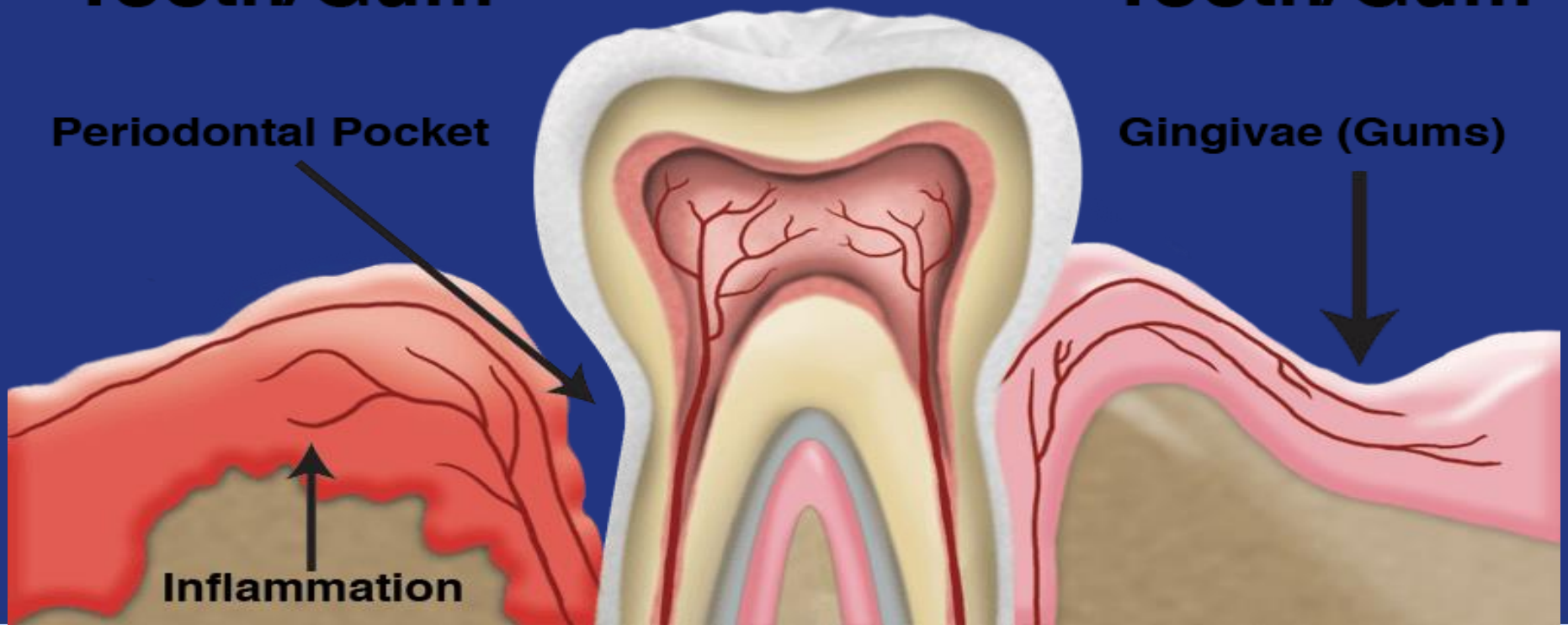
UNIVERSITATEA DE STAT DE MEDICINĂ ȘI FARMACIE
"NICOLAE TESTEMIȚANU" DIN REPUBLICA MOLDOVA

Inflammation



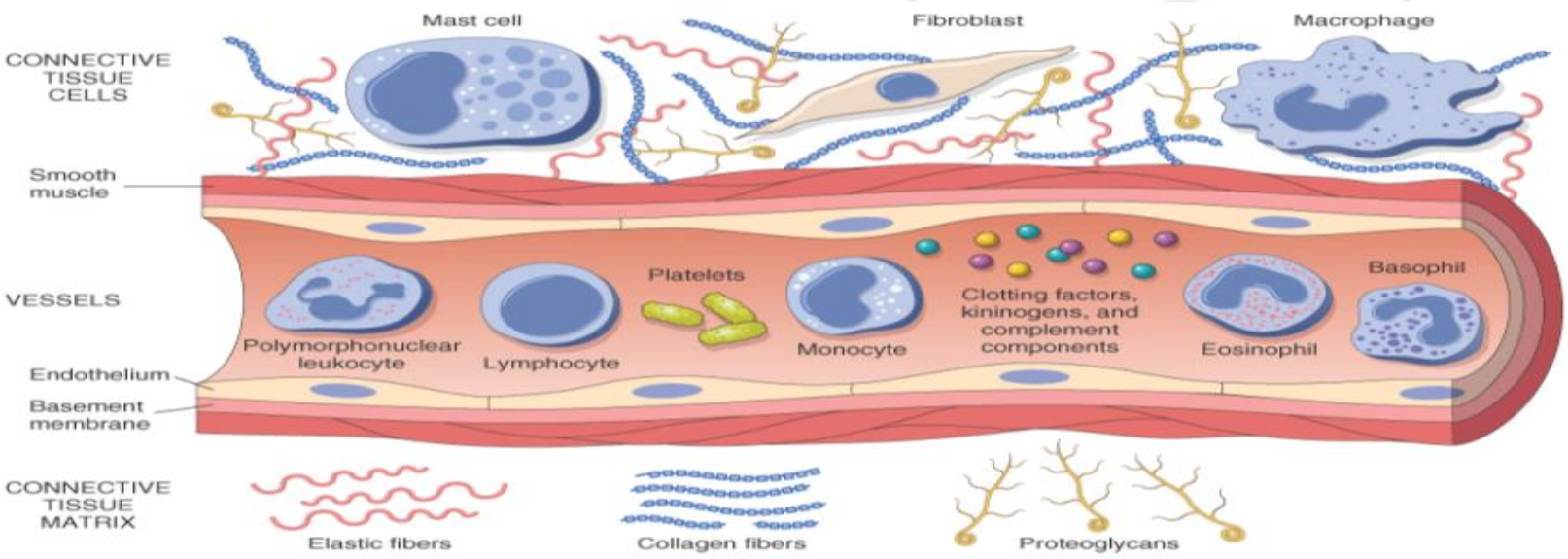
Definition

- **Inflammation – represents a typical pathological process, an answer to cellular injury of different etiology, oriented toward diminishing activity and elimination of pathogenic factors from the body, delimitation of injuries, liquidation of injured structures and their replacement with viable structures.**

- ***The clinical definition of inflammatory process in different organs is formed from Latin or Greek roots of organs name adding the suffix -it or –itis (ex: inflammation of the gum - gingivitis, of the pulp– pulpitis, of the tongue - glossitis)***

General biological characteristics of inflammation

- ***Inflammation is a pathologic process*** ;
- ***Inflammation is a typical pathologic process*** ;
- ***Inflammation is the body answer to every injury with predominant local manifestations, but also with general reactions;***
- ***Inflammation represents a complex of vascular-tissular reactions and can develop only at the level of tissues and organs.***



The role of inflammation

- **Without inflammation infections would go unchecked, wounds would never heal, and injured tissues might remain permanent festering sores.**

ETIOLOGY OF INFLAMMATION = FLOGOGENIC FACTORS

***Infections* (bacterial, viral, fungal, parasitic) and microbial toxins.**

Tissue necrosis

Foreign bodies

Immune-mediated inflammation

INFLAMMATION

A C U T E

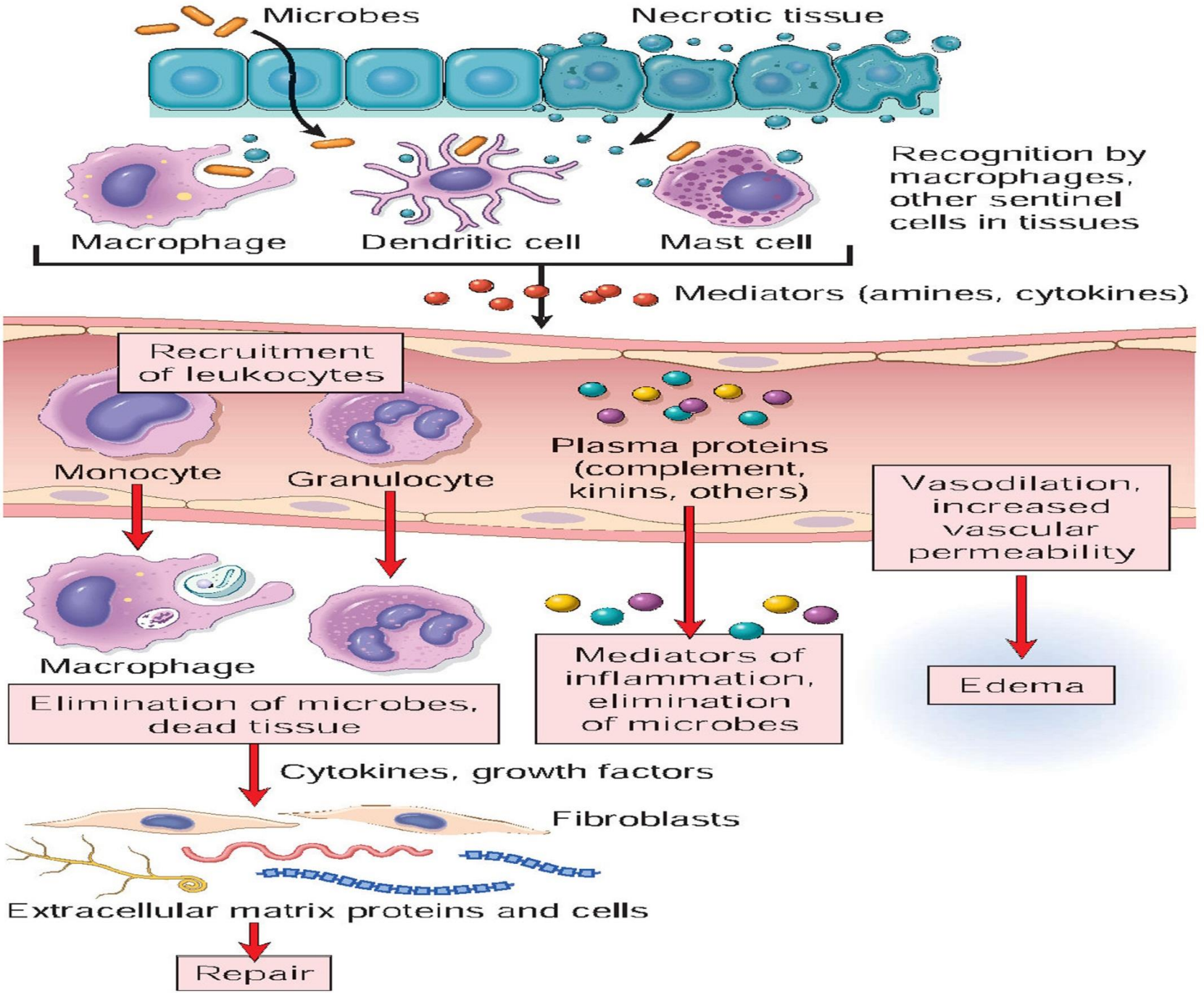
- Rapid in onset (typically minutes);
- Short duration, lasting for hours or a few days;
- It is characteristic: exudation of fluid and plasma proteins (edema) and emigration of leukocytes, predominantly neutrophils.

C H R O N I C

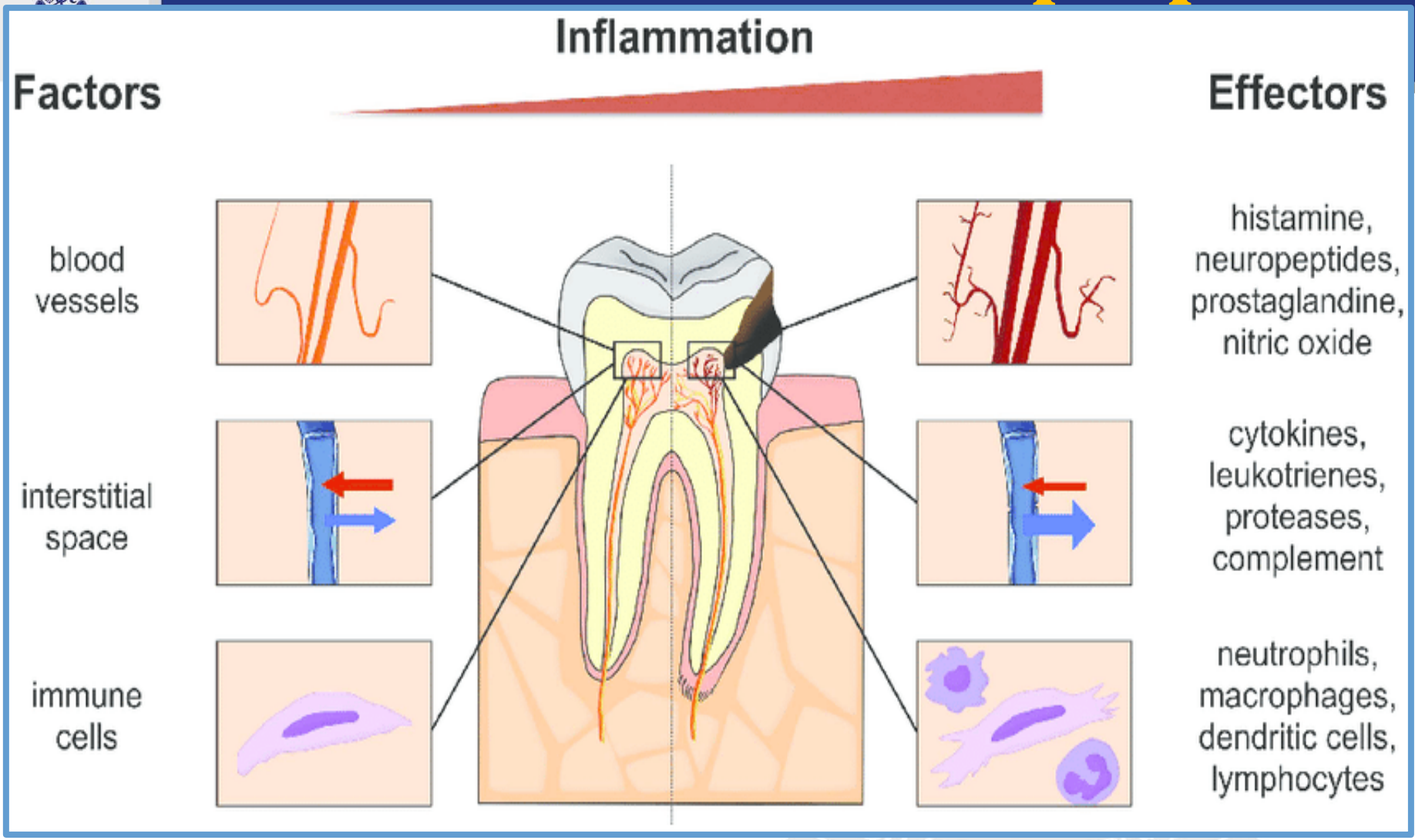
- Longer duration;
- Is associated with the presence of lymphocytes and macrophages infiltration;
- It is characteristic: proliferation of blood vessels, fibrosis, and tissue destruction.

The main pathogenic processes of inflammation are (stages of inflammation):

1. ***Alteration*** – tissular injury;
2. ***Recognition*** of flogogenic factors by innate immune cells that release, activate or de novo formation of active biological substances that maintain inflammation (**inflammation mediators**);
3. ***Vascular reactions*** – ischemia, arterial hyperemia, venous hyperemia, stasis, vascular hyperpermeability;
4. ***Exudation*** – liquid extravasation, inflammatory edema;
5. ***Blood cells emigration and infiltration*** of the affected organ or tissue with neutrophils, eosinophils, lymphocytes, monocytes;
6. ***Proliferation*** of cells of mesenchymal origin;
7. ***Regeneration*** *(repair)*


Microbes
Necrotic tissue
Macrophage
Dendritic cell
Mast cell
Recognition by macrophages, other sentinel cells in tissues
Mediators (amines, cytokines)
Recruitment of leukocytes
Monocyte
Granulocyte
Plasma proteins (complement, kinins, others)
Vasodilation, increased vascular permeability
Macrophage
Elimination of microbes, dead tissue
Mediators of inflammation, elimination of microbes
Edema
Cytokines, growth factors
Fibroblasts
Extracellular matrix proteins and cells
Repair

Inflammation of the pulp



- **Schematic illustration of a tooth with a healthy pulp (left panel) and an inflamed pulp (right panel) subjacent to a caries lesion**

I. ALTERATION IN INFLAMATORY PROCESS

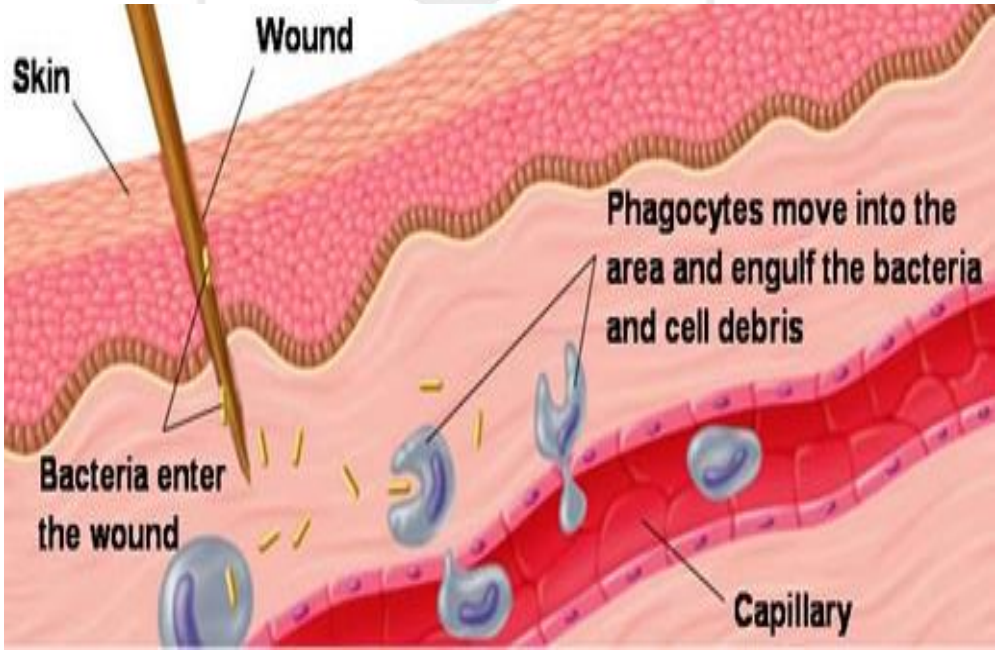
Persistent modification of cells and acellular elements structures at the level of tissues and organs accompanied by functional disorders

PRIMARY

- **Initial alteration caused by the initial harmful factor (flogogen factors).**
- **Structural and functional disorders provoked by the harmful factor directly in the place where it acts.**
- **Primary alteration represents the trigger mechanism and initiates the onset of inflammation.**

SECONDARY

Alteration as a consequence of action of pathogenic factors.



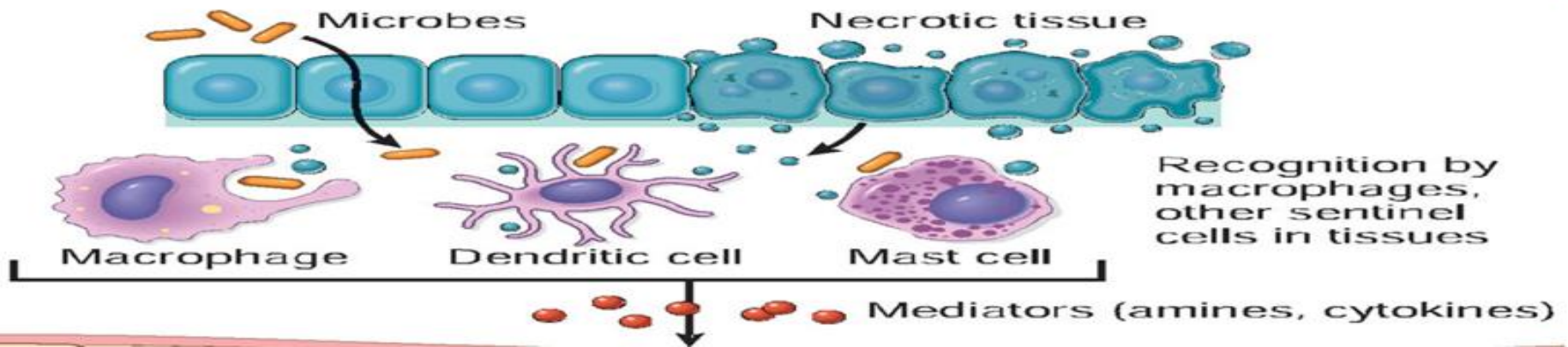
II. Recognition of pathogenic factors by innate immune cells (DAMP)

PATHOGEN ASSOCIATED MOLECULAR PATTERN (PAMP)
(lipopolysaccharides, peptidoglycan, endotoxin)

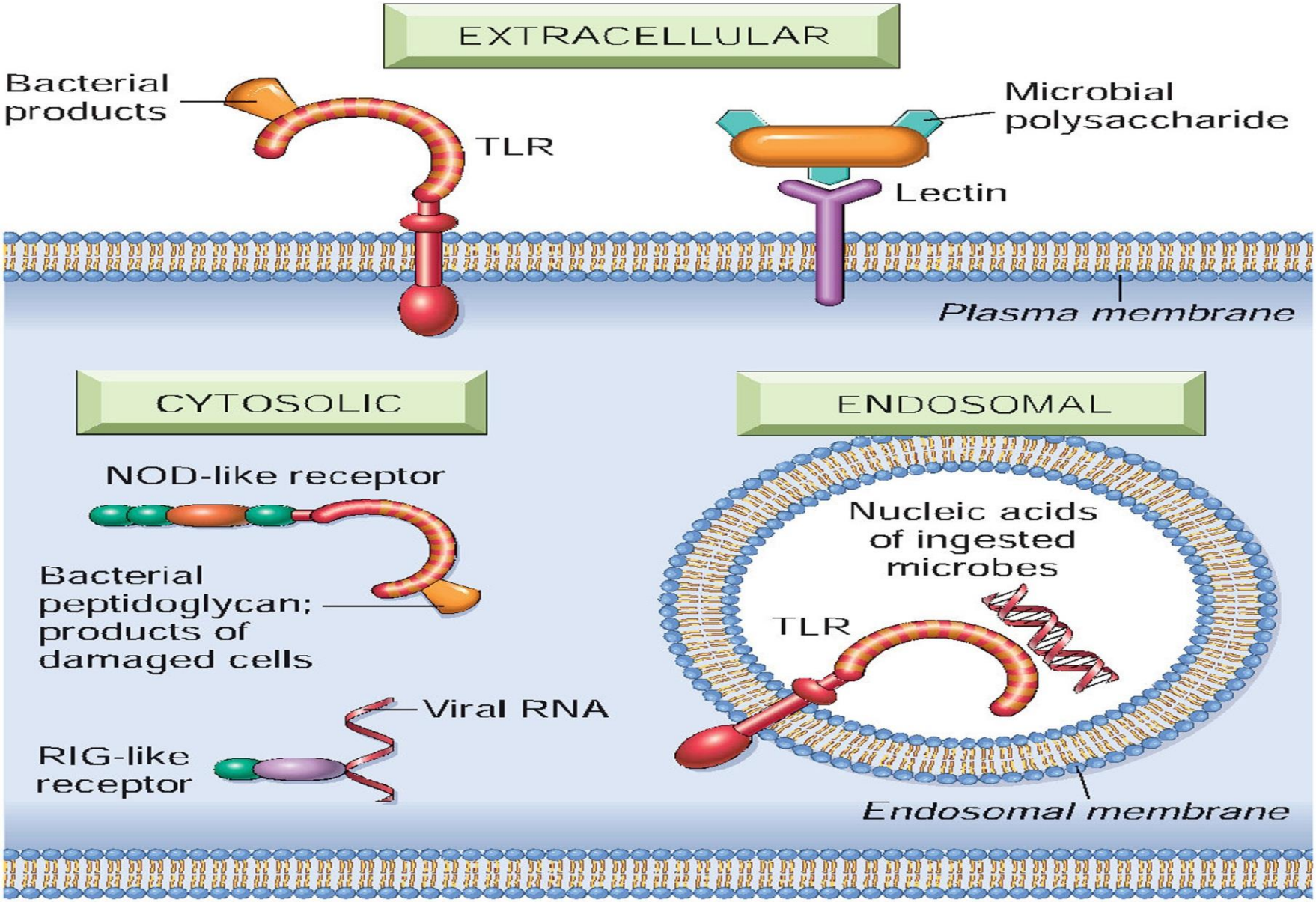
DAMAGE ASSOCIATED – MOLECULAR PATTERN (DAMP)
Products of cell injury, cell necrosis

PATTERN RECOGNITION RECEPTORS

(PAMP) (DAMP)



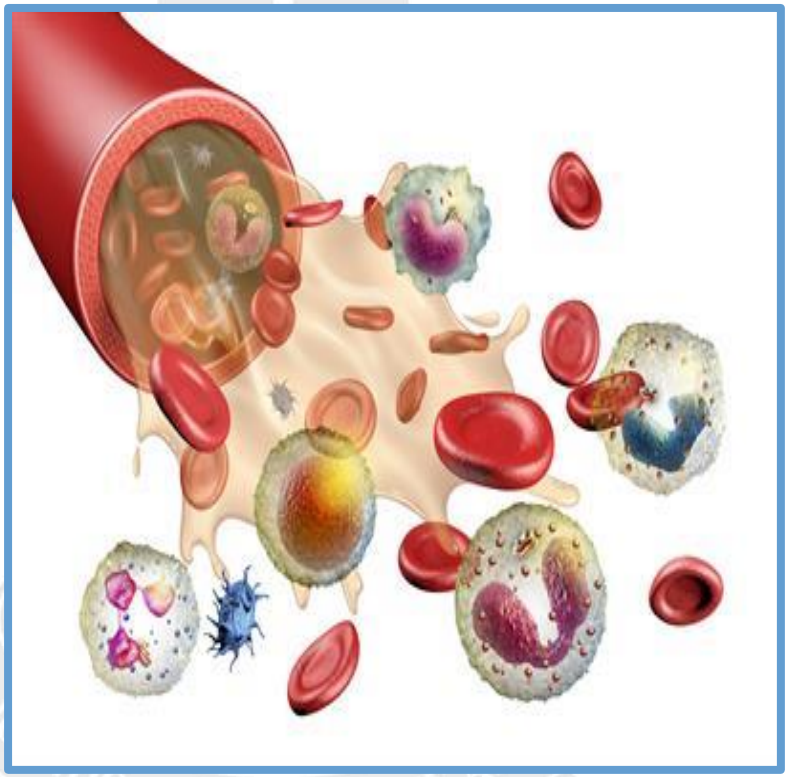
PATTERN RECOGNITION RECEPTORS



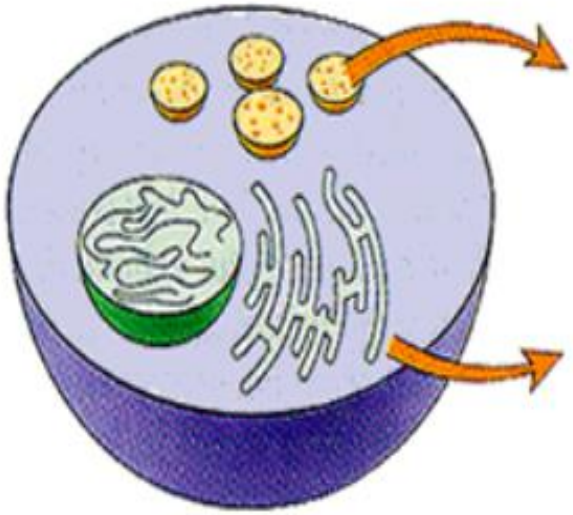
INFLAMMATORY MEDIATORS

Inflammatory mediators are soluble factors that are produced by various cells or derived from plasma proteins and are generated or activated in response to the inflammatory stimulus.

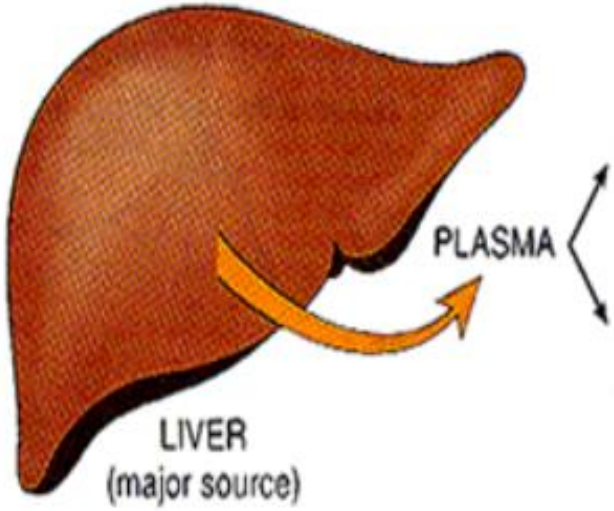
They initiate and regulate inflammatory reactions and their biological goal is: *protection* the body by diminish pathogenic activity, *delimitation and isolation* of the focus of alteration and *restoration* of the injured structures



INFLAMMATORY MEDIATORS

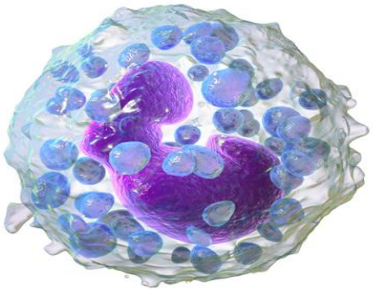


	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
	Lysosomal enzymes	Neutrophils, macrophages
Newly synthesized	Prostaglandins	All leukocytes, platelets, EC
	Leukotrienes	All leukocytes
	Platelet-activating factors	All leukocytes, EC
	Activated oxygen species	All leukocytes
	Nitric oxide	Macrophages
	Cytokines	Lymphocytes, macrophages, EC

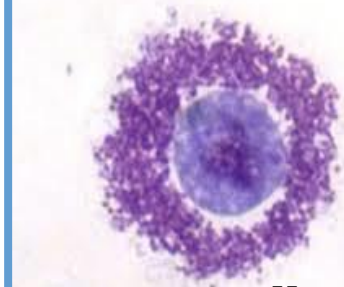


Factor XII (Hageman factor) activation	Kinin system (bradykinin)	
	Coagulation / fibrinolysis system	
Complement activation	C_{3a}, C_{5a}	anaphylatoxins
	C_{3b}	
	$C_{5b\text{-}9}$	(membrane attack complex)

1. Presynthetizied cellular inflammatory mediators

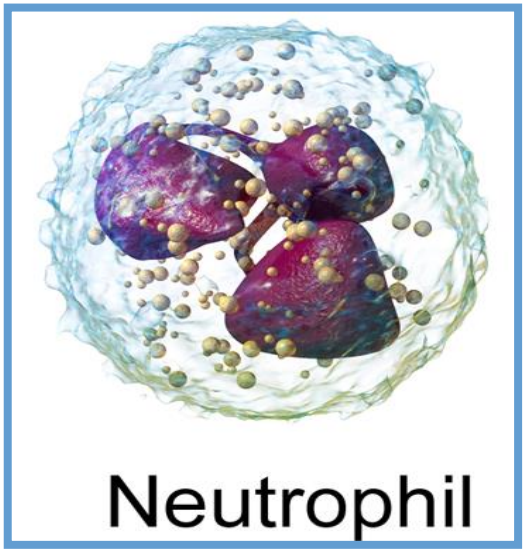


Basophil



Mast cell

Histamine;
Beta-glucosaminidase;
Triptase;
CFE (chemotactic factor for eosinophils);
CFN (chemotactic factor for neutrophils);
Heparine.

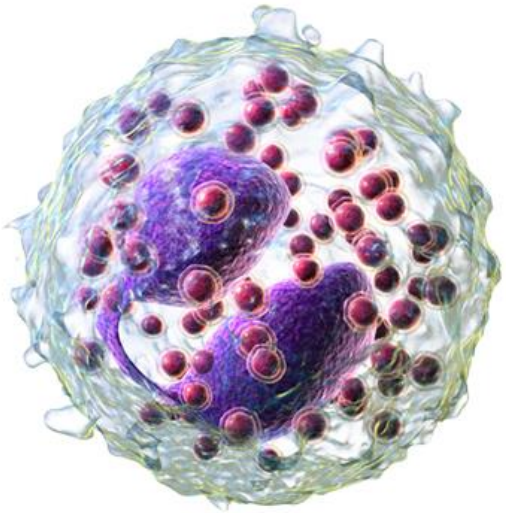


Neutrophil

- **LYSOSOMAL ENZYMES (glycolytic enzymes, photolytic enzymes, lipolytic enzymes)**

- **BACTERICIDE PRODUCTS**

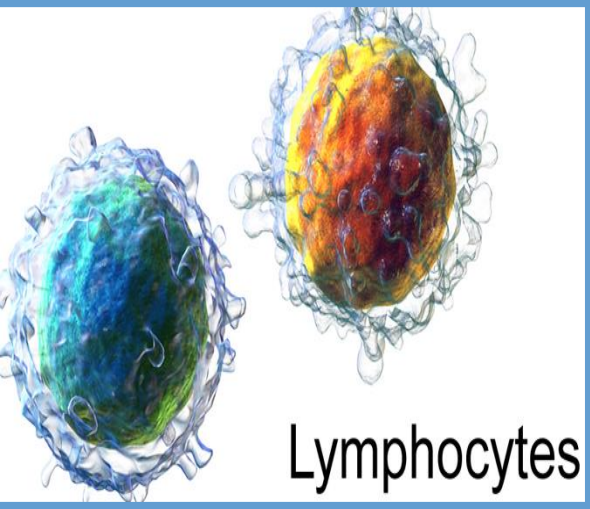
- ***Oxygen dependent*** **(H_2O_2, O_2^-, OH^-, OCl^-);**
- ***Oxygen-independent*** **(*cationic proteins*, which damage cellular membrane of microorganisms, *lysozim* (muraminidasis) - which break down the muraminic acid from mucoproteins of microbial wall, *lactoferin* that bind iron ions necessary for vital activity of the microbe.**



Eosinophil

Bactericide oxygen-dependent products (H2O2, OH-, OCl-, O2-) and specific mediators:

- ***cationic proteins*** and ***main basic protein*** with a direct anti-parasitic action;
- ***peroxidase*** – that break down oxygen peroxide till H2O2 and atomar oxygen, and in presence of halogens forms OCl-;
- ***histaminase*** – eoxidative deamination of histamine,
- ***arylsulphatase*** - inactivates leukotrienes;
- ***phospholipase D*** – inactivate the thrombocyte activator factor;
- ***perforins***

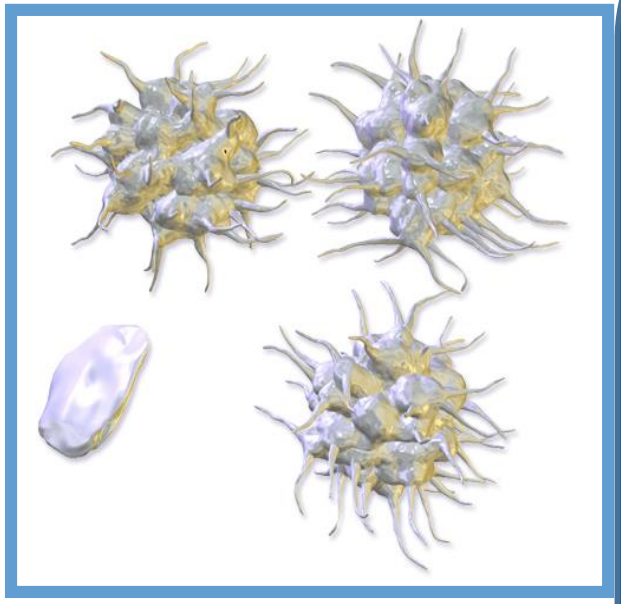


Lymphocytes

- **LYMPHOKINS**

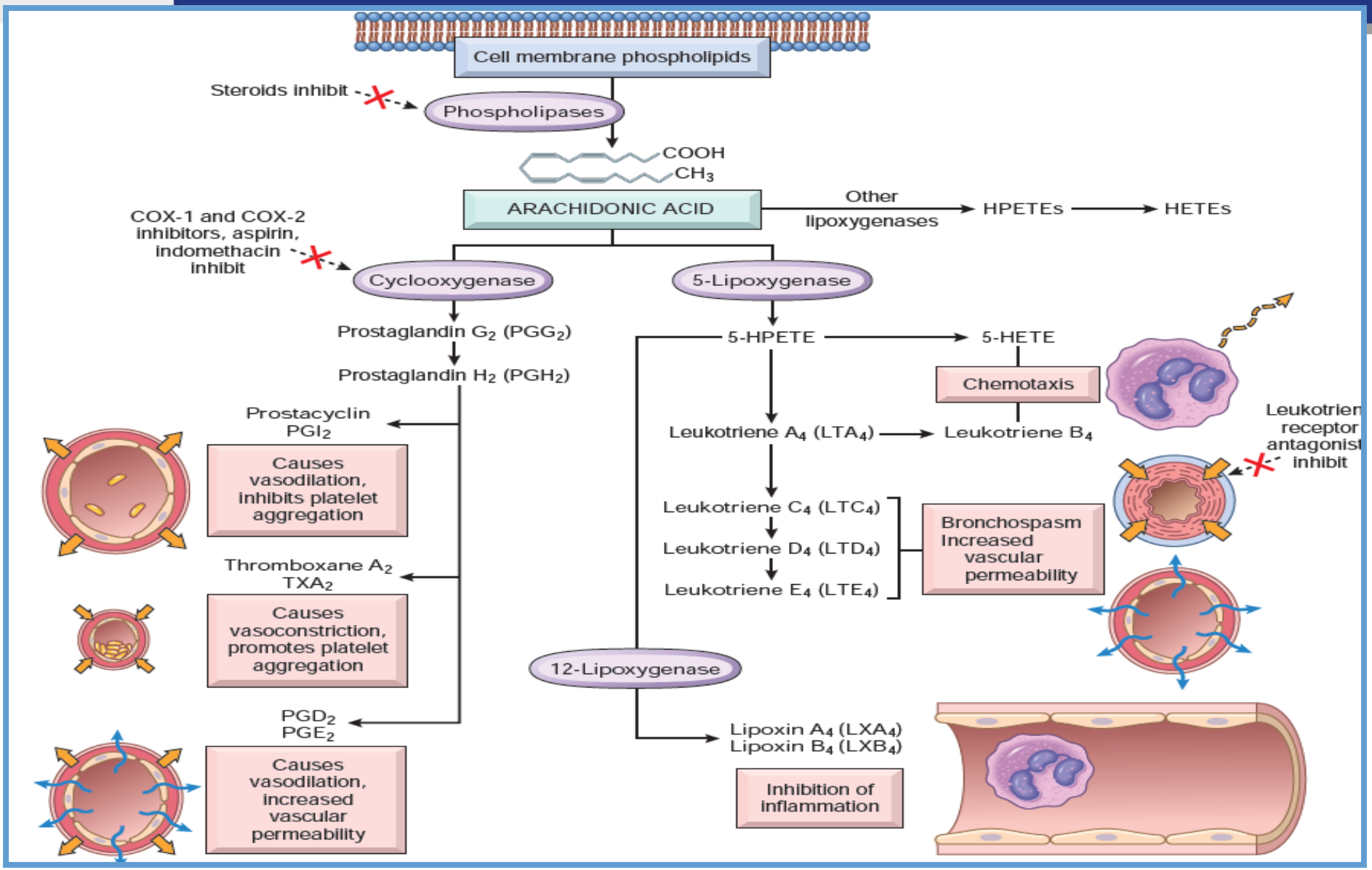
- ***Mitogen factor***, stimulates proliferation of non-sensitized lymphocyte;
- ***Factor of vascular wall hyperpermeability***;
- ***Lymphocytotoxin*** - have direct cytotoxic action;
- ***Chemoattractant factor***, which contributes to lymphocyte migration from vascular bed into inflammatory focus;
- - ***Inhibitory factor of macrophage migration***

Platelets



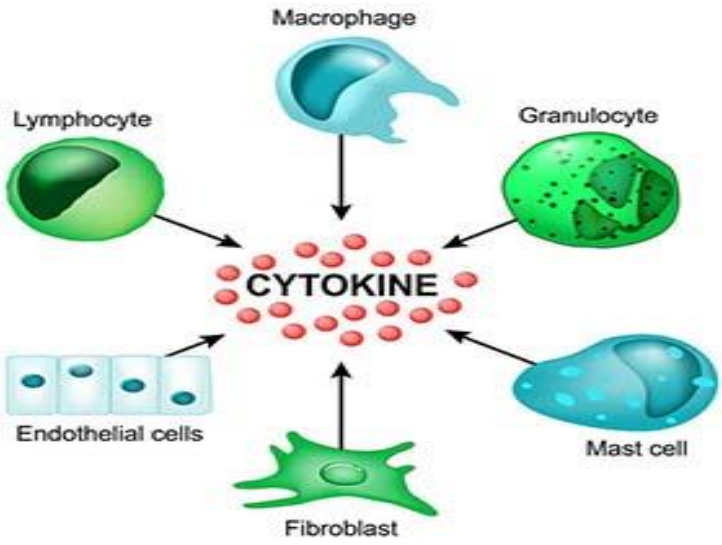
- ***Serotonin*** **(5-hydroxytryptamine) is realized from platelets, when they interact with collagen, thrombin, adenosine diphosphate, and antigen-antibody complexes. Thus, the platelets release reaction, which is a key component of coagulation, also results in increased vascular permeability. This is one of several links between clotting and inflammation.**
- **Thromboxane A2 (vasoconstriction and platelet aggregation)**

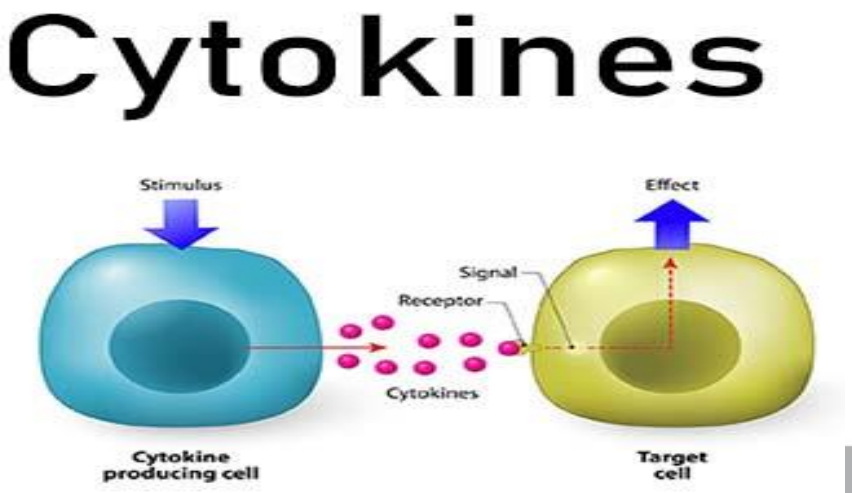
De novo synthesized inflammatory mediators



CYTOKINES - INFLAMMATORY MEDIATORS

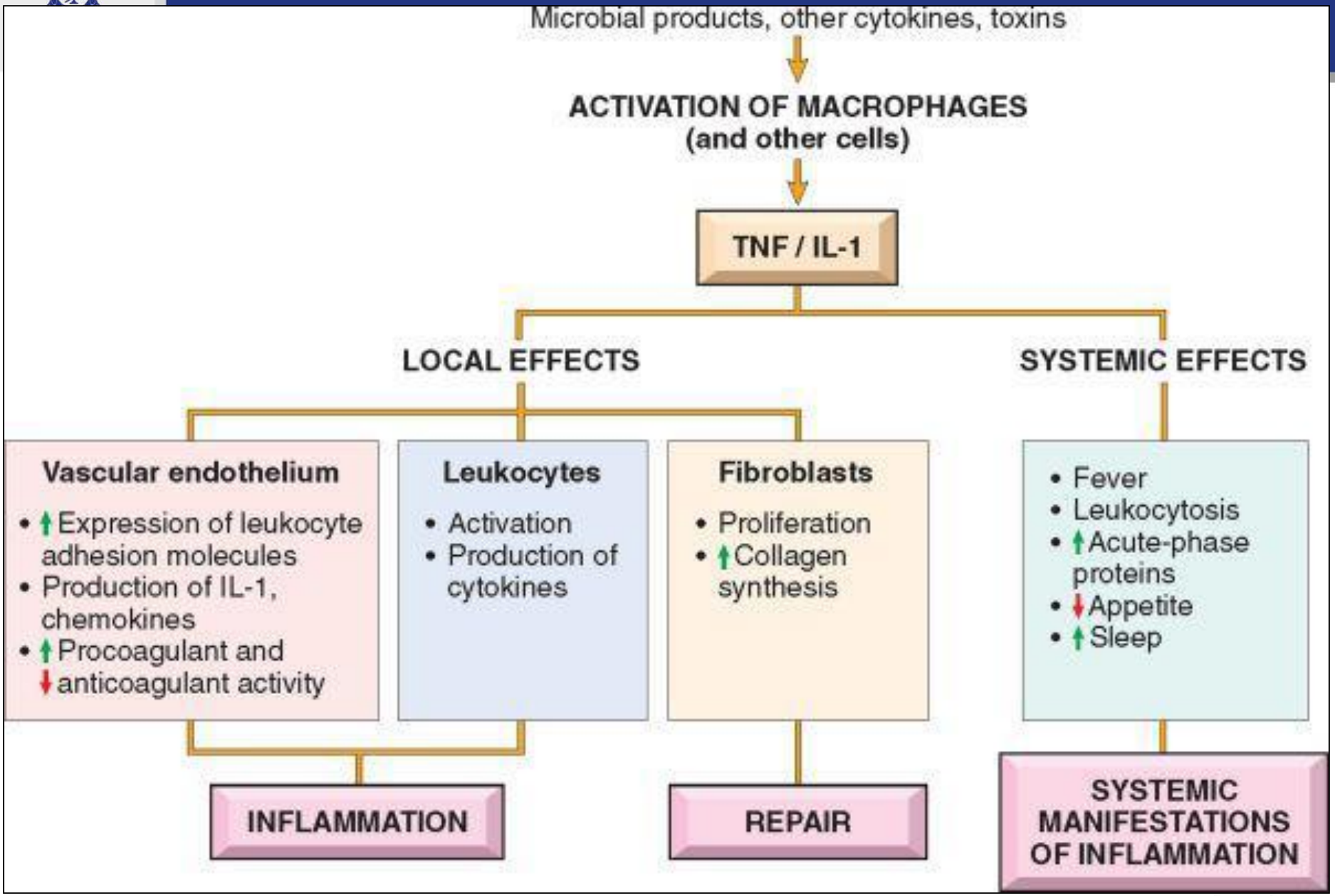
- **Cytokines are proteins produced by many cell types (principally activated lymphocytes and macrophages, but also endothelial, epithelial, and connective tissue cells) that modulate the functions of other cell types.**





Cytokine	Principal Sources	Principal Actions in Inflammation
IN ACUTE INFLAMMATION		
TNF	Macrophages, mast cells, T lymphocytes	Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effects
IL-1	Macrophages, endothelial cells, some epithelial cells	Similar to TNF; greater role in fever
IL-6	Macrophages, other cells	Systemic effects (acute-phase response)
Chemokines	Macrophages, endothelial cells, T lymphocytes, mast cells, other cell types	Recruitment of leukocytes to sites of inflammation; migration of cells to normal tissues
IN CHRONIC INFLAMMATION		
IL-12	Dendritic cells, macrophages	Increased production of IFN-γ
IFN-γ	T lymphocytes, NK cells	Activation of macrophages (increased ability to kill microbes and tumor cells)
IL-17	T lymphocytes	Recruitment of neutrophils and monocytes

Systemic action of TNF and IL-1



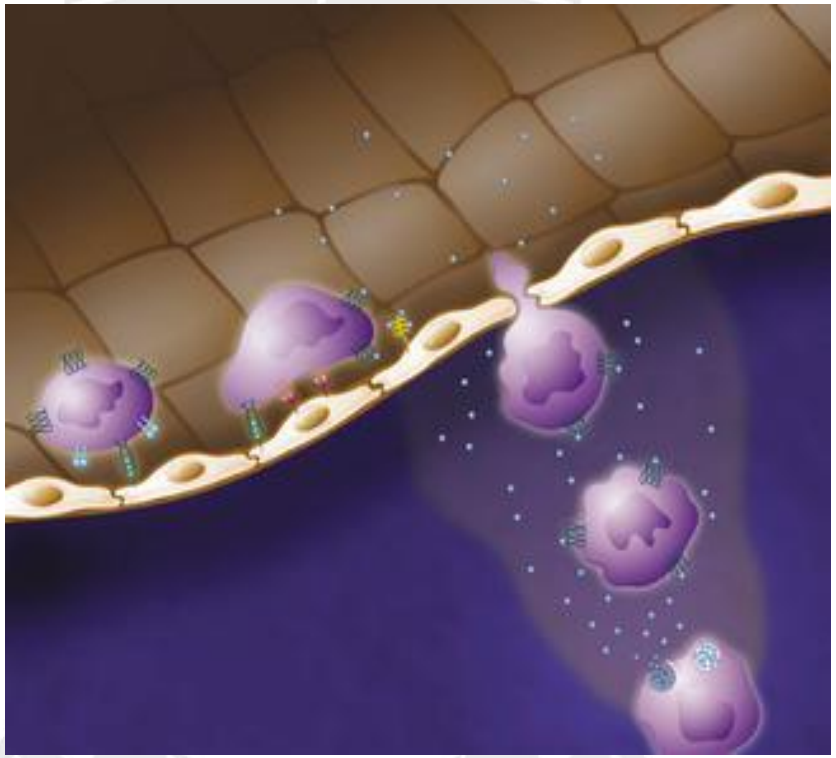
CHEMOKINES

Chemokines **(Greek *-kinos*, movement) are a family of small cytokines, (8 to 10 kD) proteins that act primarily as *chemoattractants* for specific types of leukocytes.**

They are secreted by activated macrophages, endothelial cells, and other cell types.

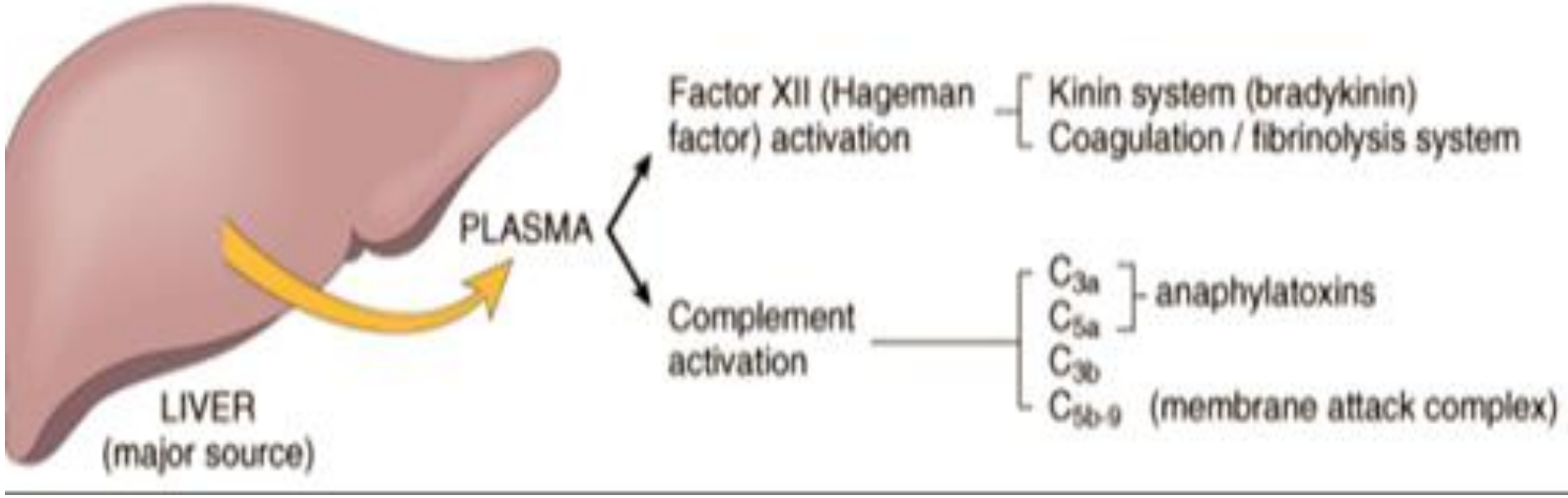
Chemokines have two main functions: they stimulate leukocyte recruitment in inflammation and control the normal migration of cells through various tissues.

Examples: *IL-8, Monocyte chemoattractant protein* (MCP-1), *eotaxin, macrophage inflammatory protein-1α (MIP-1α), Lymphotactin , Fractalkine*

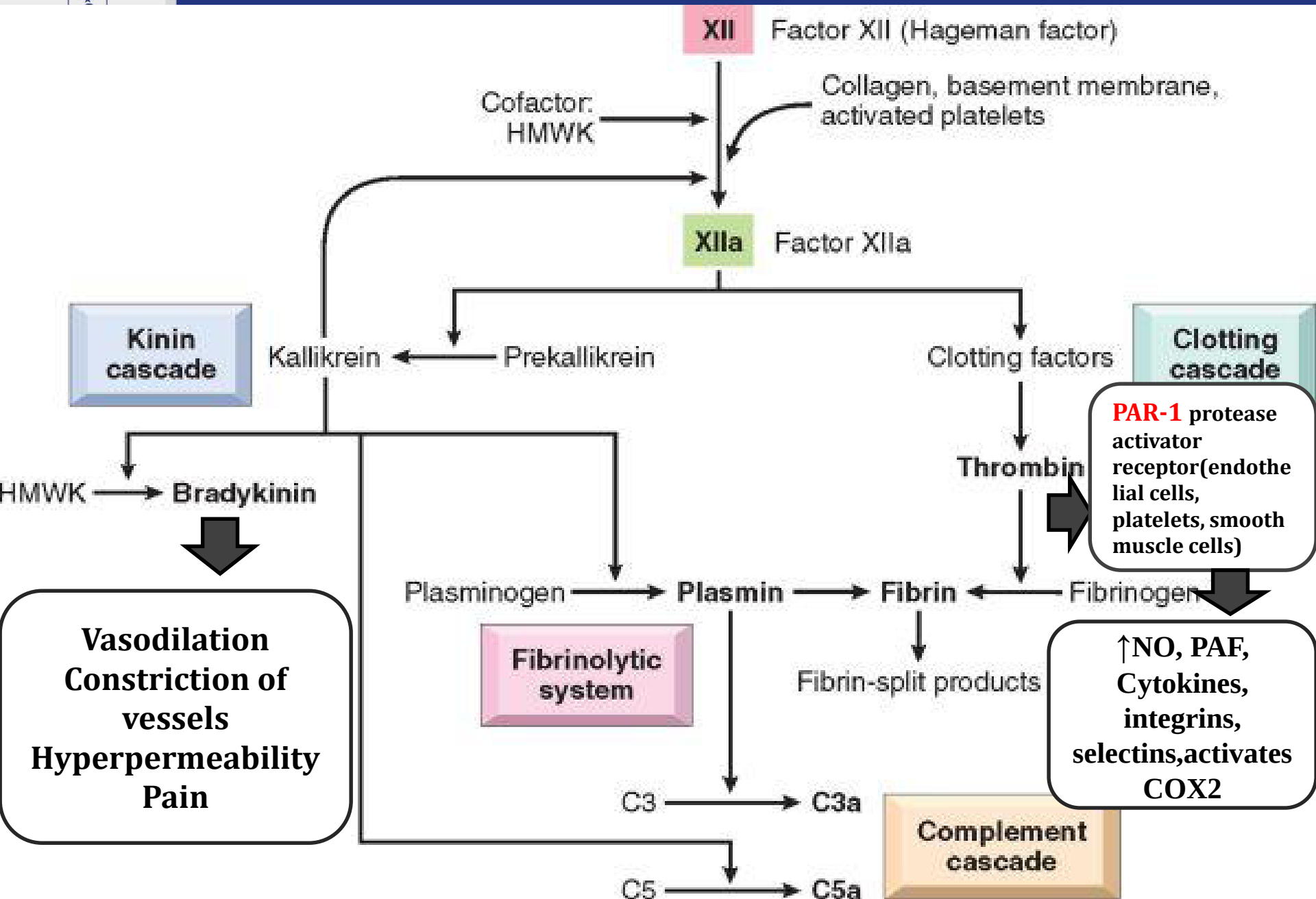


2. PLASMA DERIVED MEDIATORS

- ***Plasma-derived mediators*** **(e.g., Hageman factor, complement proteins, kinins) are produced mainly in the liver and present in the circulation as inactive precursors that must be activated, usually by a series of proteolytic cleavages, to acquire their biologic properties.**

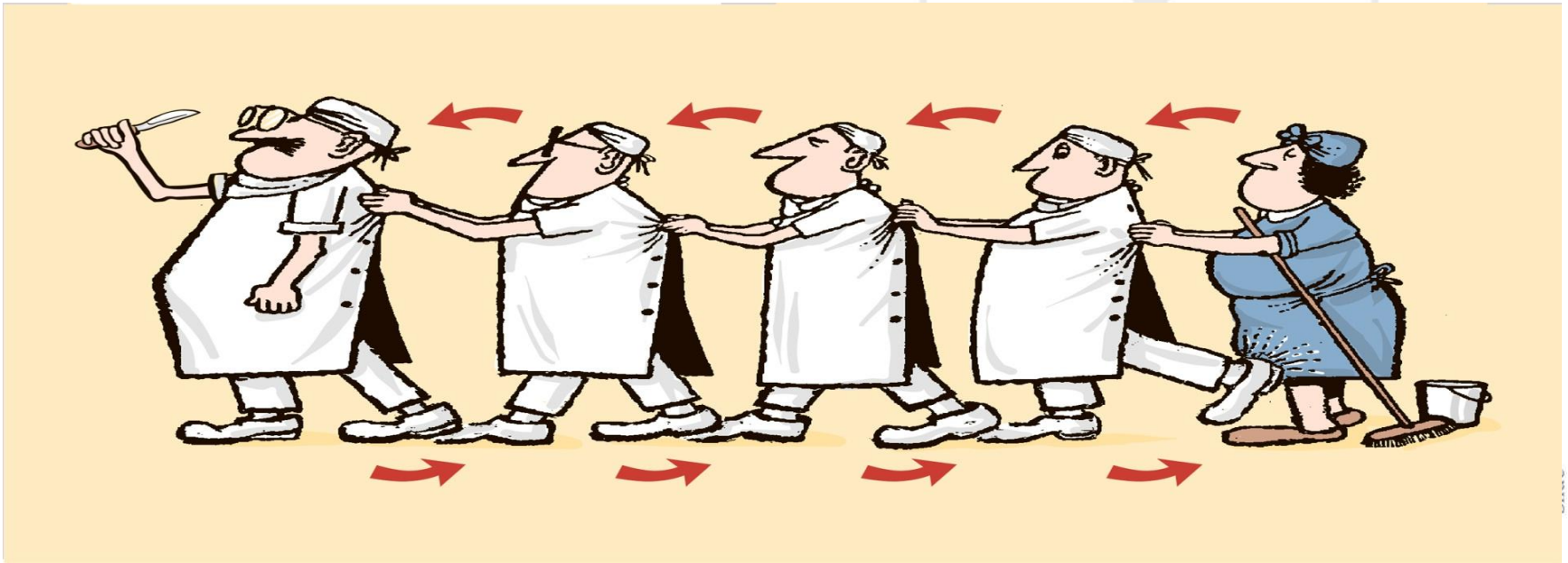


Factor XII (Hageman factor)

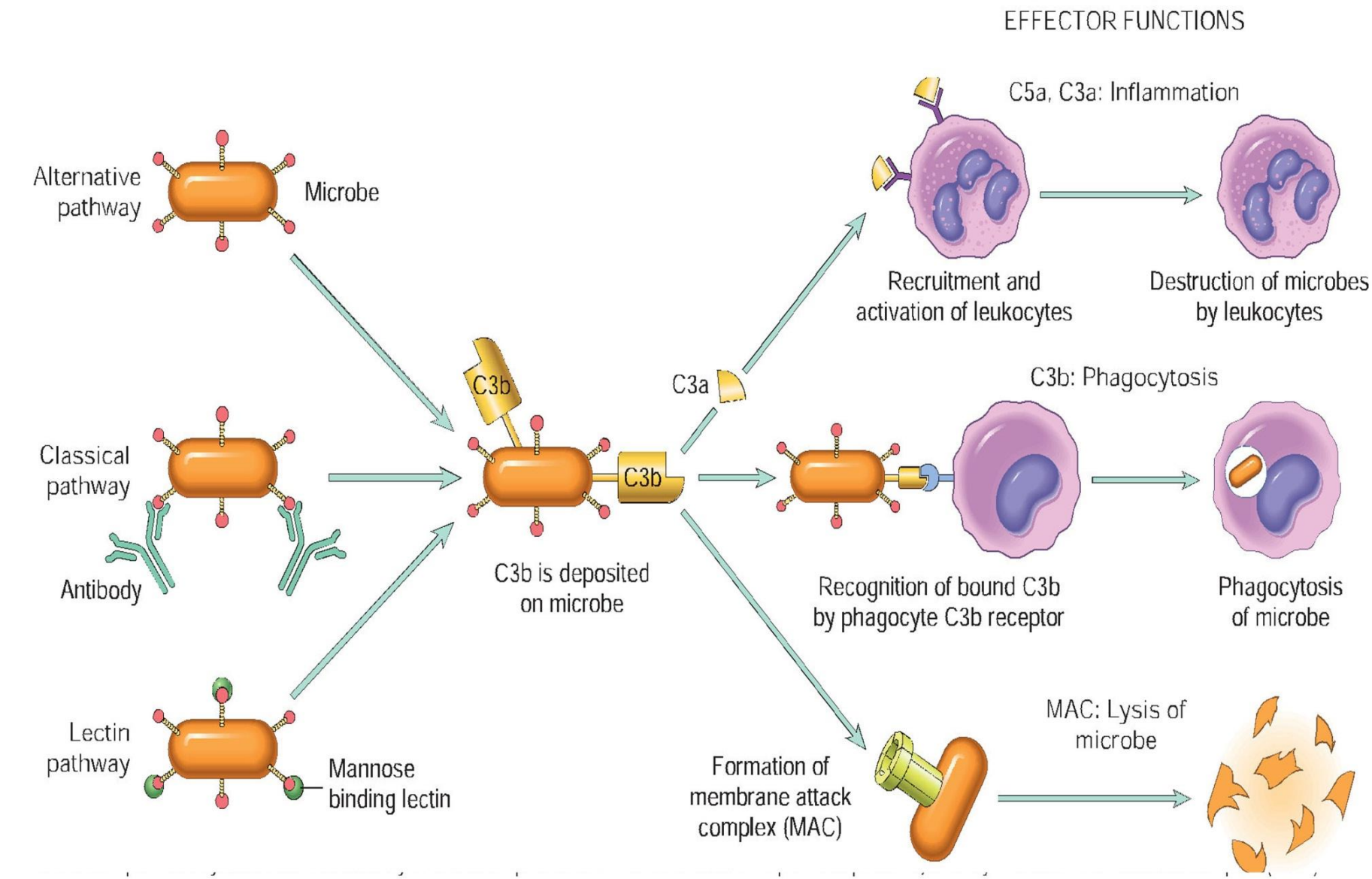


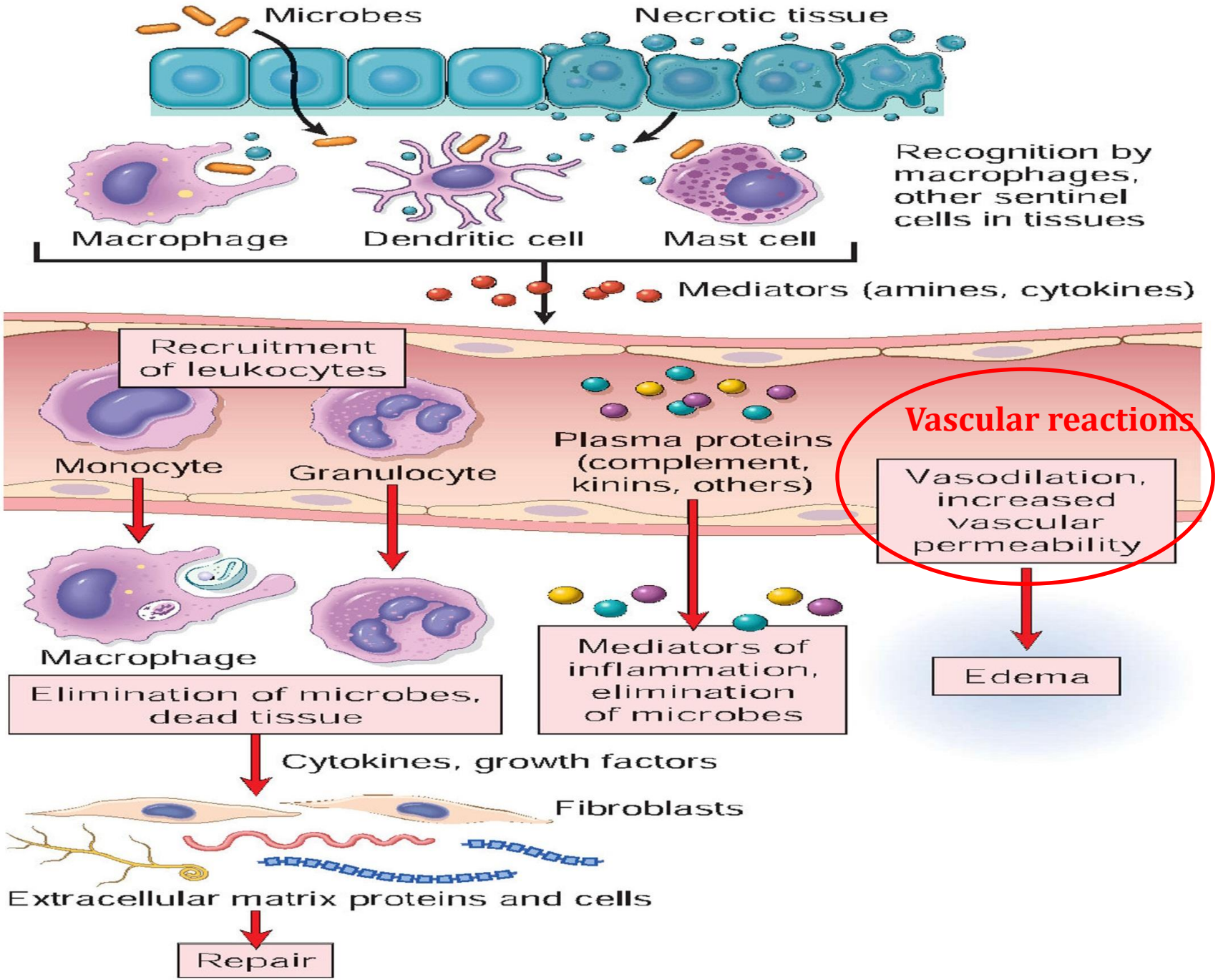
Complement System

- The complement system consists of more than 20 proteins, some of which are numbered C1 through C9.
- This system functions in both innate and adaptive immunity for defense against microbial pathogens.
- It cause vascular permeability, chemotaxis, and opsonization.



Complement system




Microbes
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Recognition by macrophages, other sentinel cells in tissues
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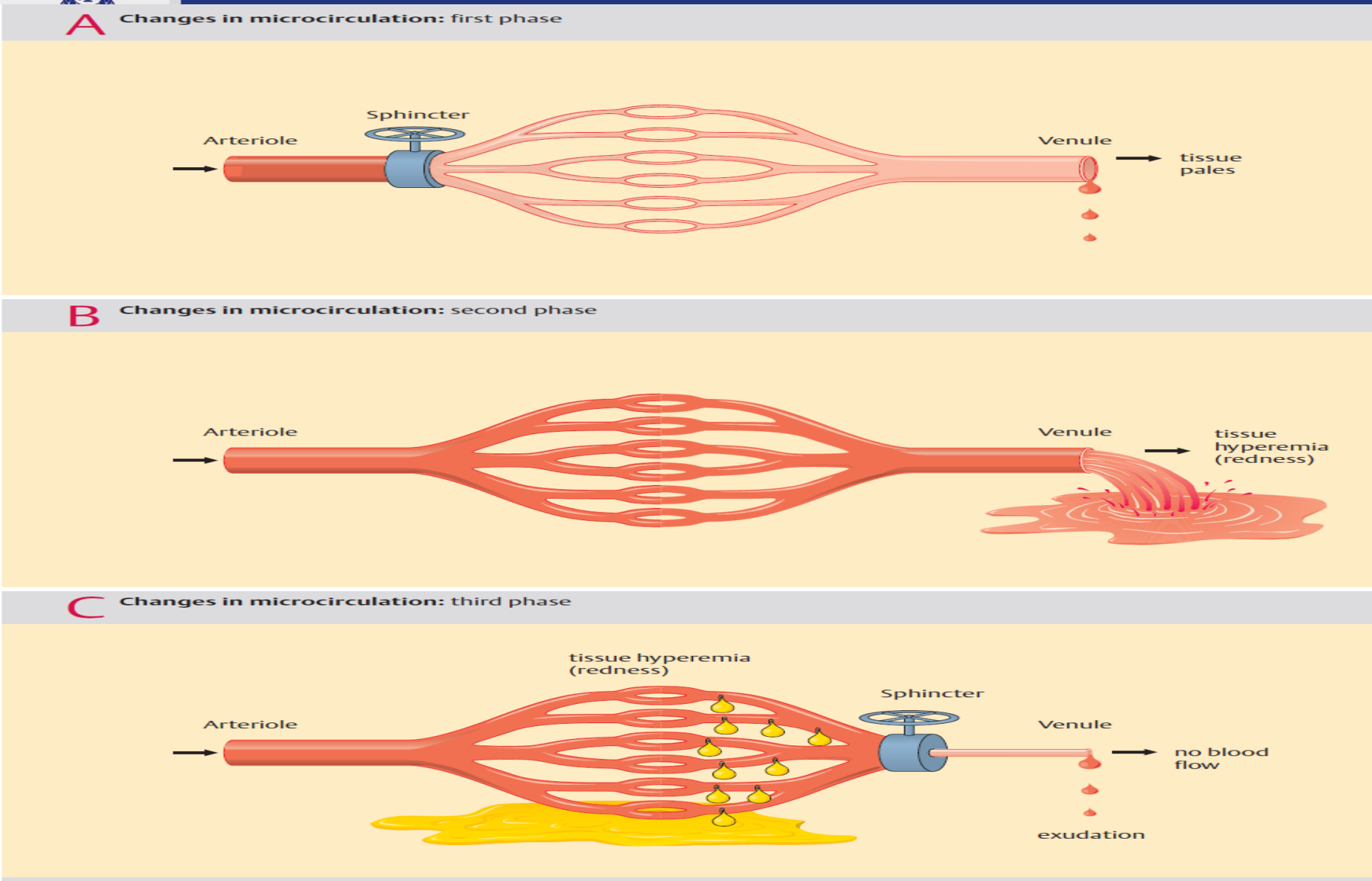
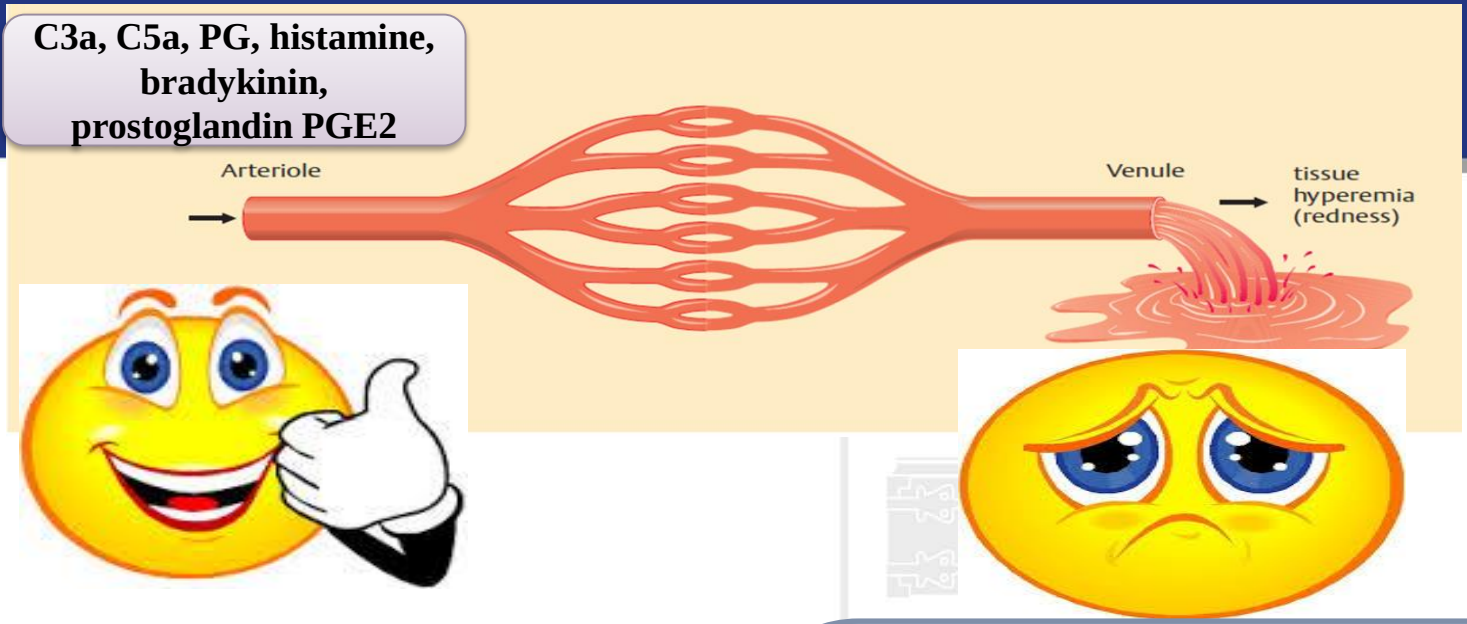
Vascular reactions
Vasodilation, increased vascular permeability
Macrophage
Elimination of microbes, dead tissue
Mediators of inflammation, elimination of microbes
Edema
Cytokines, growth factors
Fibroblasts
Extracellular matrix proteins and cells
Repair

III. Vascular reactions in inflammatory process

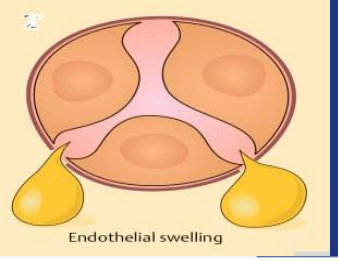


INFLAMMATORY ARTERIAL HYPEREMIA



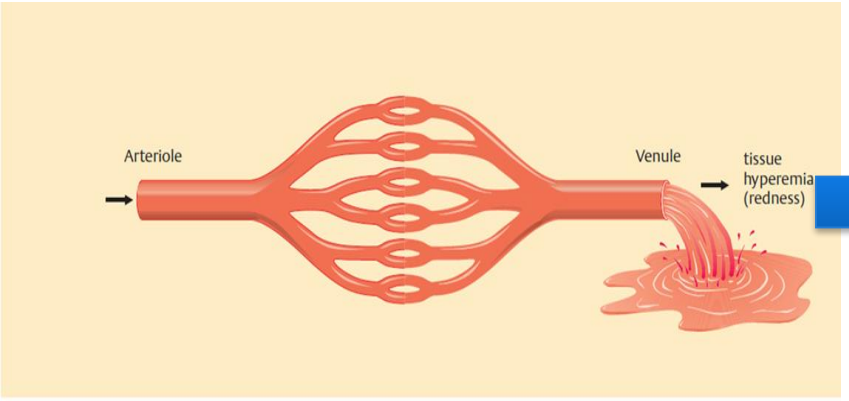
- **Increased blood flow assures optimal trophic conditions, and accumulation of leukocytes in vessels of inflammatory tissue, which later will lead to release of inflammatory mediators, phagocytosis, cellular infiltration, proliferation and regeneration**

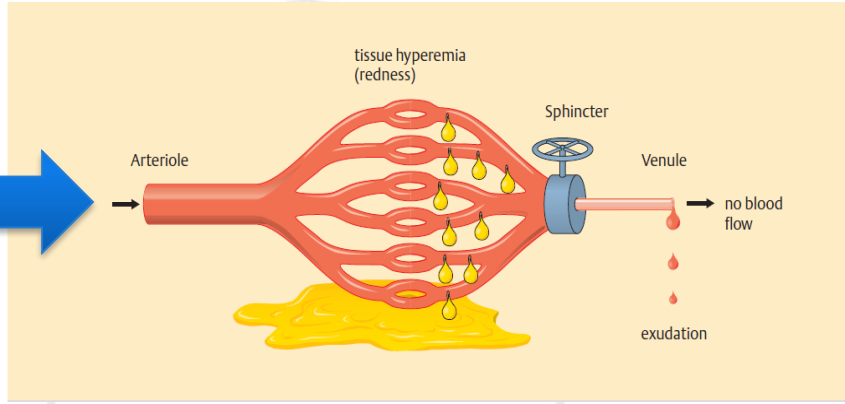
- **Hemorrhage from dilated vessels.**
- **Spread from inflammatory focus of biologic active and toxic substances, with general effects.**
- **Dissemination of pathogen agent and development of secondary inflammatory foci.**



INFLAMMATORY VENOUS HYPEREMIA, STASIS, THROMBOSIS

Mechanisms of development





- **Endothelial factors - endothelial cells become more spherical such narrowing vascular diameter; decreased negative charge of endothelium which lead to adhesion of blood cells;**
- **Plasmatic factors – hemoconcentration, increased blood viscosity and hematocrit index, increased hemocirculatory resistance;**
- **Rheological factors –thrombocyte and erythrocyte aggregation, blood coagulation and thrombosis (active Hageman factor);**
- **Extravascular factors - tissue edema as result of extravasation due to blood and lymph vessels compression, which provoke hemostasis and lymphostasis.**

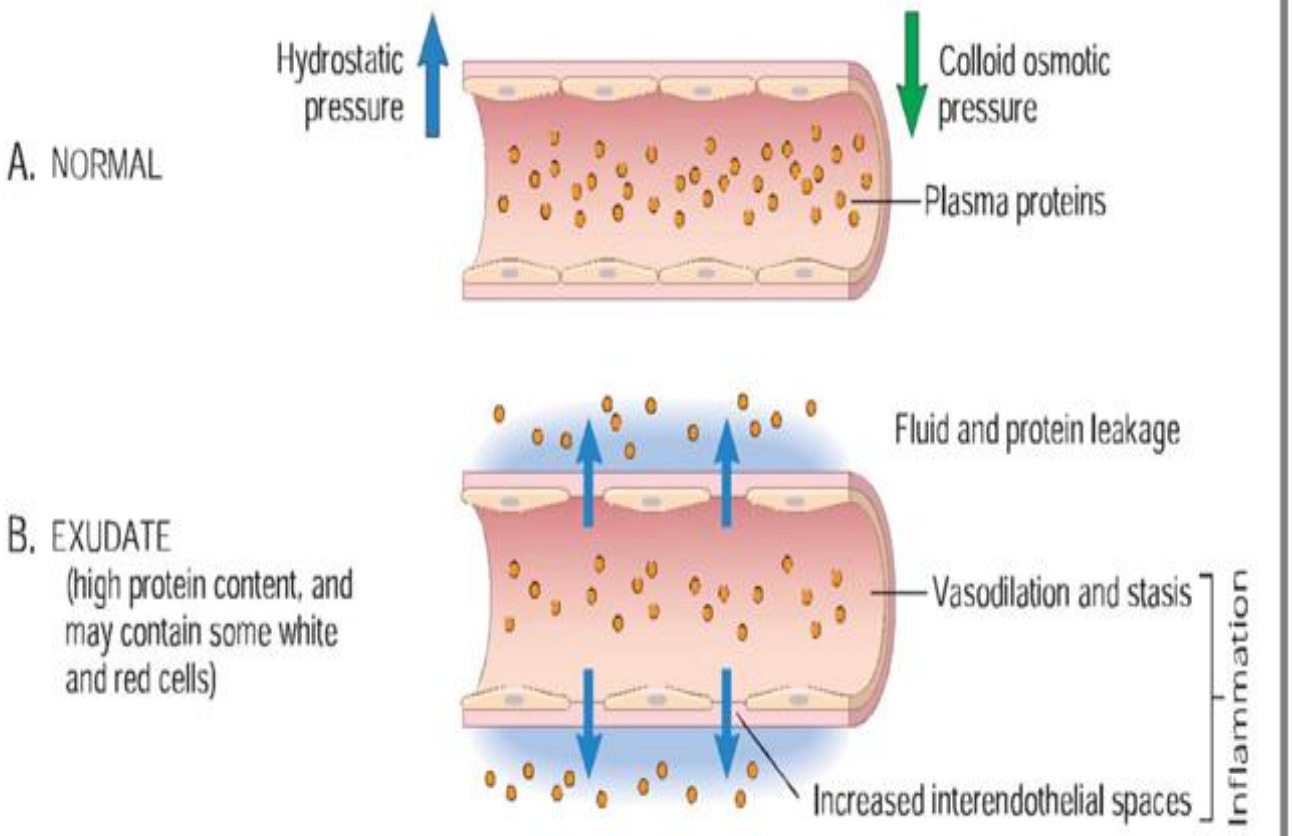
INFLAMMATORY VENOUS HYPEREMIA, STASIS, THROMBOSIS, LYMPHOSTASIS

Create necessary conditions for emigration and accumulation in the inflammatory focus of biologic active substances and blood cells.
Isolate the inflammatory focus and prevent its generalization.

Hypoxia
Hyponutrition
Hypoenergogenesis
Lactic acidosis

SECONDARY ALTERATION

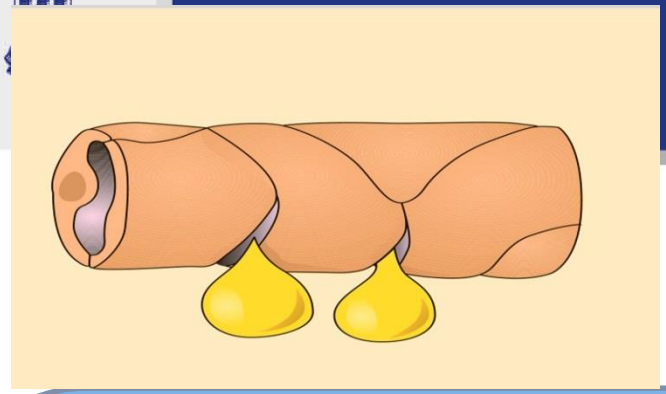
Exudation in inflammatory focus and edema

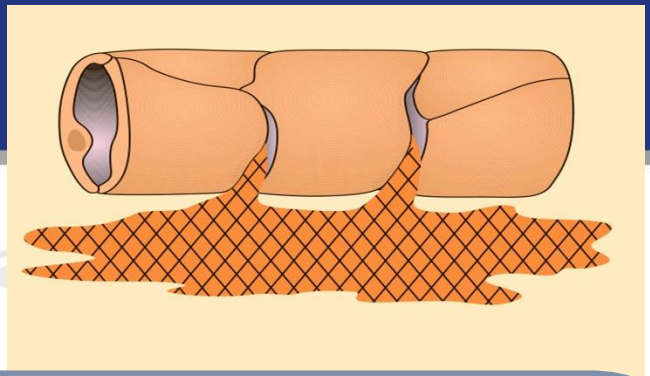


Exudation (*inflammatory edema*) represents the extravasation of intravascular liquid in the interstitial space or serous cavities of the body.

- **Contains more than 2% proteins, these having high molecular weight (globulin, fibrinogen)**
- **Contains cells (erythrocytes, thrombocyte, leucocytes);**
- **In case of infectious inflammation, exudates is septic – contains pathogenic agents and its vital products (toxins, enzymes, antigens).**

TYPES OF EXUDATE





Serous exudates – contains up to 3% low molecular weight proteins (predominantly albumins), few neutrophils, these determine its physical properties – low viscosity (watery), fluid (flow easily), almost transparent.

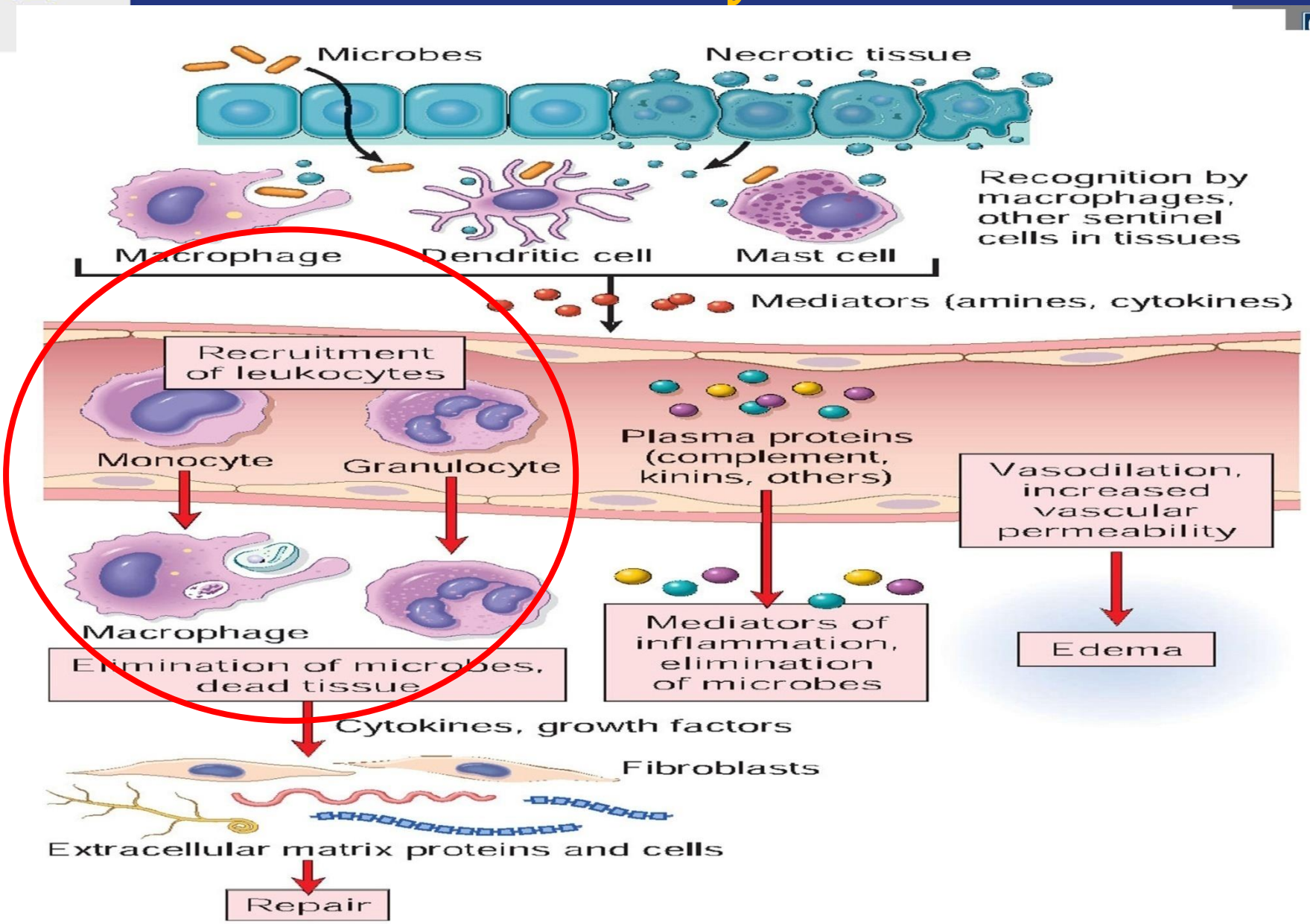
Fibrinous exudate – contains high molecular weight proteins (globulins) and fibrinogen, the last being transformed into fibrin, which causes the clotting of exudate, which has a gel consistence, and attach to the tissues, blocking the drainage

TYPES OF EXUDATE

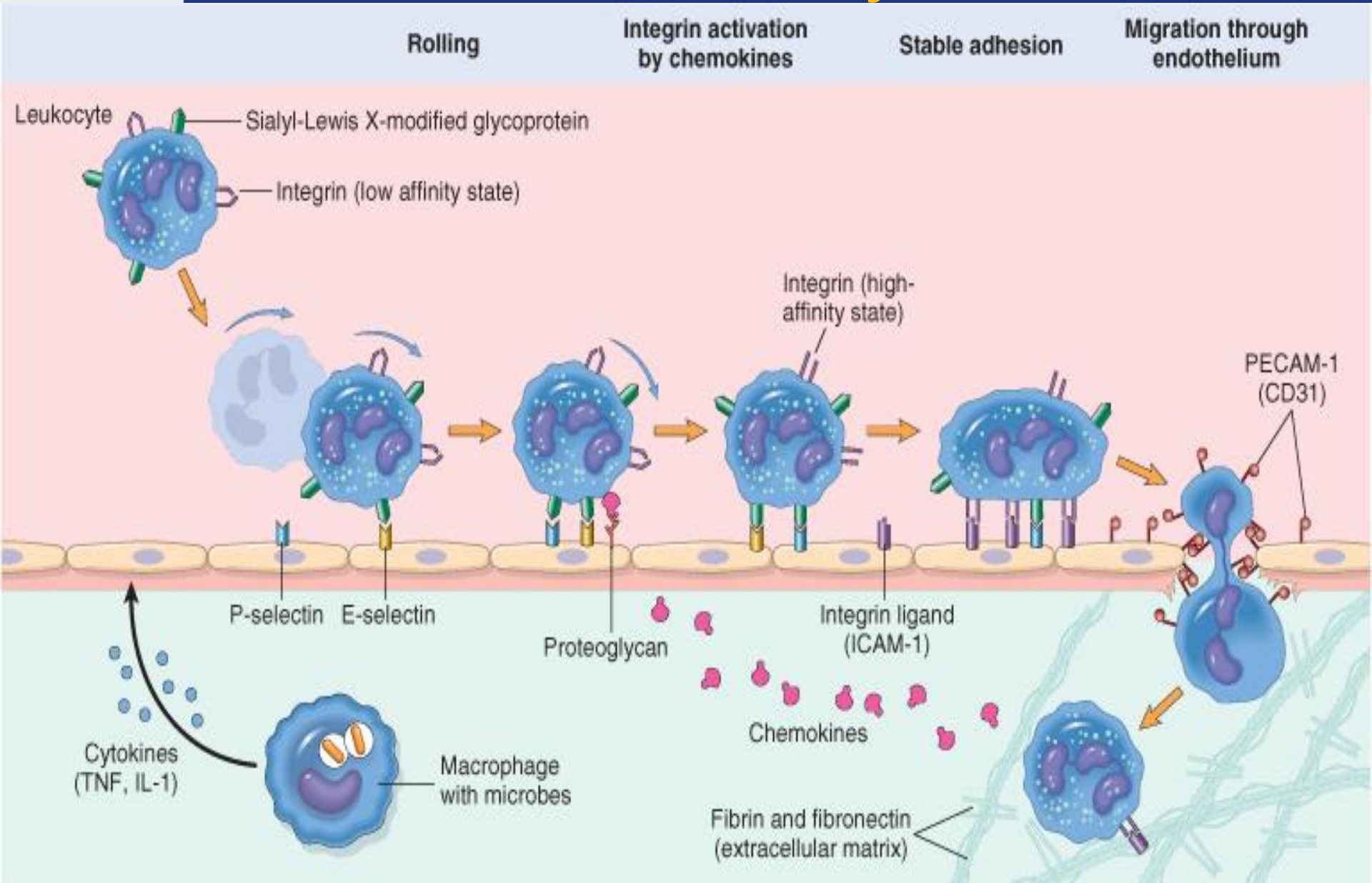
Hemorrhagic exudate **– occurs as result of increased vessel permeability and contains erythrocytes**

Purulent exudate **–is an inflammatory exudate rich in leukocytes (mostly degenerated neutrophils), the debris of dead cells and, in many cases, microbes.**

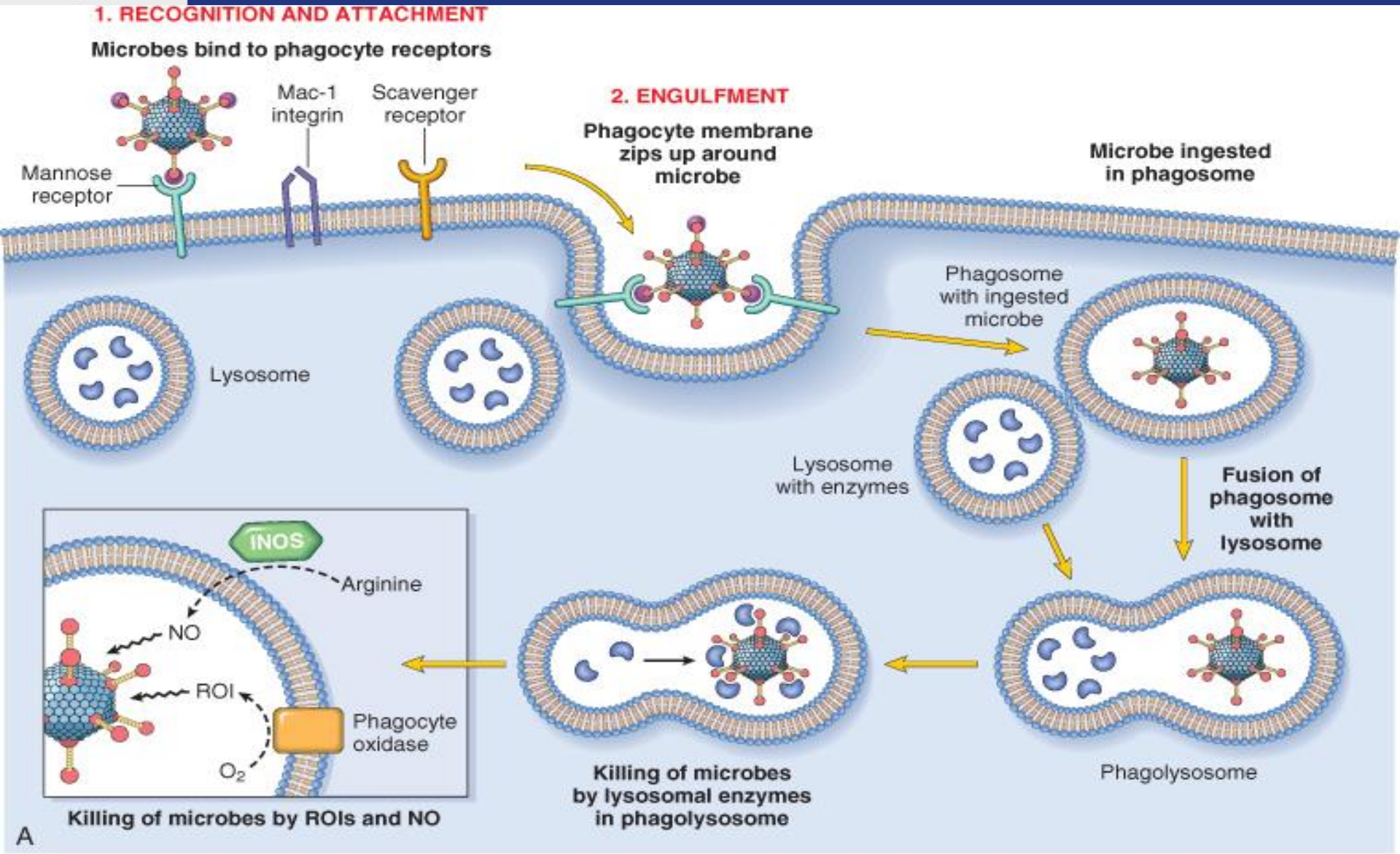
V. Leukocytes emigration in inflammatory focus



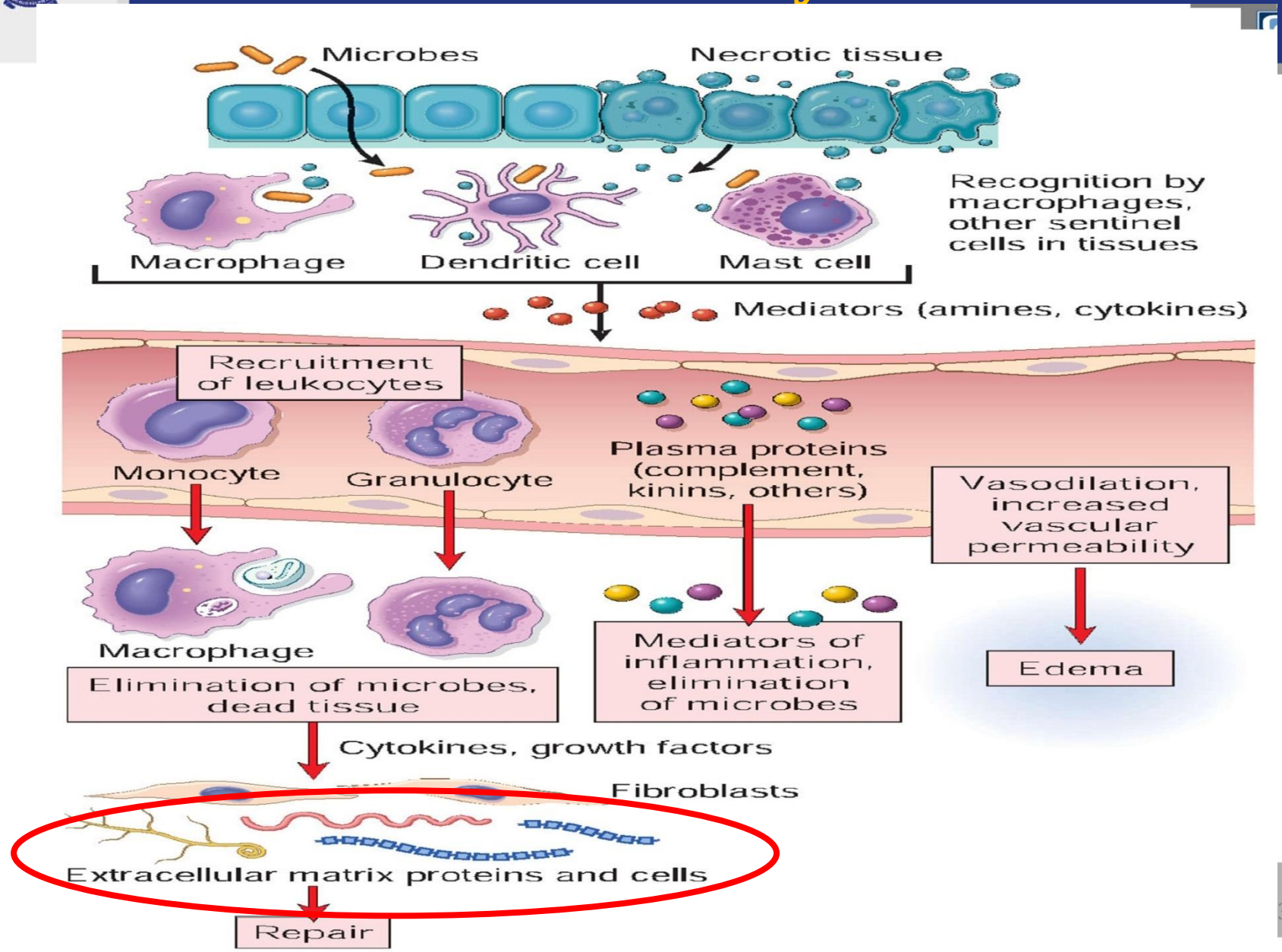
V. Leukocytes emigration in inflammatory focus



Phagocytosis



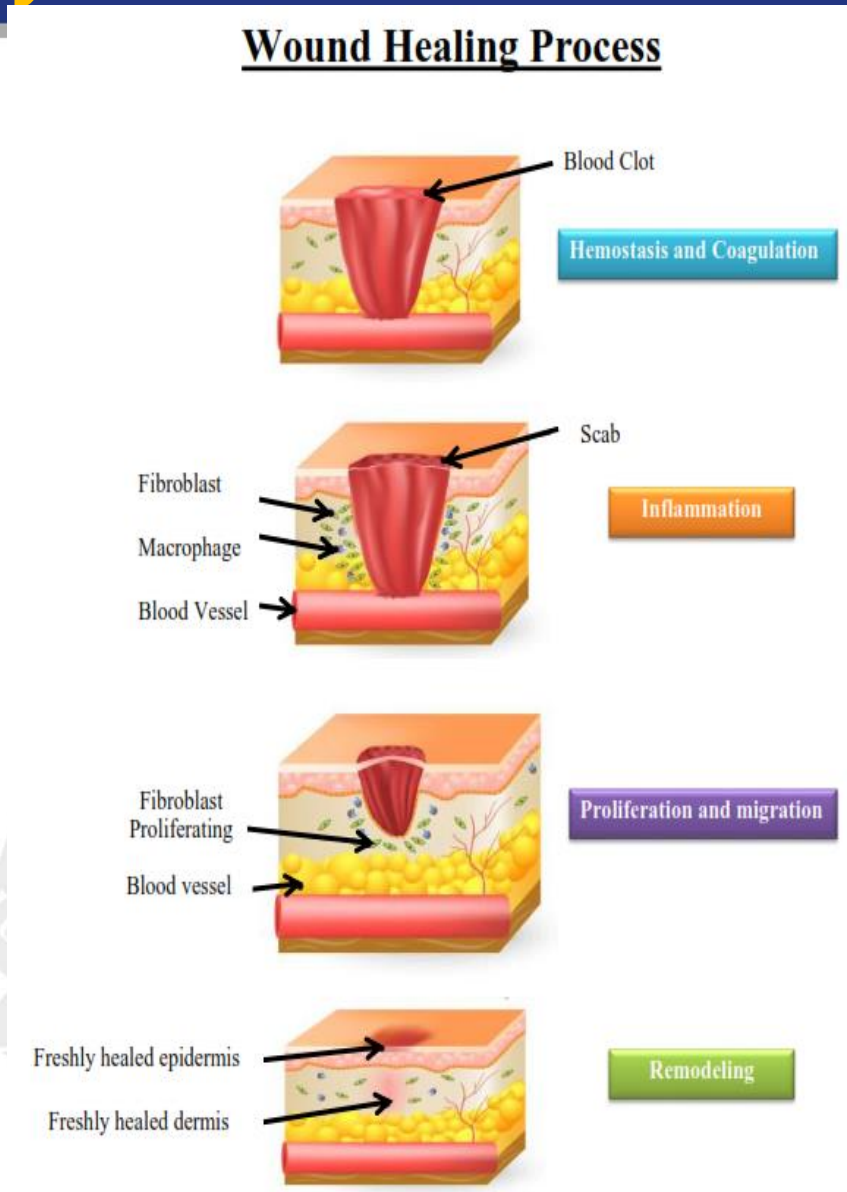
VI. Proliferation of cells in the inflammatory focus



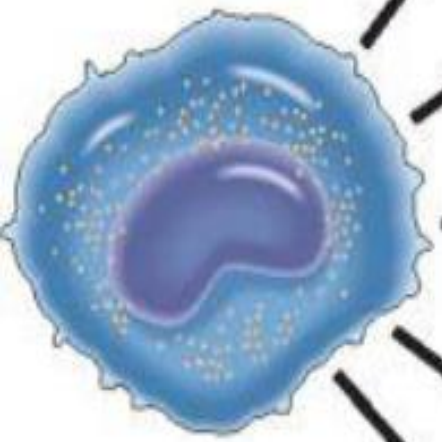
VI. Proliferation of cells in the inflammatory focus

Proliferation represents the multiplication and accumulation in the inflammatory focus of cells of mesenchymal origin:

- **hematopoietic stem-cells – monocites (macrophages), T- and B-lymphocytes, plasmocytes**
- **local fibroblasts, epithelial cambial cells.**
  - **Fibroblasts produce produce ECM proteins and collagen fibrils.**



ROLE OF MACROPHAGE IN WOUND REPAIR



Macrophage

Debridement Removal of injured tissue and debris: → Phagocytosis, collagenase, elastase

Antimicrobial activity: → Nitric acid, ROS

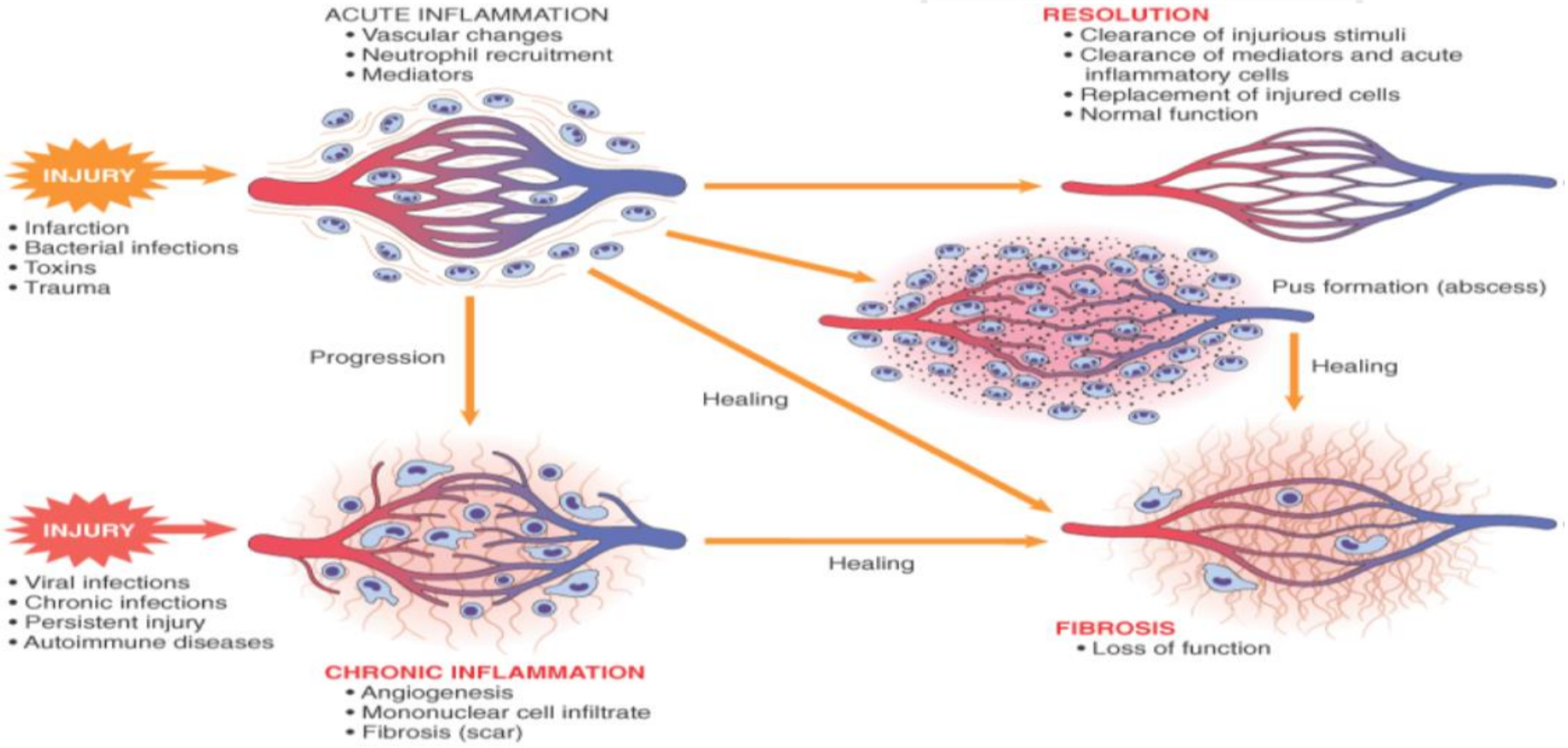
Chemotaxis and proliferation of fibroblasts and keratinocytes: → PDGF, TGF-β, TNF, IL-1, KGF-7

Angiogenesis: → VEGF, FGF-2, PDGF

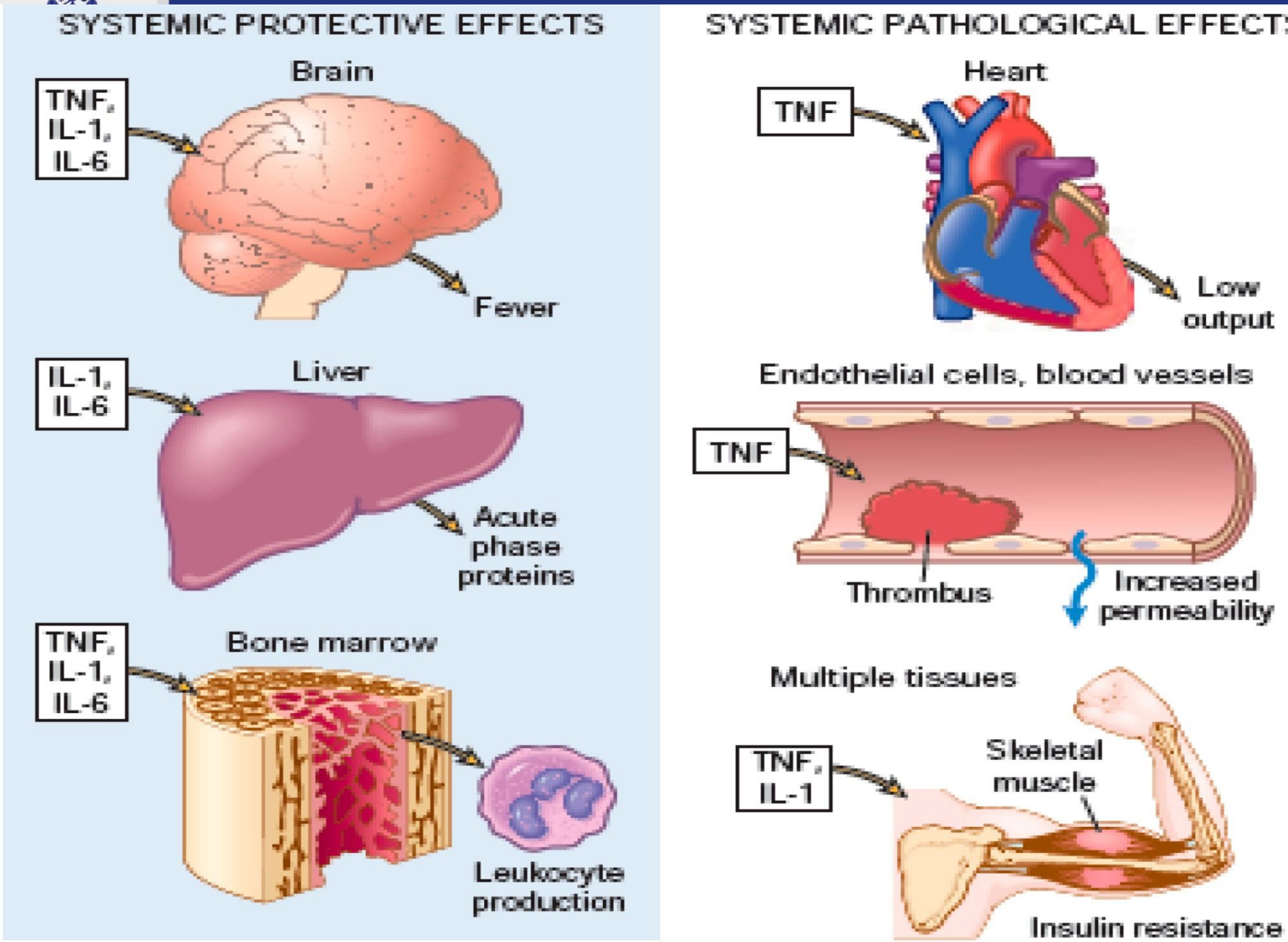
Deposition and remodeling of ECM: → TGF-β, PDGF, TNF, OPN IL-1, collagenase, MMPs

VII. Regeneration

- ***Regeneration** represents the process of recovery of injured structure in the inflammatory focus, and it is directly proportional to the volume of destruction and to the regenerative capacity of affected organ. In function of these conditions the regeneration can be complete or incomplete*



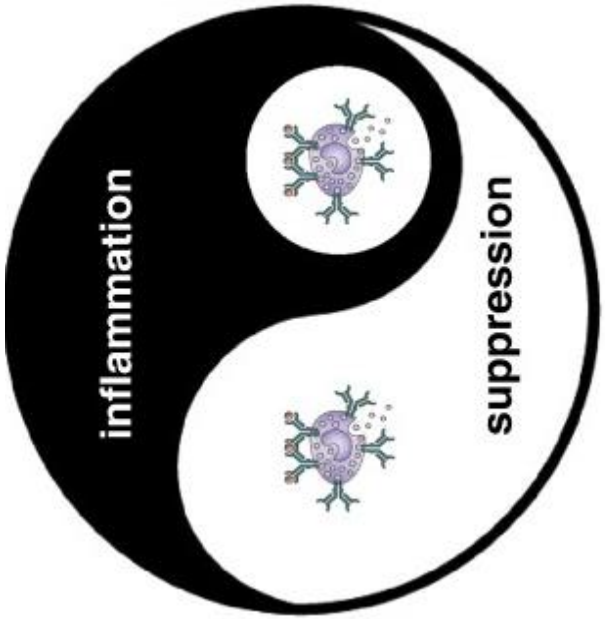
SYSTEMIC EFFECTS IN INFLAMMATORY REACTION - = *ACUTE PHASE RESPONSE*



Termination of the acute inflammatory response

Pro –inflammatory mediators

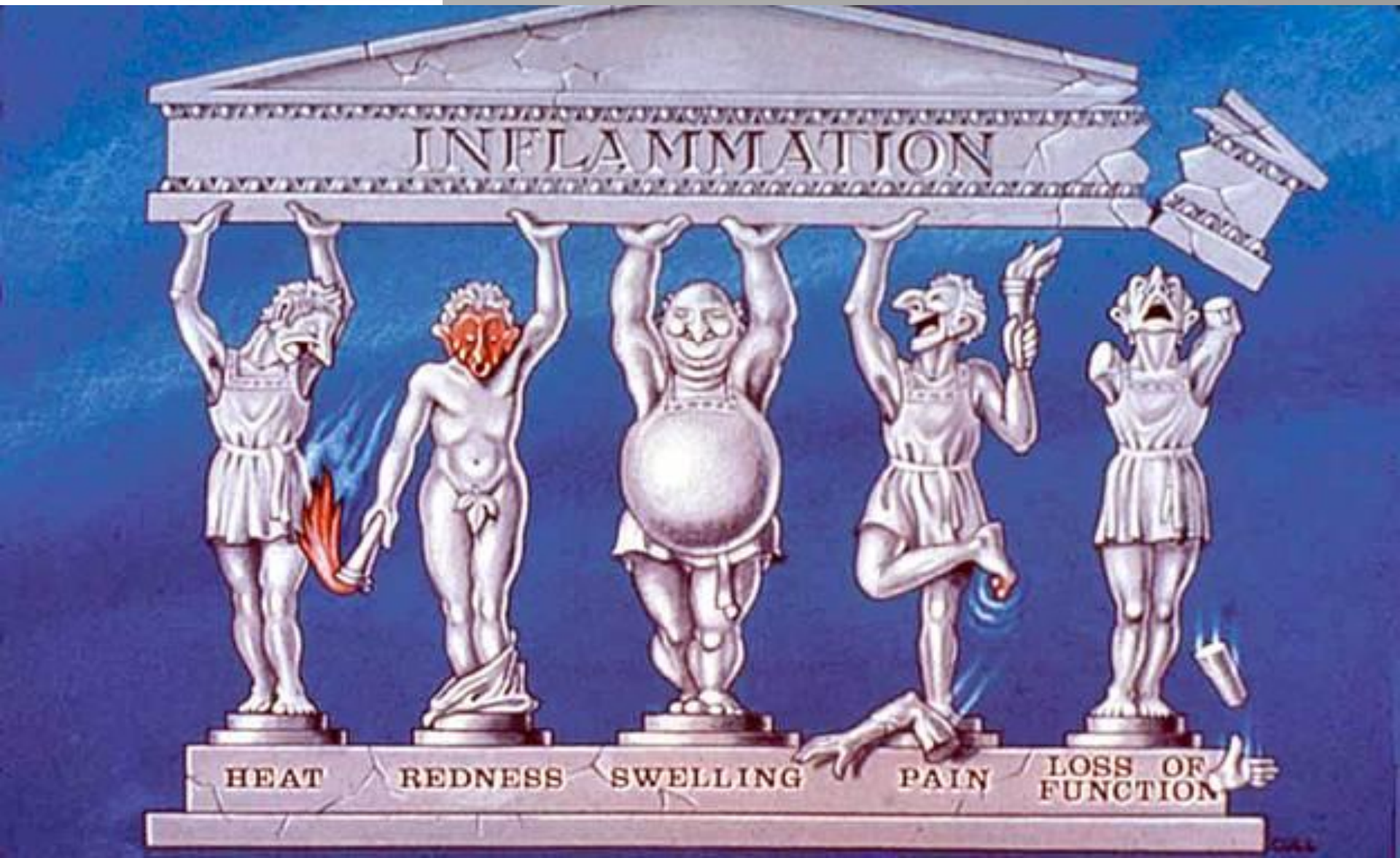
- Leukotriens (LTB_4, LTC_4, LTD_4)
- TNF – α and IL-1 from macrophages and other cells
- pro-inflammatory lipid mediators
- TNF in macrophages



Anti-inflammatory mediators

- Lipoxins (LXA_4, LXB_4)
- transforming growth factor-β (TGF-β) and IL-10, from macrophages and other cells
- anti-inflammatory lipid mediators - *resolvins* and *protectins*
- Neural impulses (cholinergic discharge)

5 cardinal signs of inflammation



Happiness is the highest form of health.

Dalai Lama