2) extravasation and deposition of plasma fluid and proteins (edema), and (3) leukocyte (mainly neutrophil) emigration and accumulation in the site of injury.

Reactions of Blood Vessels in Acute Inflammation

The vascular reactions of acute inflammation include changes in the flow of blood and the permeability of vessels, both increase the movement of plasma proteins and leukocytes from circulation to the site of infection or injury .

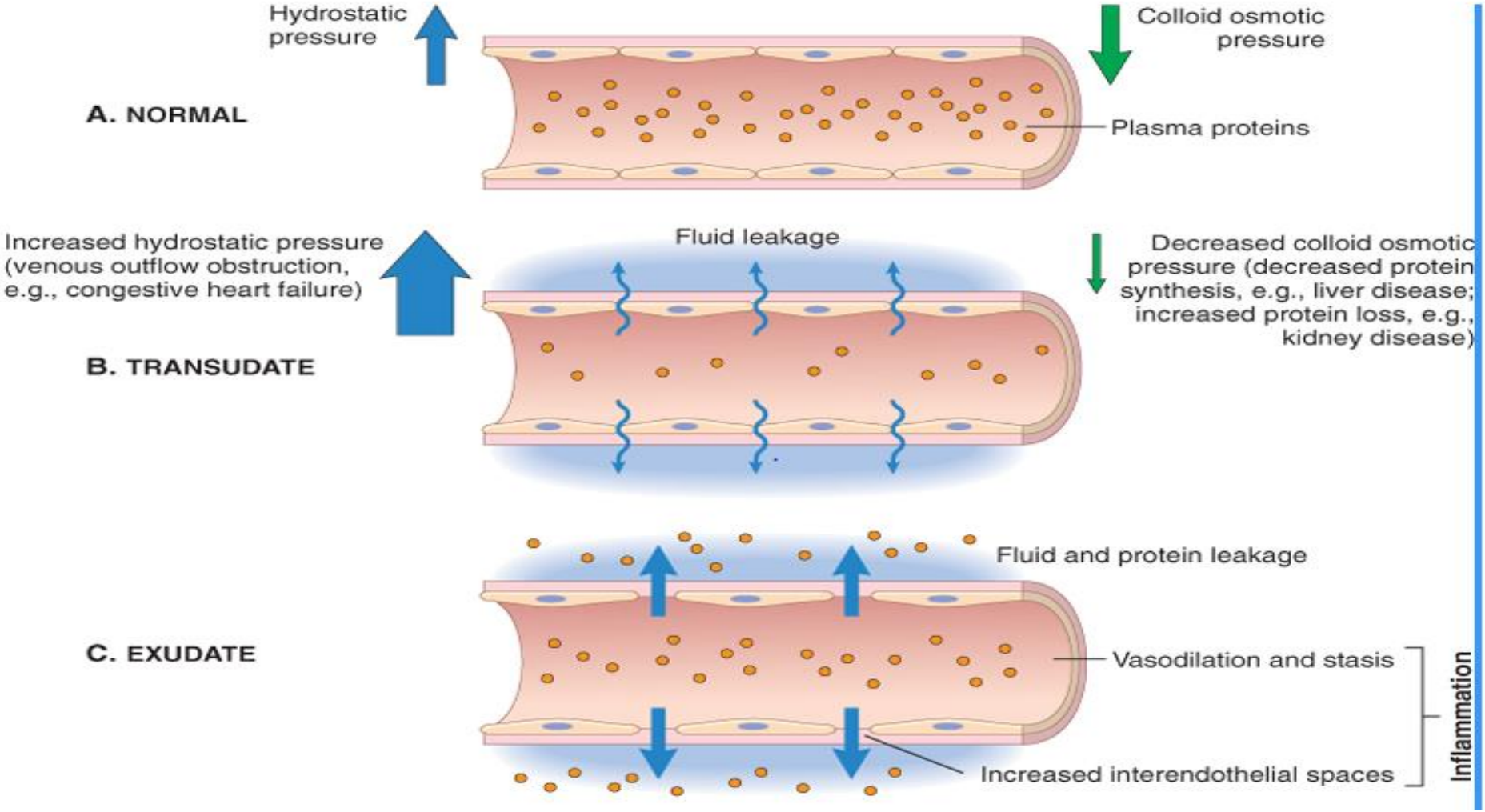
The escape of fluid, proteins, and blood cells from the vascular system into interstitial tissues or body cavities is known as **exudation**.

-Transudate are accumulation of protein poor fluid in the interstitium caused by increased hydrostatic pressure . transudates accumulate in noninflammatory conditions.

- Exudates are accumulation of protein rich fluid in the interstitium due to increases the osmotic pressure . exudates are typical of Inflammation.

- Edema; Accumulation of fluid in extravascular spaces and serous cavities . this fluid may be a transudate or exudate.

- Pus (a purulent exudate), is an inflammatory exudate rich in leukocytes (mostly neutrophils), the debris of dead cells, and, in many cases, microbes .



Formation of transudates and exudates A, Normal hydrostatic pressure (*blue arrows*). B, A transudate is formed when fluid leaks out because of increased hydrostatic pressure or decreased osmotic pressure. C, An exudate is formed in inflammation because vascular permeability increases as a result of increased interendothelial spaces.

Vascular Changes

A- Changes in Vascular Caliber and Flow is begin early after injury and consist of the following :

* After transient vasoconstriction (lasting only for seconds), arteriolar *vasodilation* is occur by the action of histamine on vascular smooth muscle, resulting in increased blood flow and engorgement of the down-stream capillary bed . This vascular expansion is the cause of the redness (*erythema*) and heat (warmth) at the site of inflammation.

* Vasodilation is quickly followed by increased permeability of the microvasculature, and protein-rich fluid moves into the extravascular tissues. This causes the red blood cells to become concentrated, then increasing blood viscosity and slowing the circulation. These changes lead to a process called ***stasis*** .

*As stasis develops, leukocytes (principally neutrophils) begin to accumulate along the vascular endothelial surface, a process called ***margination*** .

B- Increased Vascular Permeability (Vascular Leakage)

Several mechanisms increased vascular permeability in acute inflammation.

1- ***Endothelial cell contraction*** resulting in opening of interendothelial spaces is the most common mechanism of vascular leakage. It is elicited by histamine, bradykinin, leukotrienes, and other chemical mediators.

2- ***Endothelial injury :*** resulting in endothelial cell necrosis and detachment . Direct damage to the endothelium is encountered in burns, or the actions of microbes and microbial toxins that target endothelial cells.

Neutrophils that adhere to the endothelium during inflammation may injure the endothelial cells.

3- ***Increased transport of*** **proteins and fluid** called **transcytosis** . may involve intracellular channels that open through the endothelial cell in response to vascular endothelial growth factor (VEGF), that lead to vascular leakage.

Cellular changes: Leukocyte Recruitment and Activation

the important function of the inflammatory response is to deliver leukocytes to the site of injury and activate them to ingest offending agents, kill bacteria and other microbes, and eliminate necrotic tissue and foreign substances .

-Leukocyte Recruitment

Is the journey of leukocytes from the vascular lumen to the tissue (to the site of inflammation). It is mediated by adhesion molecules and cytokines.

the sequence events of the recruitment consists of :-

1-Margination and rolling along the vessel wall.

2-Firm adhesion to the endothelium.

3-Transmigration between endothelial cells.

4- Migration in interstitial tissues toward a chemotactic stimulus .

1-Margination and Rolling

When blood flows from capillaries into postcapillary venules , circulating cells are move in laminar flow . Because the smaller red cells move faster than the larger white cells As a result, red cells are confined to the central axial column, and leukocytes are pushed out toward the wall of the vessel, but the flow prevents the cells from attaching to the endothelium .

As the blood flow slows in inflammation (stasis). This process accumulate of leukocyte at the periphery along the endothelial surface is called ***margination*** . Subsequently, leukocytes bind and detach and thus begin to tumble on the endothelial surface, a process called ***rolling***.

The attachment of leukocytes to endothelial cells is weak and mediated by adhesion molecules called ***selectins*** . Selectins are receptors expressed on leukocytes and endothelium.

There are three members selectins are:-

1- E-selectin (also called CD62E), expressed on endothelial cells.

2- P-selectin (CD62P), present on endothelium and platelets;
3-L-selectin (CD62L), on the surface leukocytes.

Selectins bind **sialyl–Lewis X modified glycoprotein** on leukocytes.

The endothelial selectins are low in levels or are not present at all on normal endothelial cells . They are elevated after stimulation by cytokines and other mediators in the site of infection . Therefore, binding of leukocytes to endothelium is restricted at sites of infection or tissue injury (where the mediators are produced).

2- Firm adhesion

firm adhesion to endothelial cells is mediated by ***integrins*** expressed on leukocyte interacting with their ligands on endothelial cells. integrins are glycoproteins that mediate the adhesion of leukocytes to endothelium . Integrins are normally expressed on leukocyte in a low-affinity form and do not adhere to their appropriate ligands until the leukocytes are activated by chemokines .

Chemokines are chemoattractant cytokines that are secreted by many cells at sites of inflammation .

3- Transmigration

leukocytes migrate through the vessel wall by squeezing between endothelial cells at intracellular junctions . This extravasation of leukocytes called **diapedesis.**

4- Migration and Chemotaxis

Migration is movement of leukocytes along a chemical gradient is driven by chemokines produced in extravascular tissues . In addition, PECAM-1 (Platelet Endothelial Cell Adhesion Molecule 1) a cellular adhesion molecule expressed on leukocytes and endothelial cells , mediates the binding needed for leukocytes to traverse the endothelium. After passing through the endothelium, leukocytes secrete **collagenase** that enable them to pass through the vascular basement membrane.

Chemotaxis

After existing from the blood vessel, leukocytes migrate toward sites of injury along a chemical gradient by a process called ***chemotaxis***

Both exogenous and endogenous substances can be chemotactic for leukocytes, including

(1)bacterial products, particularly peptides

(2) cytokines, especially those of the *chemokine* family.

(3) components of the complement system, particularly C5a.

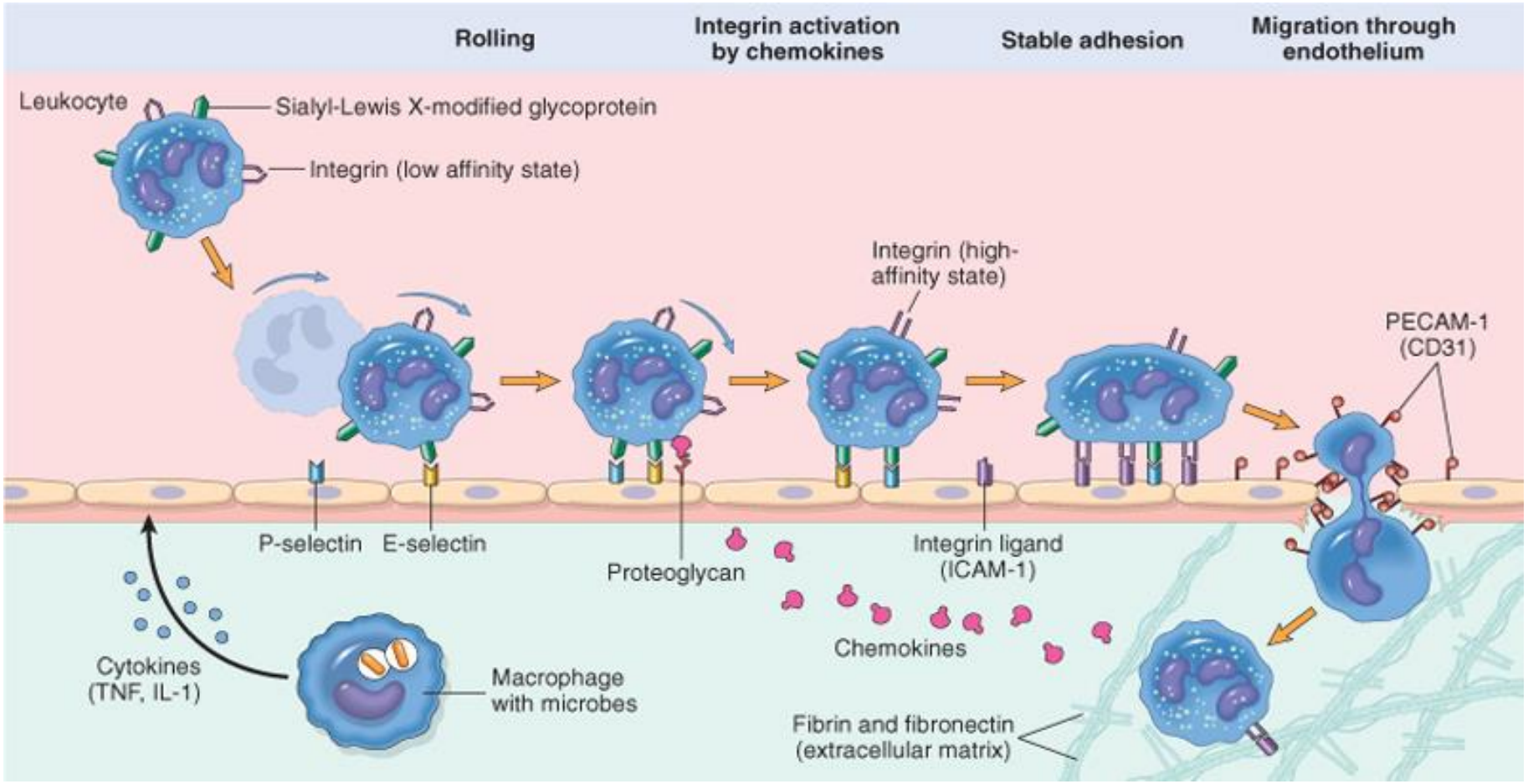
(4) products of arachidonic acid (AA) metabolism.

Chemotactic molecules bind to specific cell surface

receptors, which triggers of cytoskeletal contractile elements necessary for movement .

Leukocytes move by extending pseudopods that anchor to the ECM and then pull the cell in the direction of the extension.

The type of emigrating leukocyte varies with the age of the inflammatory response and with the type of stimulus. In acute inflammation , *neutrophils are predominate in the first 6 to 24 hours and are replaced by monocytes in 24 to 48 hours.* after entering tissues, neutrophils are short-lived-they die by apoptosis and disappear within 24 to 48 hours-while monocytes survive longer .



The complex process of leukocyte migration through blood vessels, The leukocytes first roll, then become activated and adhere to endothelium, then transmigrate across the endothelium, pierce the basement membrane, and migrate toward chemoattractants emanating from the source of injury. Different molecules play predominant roles in different steps of this process - selectins in rolling; chemokines (usually displayed bound to proteoglycans) in activating the neutrophils t\ao increase avidity of integrins; integrins in firm adhesion; and CD31 (PECAM-1) in transmigration. ICAM-1, intercellular adhesion molecule 1; IL-1, interleukin 1; PECAM-1, platelet endothelial cell adhesion molecule 1; TNF, tumor necrosis factor.

-Leukocyte Activation

Once leukocytes have been arrived to the site of infection or tissue necrosis, they must be activated to perform their functions. Stimuli for activation of leukocytes include **microbes, products of necrotic cells , and several mediators** .

Phagocytosis

Is the engulfment and degradation of the bacteria and cellular debris by neutrophils and macrophages .

Phagocytosis consists of three distinct but interrelated steps :-

(1) recognition and attachment of the particle to the ingesting leukocyte.

(2) engulfment, with formation of a phagocytic vacuole

(3) killing and degradation of the ingested material

(1) recognition and attachment of the particle to the ingesting leukocyte (opsonization)

Leukocytes bind microorganisms and dead cells via specific surface receptors. Some of these recognize components of the microbes and dead cells , other receptors recognize host proteins (***opsonins)*** , that coat microbes and target them for phagocytosis (**a process called *opsonization***).

The most important opsonins are

1- **Antibodies (IgG)** that bind to microbial surface antigens.

2- Breakdown products of the complement protein **C3** .

3- plasma carbohydrate-binding lectins called ***collectins .***

These opsonins either are present in the blood ready to coat microbes or are produced in response to the microbes.

2- Engulfment

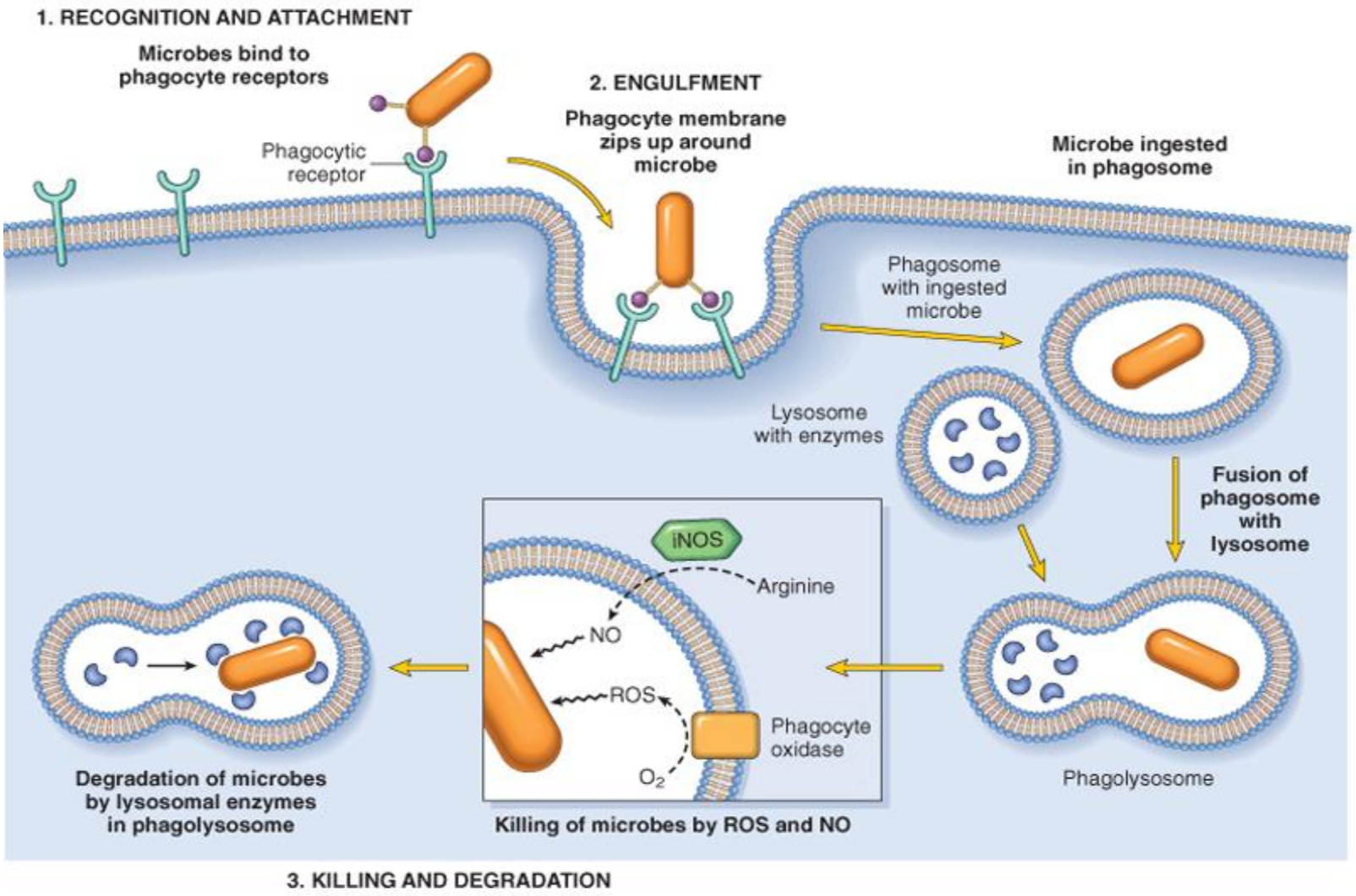
In engulfment, extensions of the cytoplasm (**pseudopods)** are extended around the particle to be engulfed , eventually forming a **phagocytic vacuole**. The membrane of this vacuole then fuses with the membrane of a **lysosomal granule** to form **phagolysosome** resulting in discharge of the granule's contents

3- Killing and Degradation of Microbes

the phagocytosis is ended by killing and degradation of the ingested microbes .

The key steps in this reaction are the production of microbicida substances within lysosomes and fusion of the lysosomes with phagosomes .

The most important microbicidal substances are reactive oxygen species (ROS) and lysosomal enzymes .



Phagocytosis of a particle (e.g., a bacterium) involves (1) attachment and binding of the particle to receptors on the leukocyte surface, (2) engulfment and fusion of the phagocytic vacuole with granules (lysosomes), and (3) destruction of the ingested particle. iNOS, Inducible nitric oxide synthase; NO, nitric oxide; ROS, reactive oxygen species.

Outcomes of Acute Inflammation

Outcomes of Acute Inflammation depends on:-

1-The nature and intensity of the injury .

2-The site and tissue affected .

3-The responsiveness of the host .

Acute inflammation generally has one of three outcomes:-

1-Resolution .

- When the injury is limited or short-lived,
- When there has been no or minimal tissue damage,
- When the tissue is capable of replacing any irreversibly injured cells,

The usual outcome is restoration to histologic and functional normalcy.

2- Progression to chronic inflammation

may follow acute inflammation if the offending agent is not removed .

3-Scarring or fibrosis

It means replacement destructed or injured tissue by fibrous connective tissue . This occur when large tissue destruction or if the inflammation occur in tissue that do not regenerate

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