Foundation block: pathology

INFLAMMATION AND REPAIR
Lecture 3

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1. Outcomes of acute inflammation
2. Different patterns of inflammation
3.Chemical mediators

Objectives

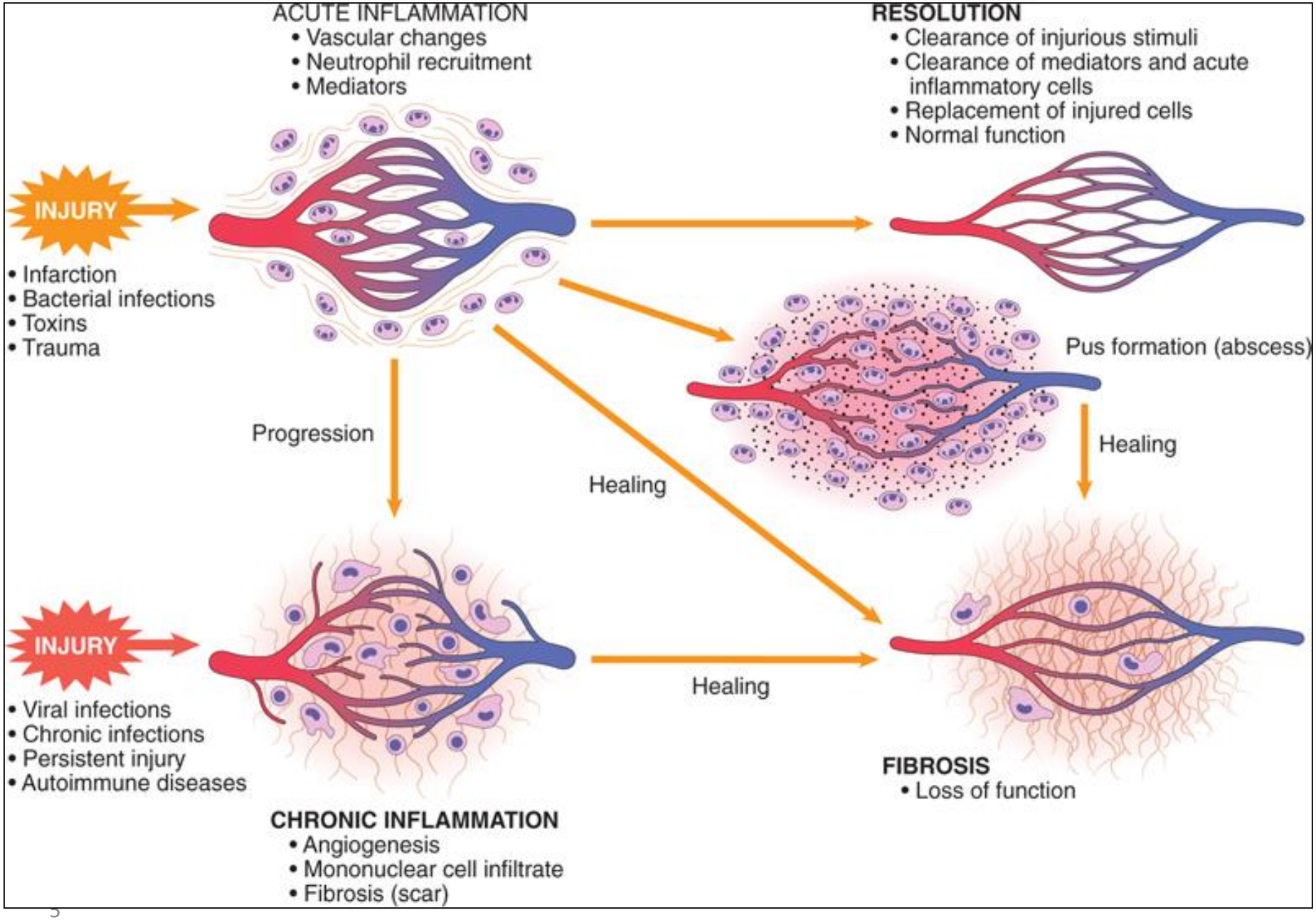
1. **List and describe the outcome of acute inflammation.**
2. **Recognize the different patterns of inflammation.**
3. **Chemical mediators of inflammation:**
   I. **Definition**
   II. **Know the general principles for chemical mediators.**
   III. **Know the cellular sources and major effects of the mediators.**
   IV. **List the most likely mediators of each of the steps of inflammation.**

1. List and describe the outcome of acute inflammation.

Outcomes of Acute Inflammation

- Acute inflammation may have one of the four outcomes:
  - *Complete resolution*
  - *Healing by connective tissue replacement (fibrosis)*
  - *Progression of the tissue response to chronic inflammation*
  - *Abscess formation*

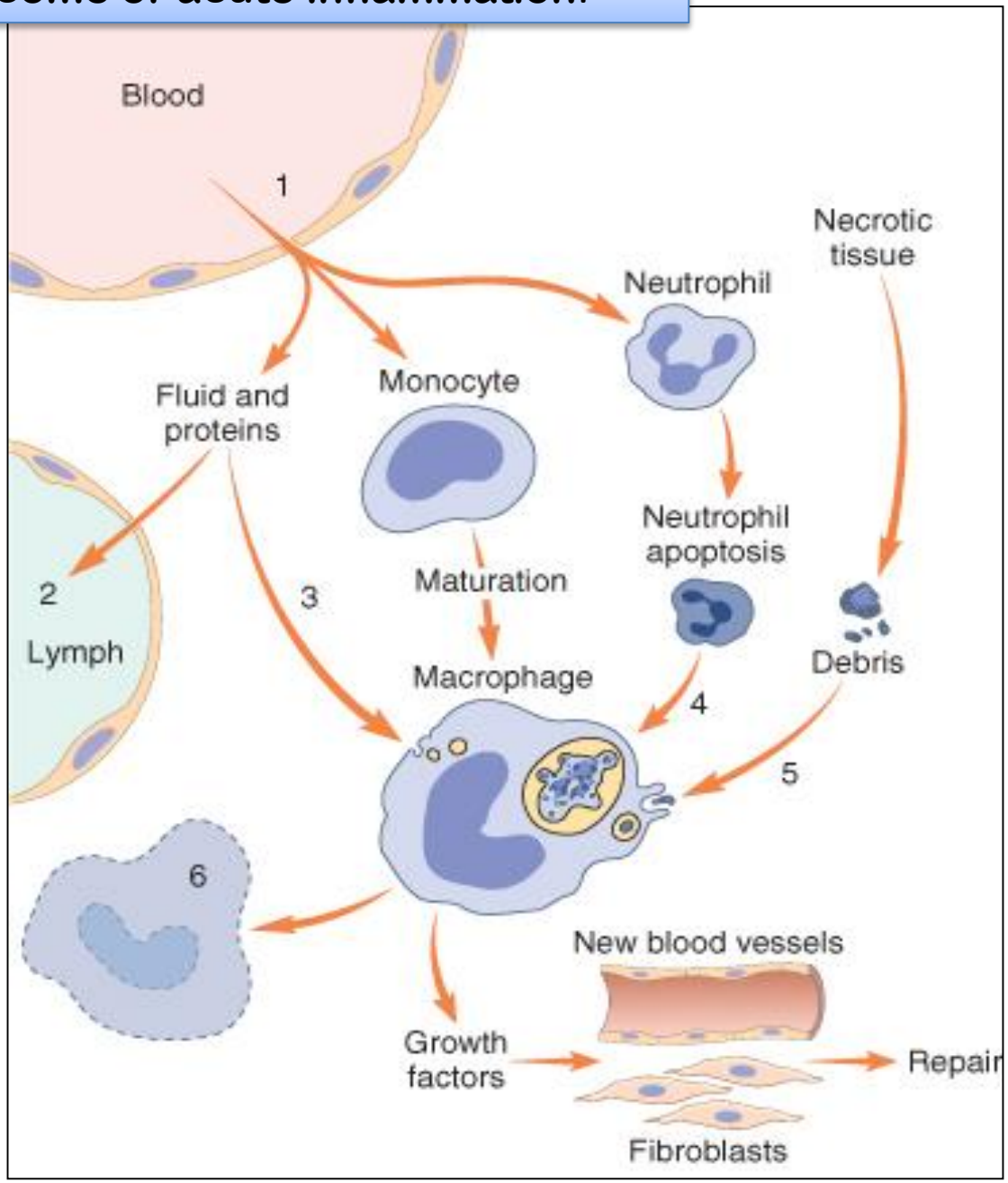
1. List and describe the outcome of acute inflammation.



1. List and describe the outcome of acute inflammation.

Events in the resolution of inflammation

- This involves neutralization, decay, or enzymatic degradation of the various chemical mediators; normalization of vascular permeability; and cessation of leukocyte emigration and apoptosis
- The necrotic debris, edema fluid, and inflammatory cells are cleared by phagocytes and lymphatic drainage



Objectives

Upon completion of this lecture, the student should:

1. **List and describe the outcome of acute inflammation.**
2. **Recognize the different pattern of inflammation.**
3. **Define the chemical mediators of inflammation.**
   - I. **Definition**
   - II. **Know the general principles for chemical mediators.**
   - III. **Know the cellular sources and major effects of the mediators.**
   - IV. **List the most likely mediators of each of the steps of inflammation.**

2. Recognize the different patterns of inflammation.

Morphologic Patterns of Acute Inflammation

- Several types of inflammation vary in their morphology and clinical correlates. Why?
  - The severity of the reaction
  - specific cause
  - the particular tissue
  - site involved

2. Recognize the different patterns of inflammation.

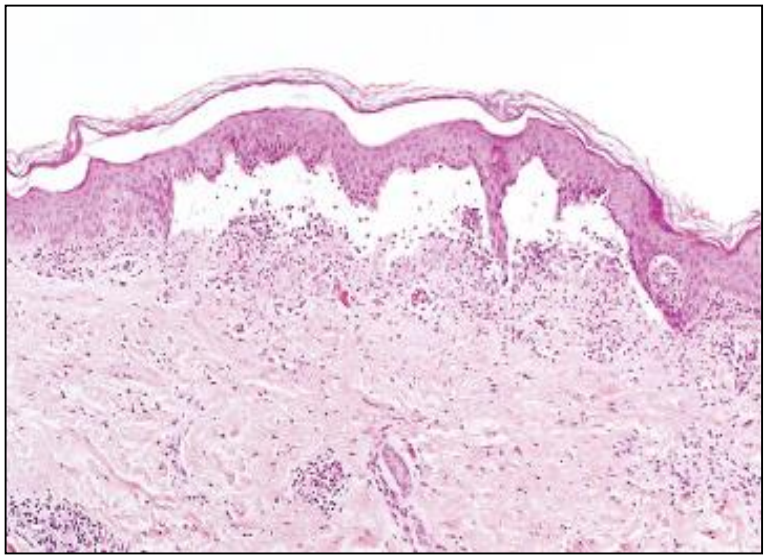
Morphologic Patterns of Acute Inflammation

- **SEROUS INFLAMMATION**
- **FIBRINOUS INFLAMMATION**
- **SUPPURATIVE OR PURULENT INFLAMMATION**
- **ULCERS**

2. Recognize the different patterns of inflammation.

SEROUS INFLAMMATION:

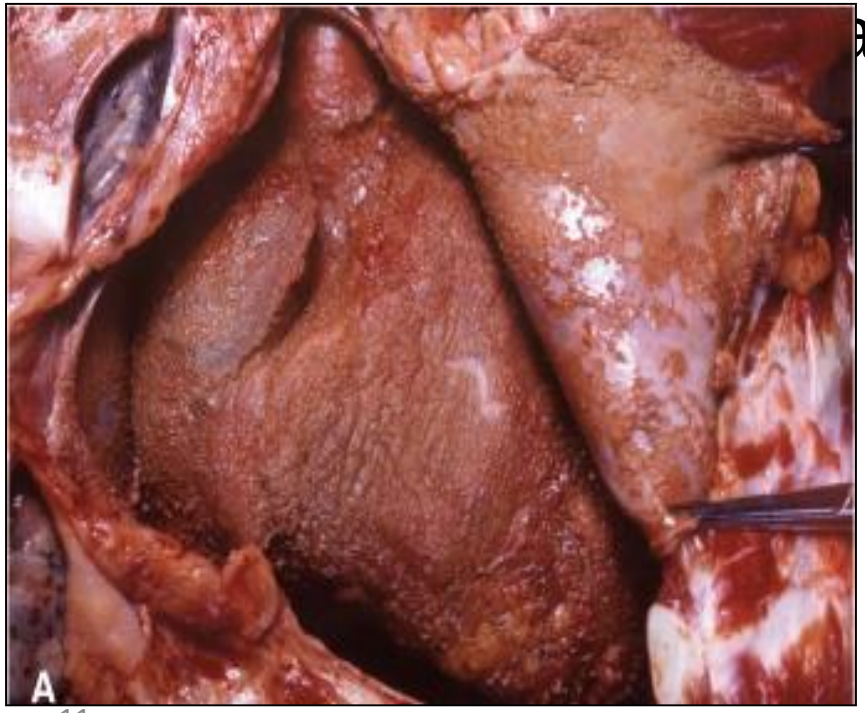
marked by the outpouring of a thin fluid

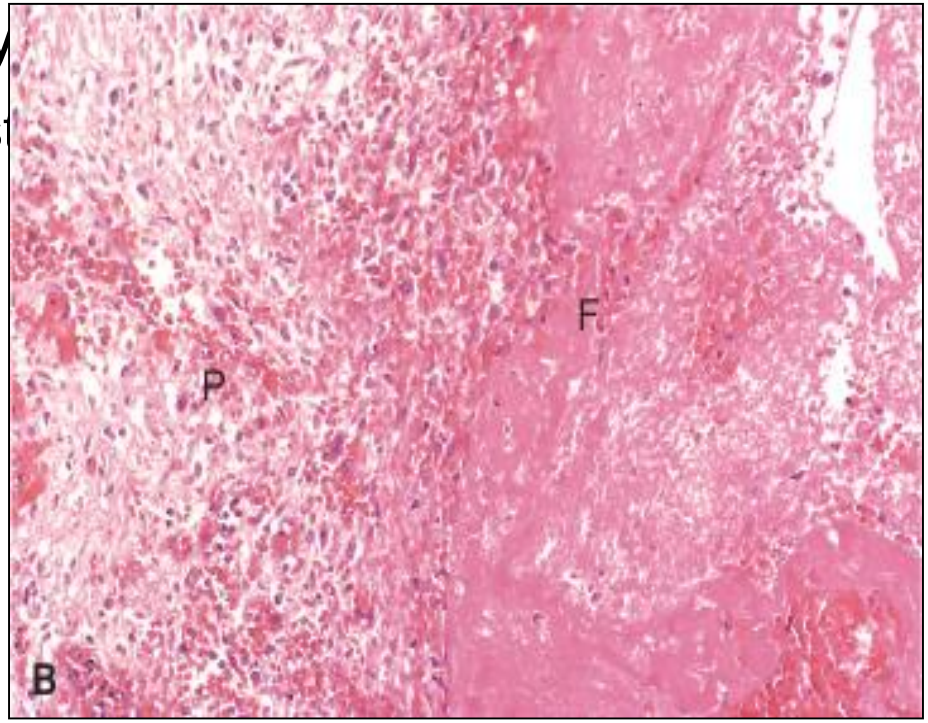


2. Recognize the different patterns of inflammation.

FIBRINOUS INFLAMMATION

– A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura (larger molecules such as fibrinogen pass the vascular barrier)

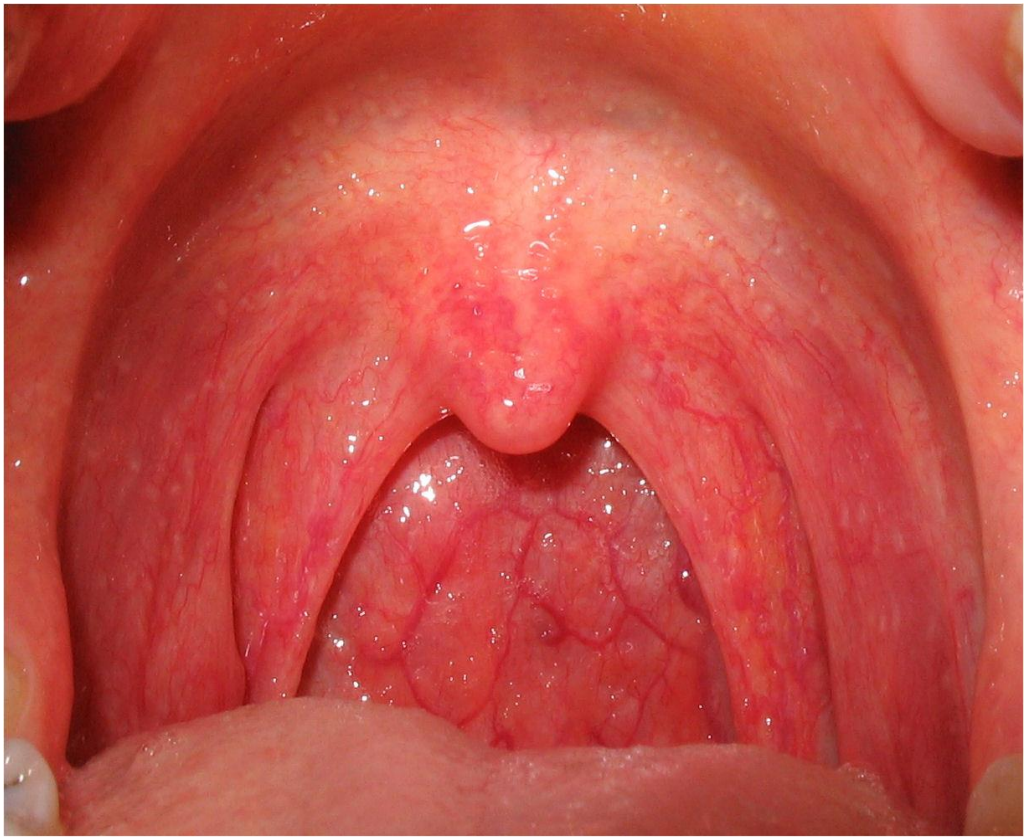




2. Recognize the different patterns of inflammation.

Catarrhal inflammation

- Inflammation affects mucosa-lined surfaces with the outpouring of **watery mucus**



2. Recognize the different patterns of inflammation.

SUPPURATIVE OR PURULENT INFLAMMATION

characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, necrotic cells, and edema fluid caused by pyogenic (pus-producing) bacteria

2. Recognize the different patterns of inflammation.

Suppurative abscess.

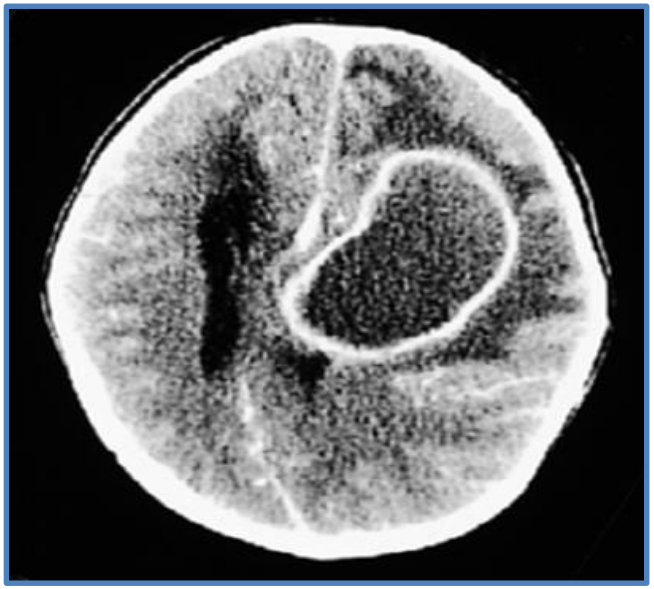
- An enclosed collection of pus consisits of a mixture of neutrophils and necrotic debris.

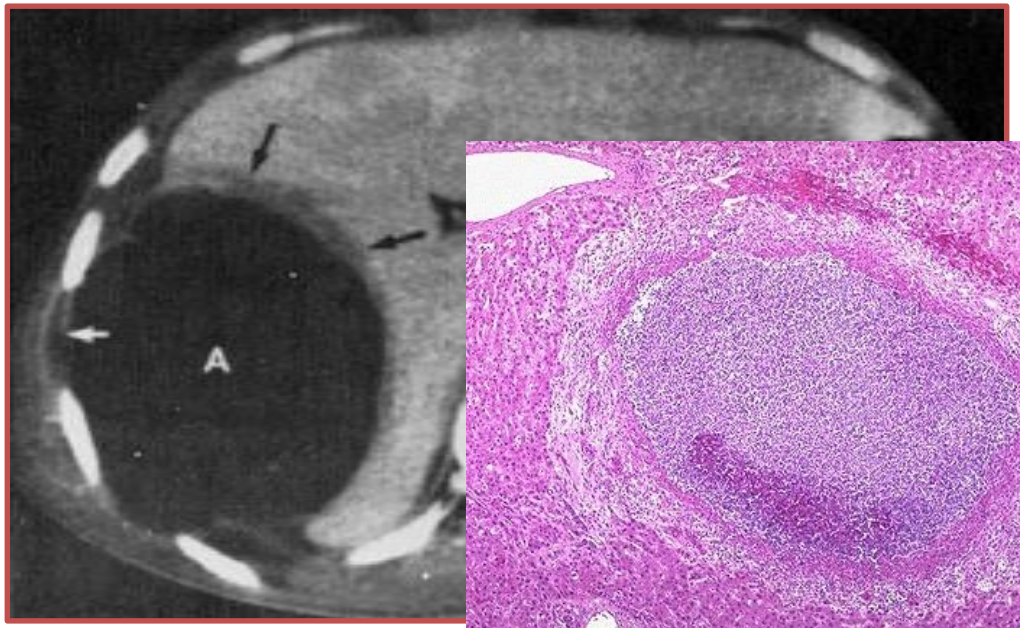
2. Recognize the different patterns of inflammation.

Morphologic Patterns of Acute Inflammation

SUPPURATIVE OR PURULENT INFLAMMATION

- **Abscesses : localized collections of purulent inflammatory tissue caused by suppuration buried in a tissue, an organ, or a confined space**

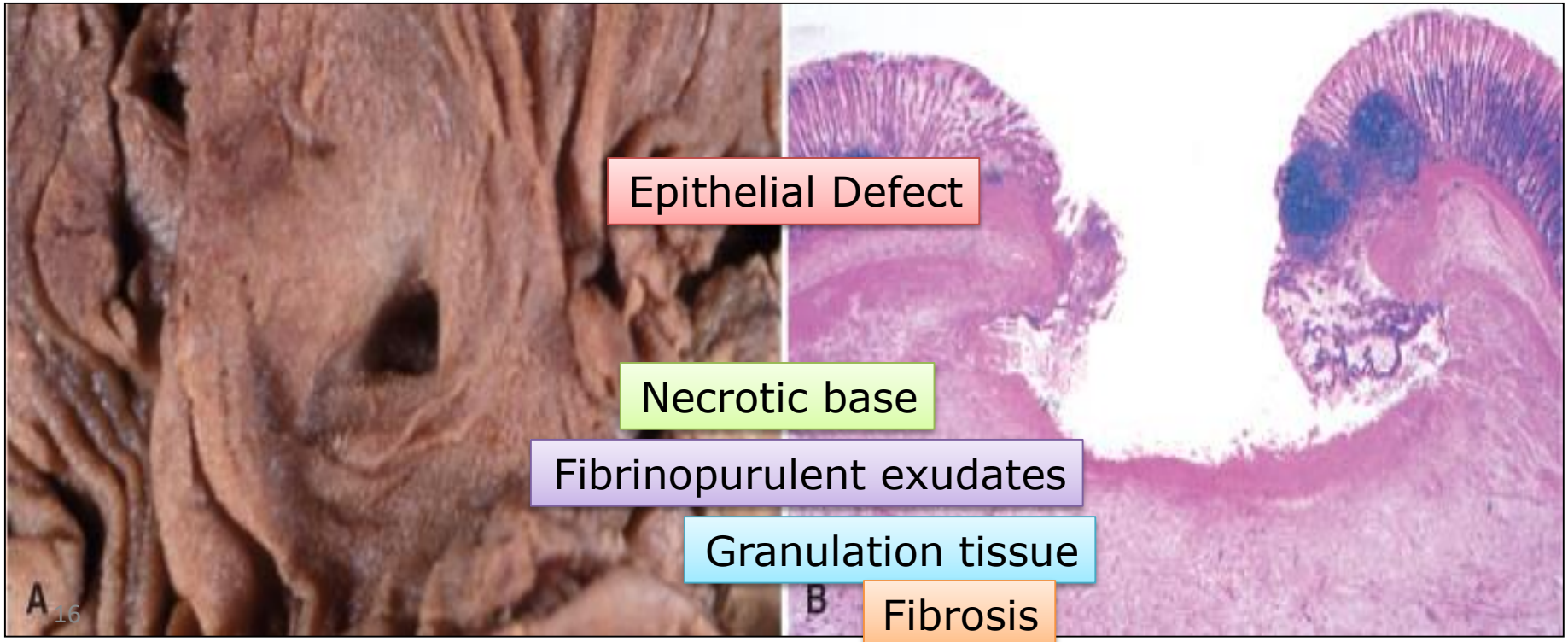




2. Recognize the different patterns of inflammation.

ULCERS

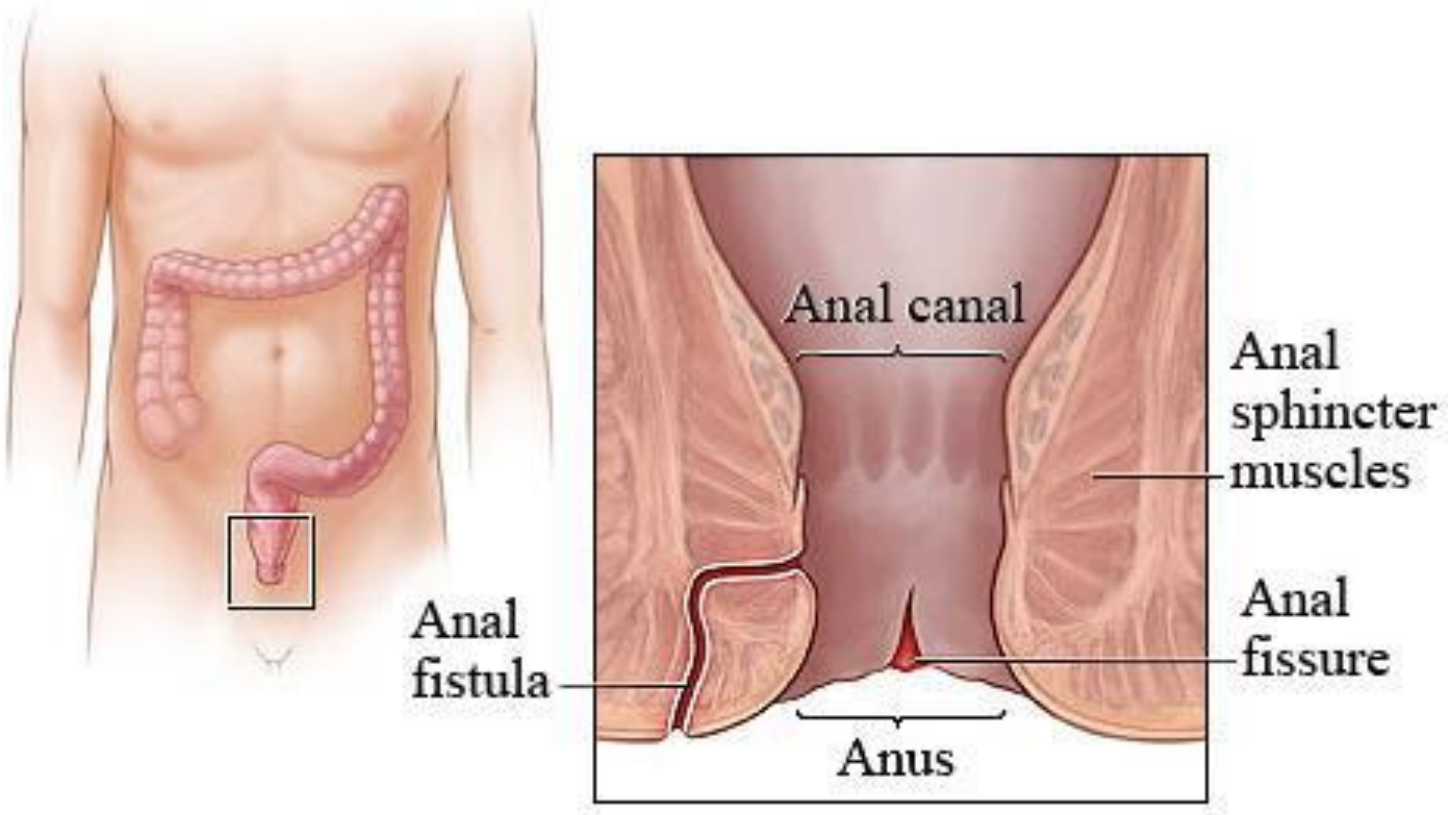
An ulcer is a local defect of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflammatory necrotic tissue



2. Recognize the different patterns of inflammation.

Fistula

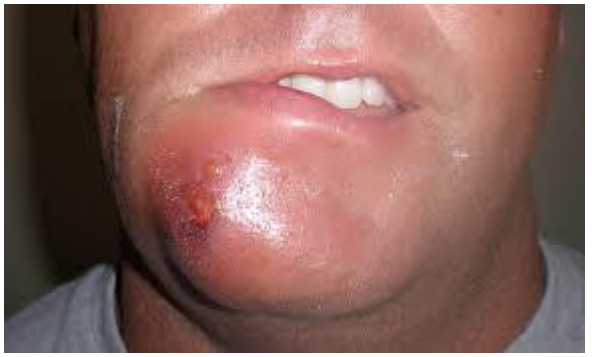
- A tract between two surfaces.

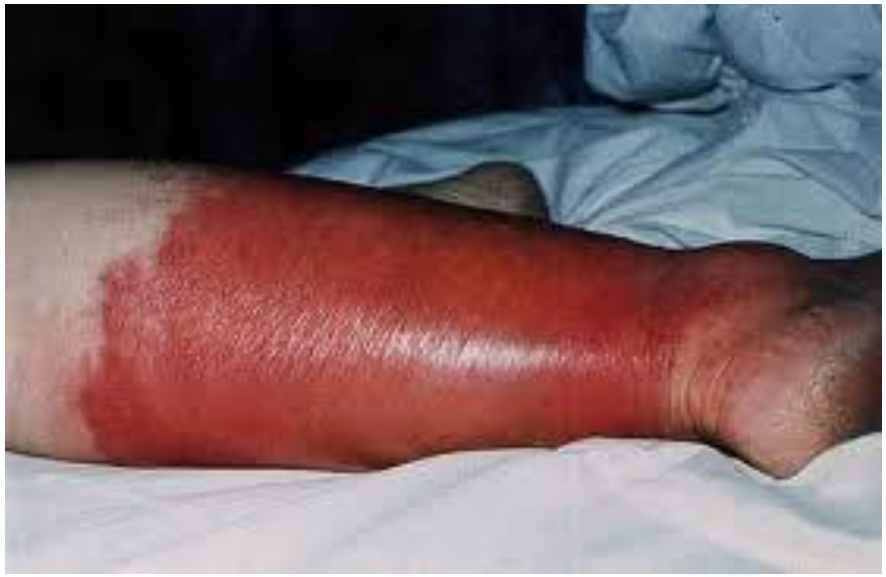


2. Recognize the different patterns of inflammation.

Cellulitis

- denotes a spreading acute inflammation through interstitial tissues.





Type	Features	Common Causes
Classic type	Hyperemia; exudation with fibrin and neutrophils	Bacterial infections; response to cell necrosis of any cause.
Acute inflammation without neutrophils	Paucity of neutrophils in exudate; lymphocytes and plasma cells predominant	Viral and rickettsial infections (immune response contributes).
Allergic acute inflammation	Marked edema and numerous eosinophils; eosinophilia in blood.	Certain hypersensitivity immune reation
Serous inflammation (inflammation in body cavities)	Marked fluid exudation.	Burns; many bacterial infections.
Catarrhal inflammation (inflammation of mucous membranes)	Marked secretion of mucus.	Infections, eg, common cold (rhinovirus); allergy (eg, hay fever).
Fibrinous inflammation	Excess fibrin formation.	Many virulent bacterial infections.
Necrotizing inflammation, hemorrhagic inflammation	Marked tissue necrosis and hemorrhage.	Highly virulent organisms (bacterial, viral, fungal), eg, plague (*Yersinia pestis*), mucormycosis.
Membranous (pseudomembranous) inflammation	Necrotizing inflammation involving mucous membranes. The necrotic mucosa and inflammatory exudate form an adherent membrane on the mucosal surface.	Toxigenic bacteria, eg, diphtheria bacillus (*Corynebacterium diphtheriae*) and *Clostridium difficile*.
Suppurative (purulent) inflammation	Exaggerated neutrophil response and liquefactive necrosis of parenchymal cells; pus formation. Marked neutrophil leukocytosis in blood.	Pyogenic bacteria, eg, staphylococci, streptococci, gram–negative bacilli, anaerobes.

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What are mediators?

- Chemical mediators of inflammation are substances produced during inflammation inducing a specific events in acute inflammation.

General principles for chemical mediators

The production of active mediators is triggered by:

1. microbial products
2. host proteins, such as the proteins of the complement, kinin and coagulation systems
   - (these are themselves activated by microbes and damaged tissues)

General principles for chemical mediators

Most mediators have the potential to cause harmful effects.

- **Therefore, there should be a mechanism to checks and balances their action.**

◘ Mediator function is tightly regulated by:

1) **decay (e.g. AA metabolites)**
2) **inactivated by enzymes (kininase inactivates bradykinin)**
3) **eliminated (antioxidants scavenge toxic oxygen metabolites)**

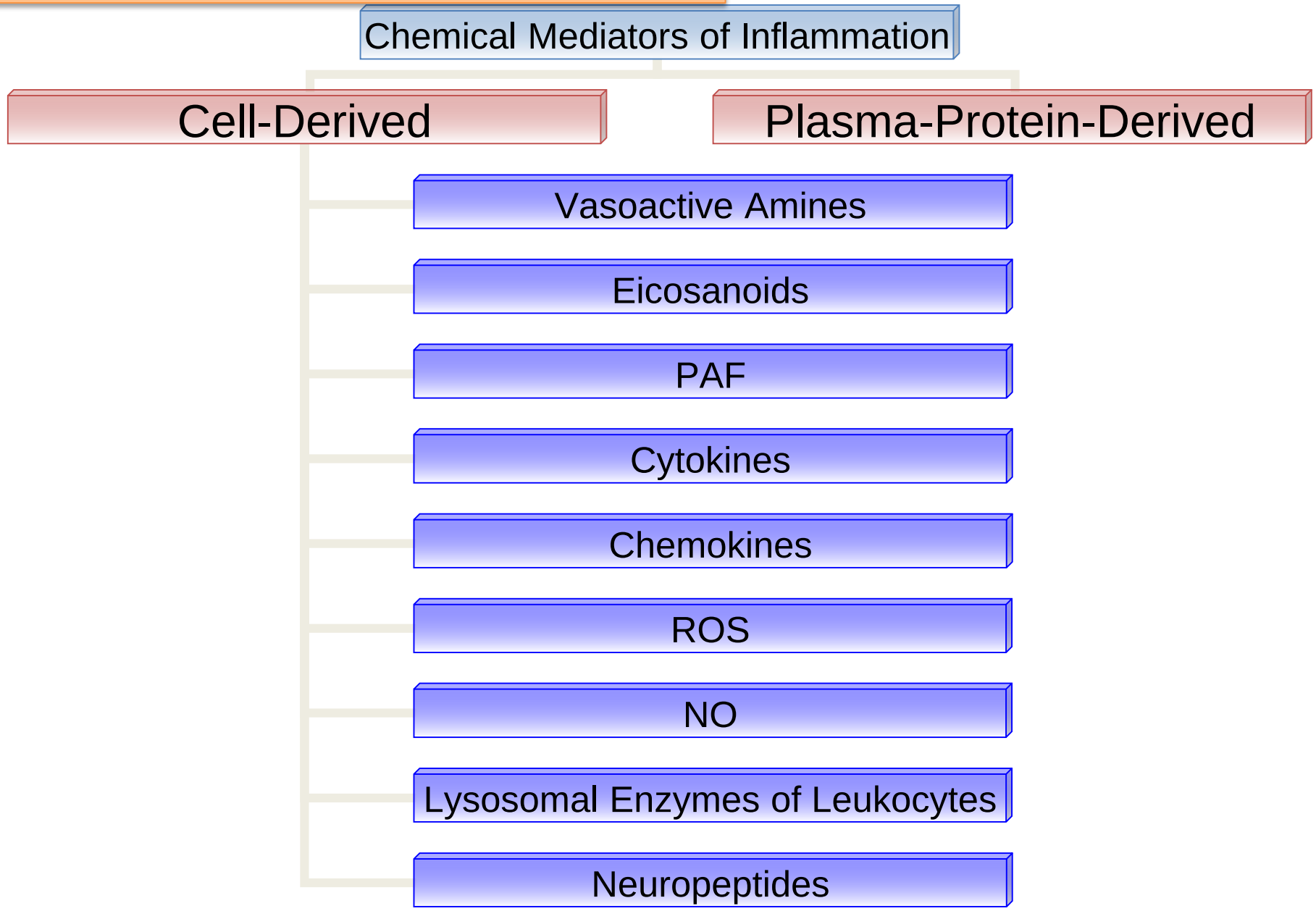
Source of Chemical mediators

- Plasma-derived:
  1. Complement
  2. kinins
  3. coagulation factors

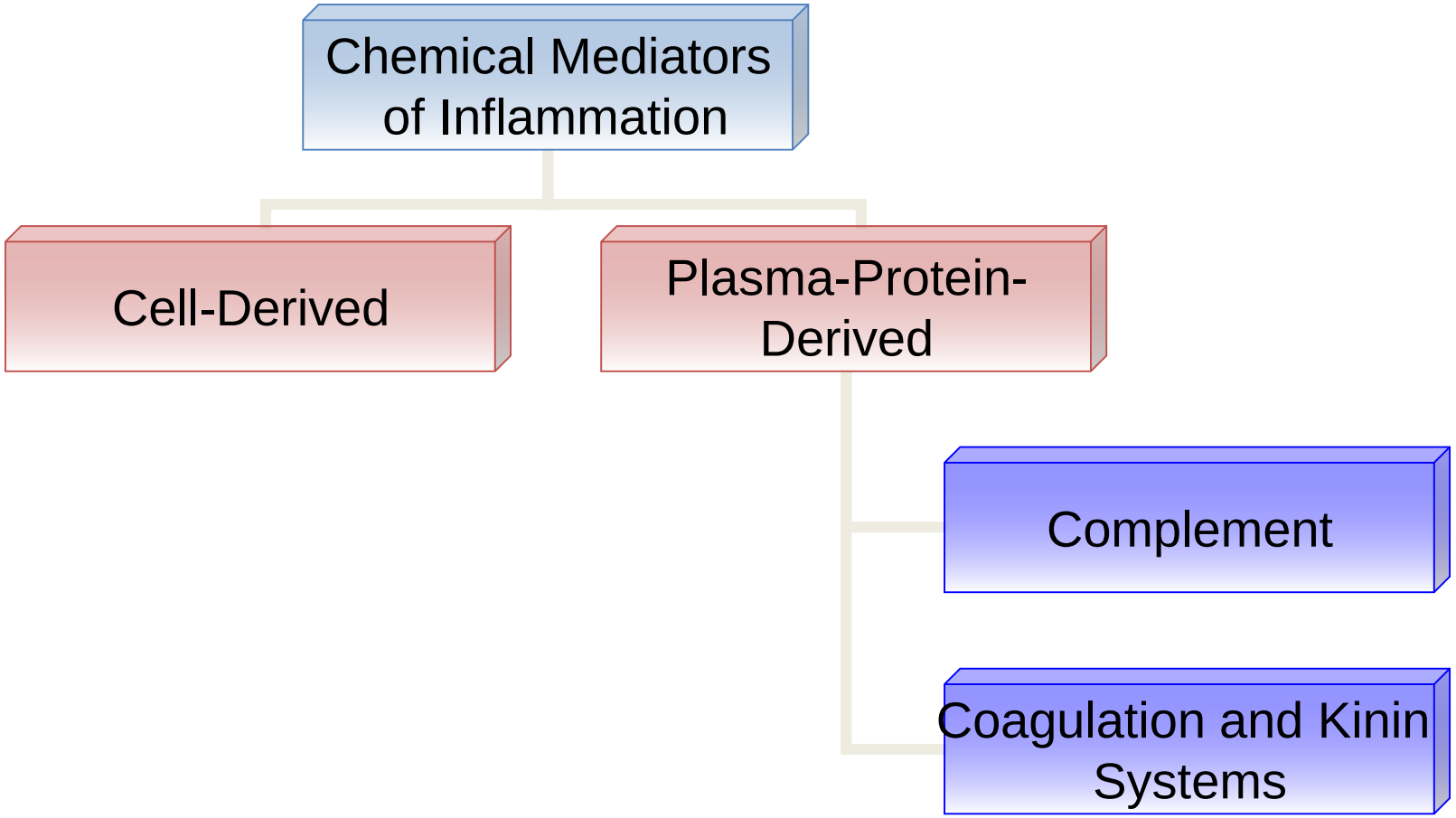
  – Many in “pro-form” requiring activation (enzymatic cleavage)

- Cell-derived:
  1. Synthesized as needed (prostaglandin)
  2. Preformed, sequestered and released (mast cell histamine)

3. Chemical mediators of inflammation

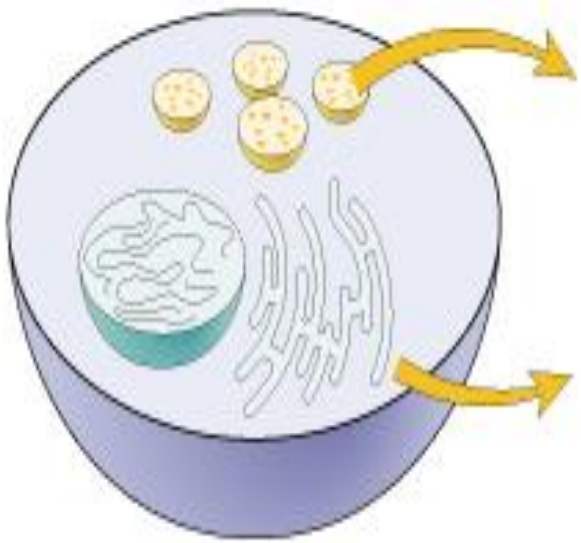


3. Chemical mediators of inflammation



Cell-Derived Mediators

Producing cells:



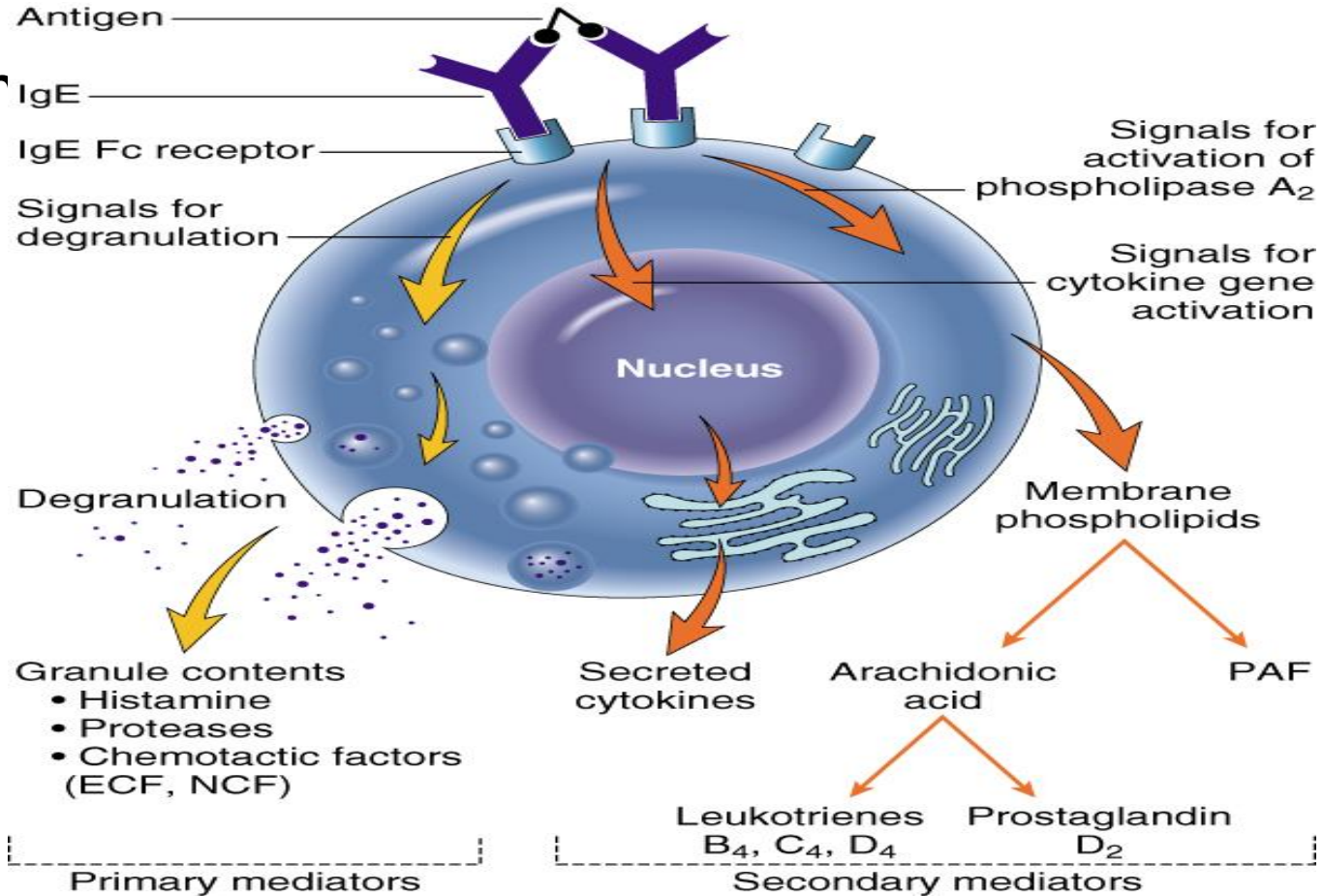
	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
	Lysosomal enzymes	Neutrophils, macrophages
Newly synthesized	Prostaglandins	All leukocytes, platelets, EC
	Leukotrienes	All leukocytes
	Platelet-activating factors	All leukocytes,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

Vasoactive Amines

Histamine & Serotonin

Among first mediators in acute inflammatory reactions

- Preformed r



Histamine

Source:

many cell types, esp. *mast cells*, *circulating basophils*, and *platelets*

Stimuli of Release:

Physical injury
Immune reactions
C3a and C5a fragments
Leukocyte-derived histamine-releasing proteins
Neuropeptides
Cytokines (e.g. IL-1 and IL-8)

Actions:

1. ARTERIOLAR DILATION
2. INCREASED VASCULAR PERMEABILITY (venular gaps)
3. ENDOTHELIAL ACTIVATION

Inactivated by:
Histaminase

3. Chemical mediators of inflammation

Serotonin (5-HT)

Source:

Platelets

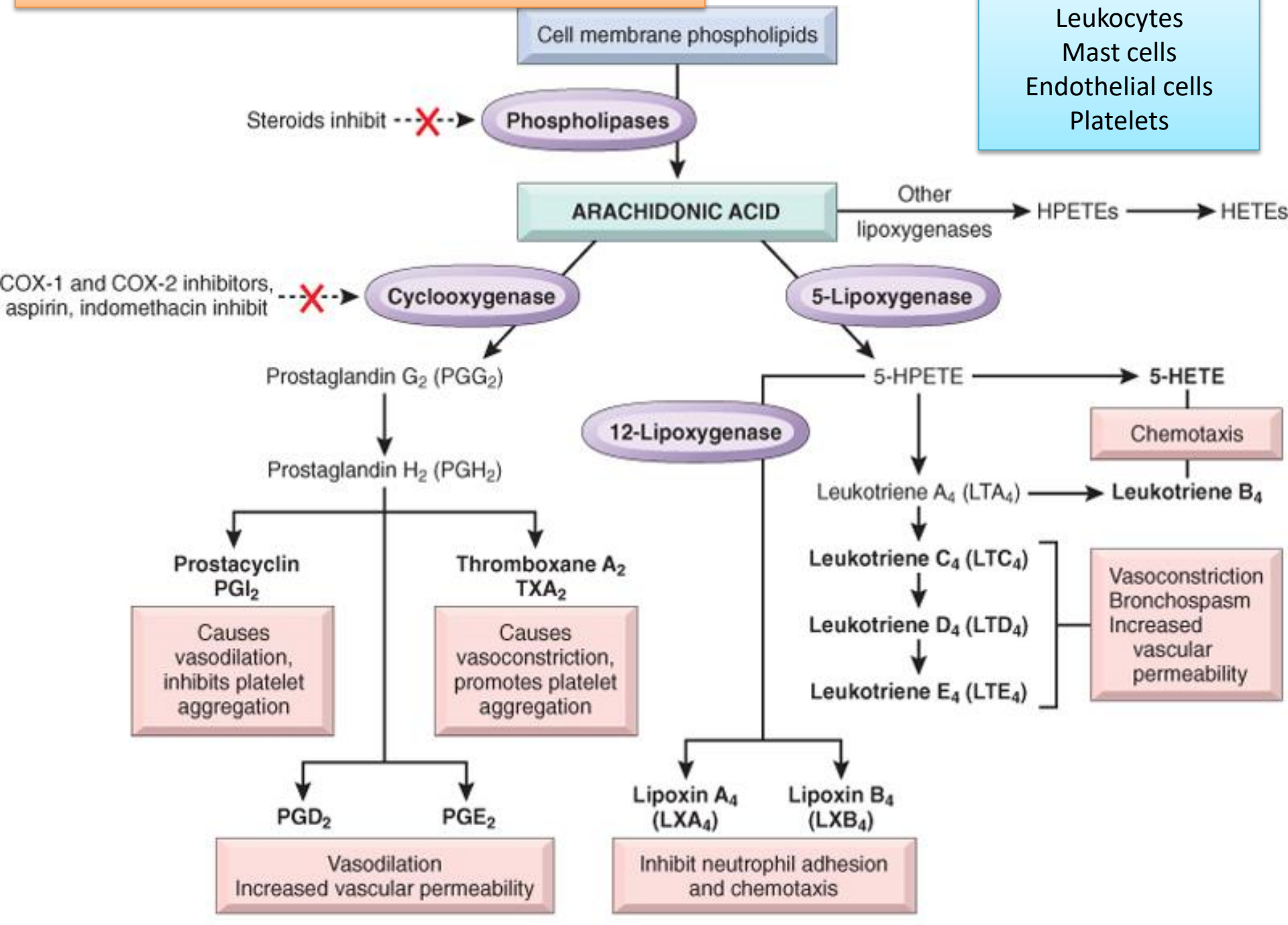
Action:

Similar to histamine

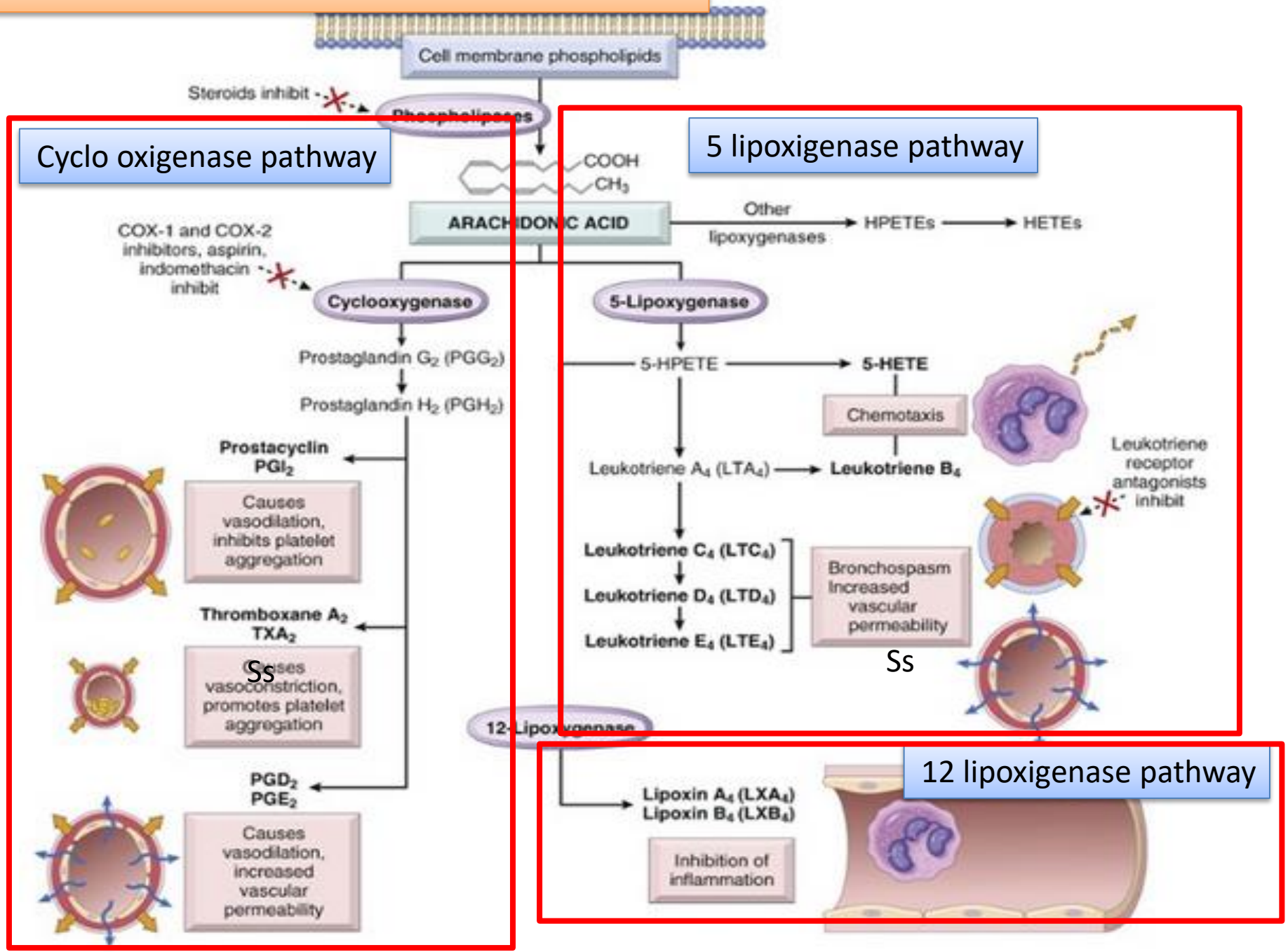
Stimulus:

Platelet aggregation

3. Chemical mediators of inflammation

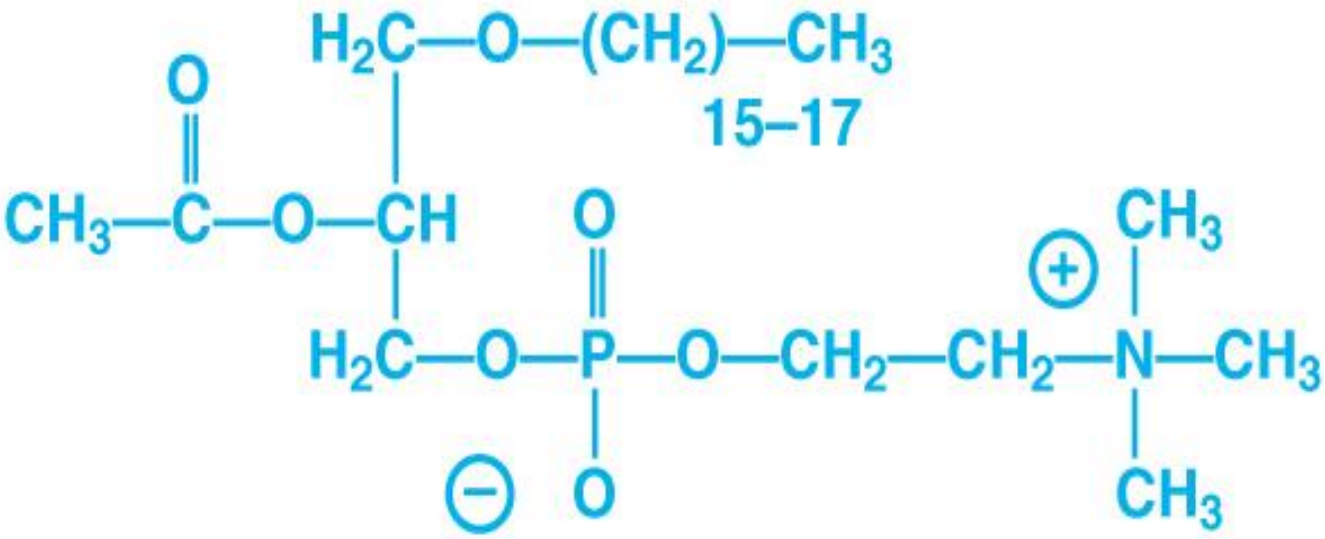


3. Chemical mediators of inflammation



3. Chemical mediators of inflammation

SOURCES	MAJOR INFLAMMATORY ACTIONS
Mast cells/basophils	Increased vascular permeability
Neutrophils	Leukocyte aggregation
Monocytes/macrophages	Leukocyte adhesion
Endothelium	Leukocyte priming/chemotaxis
Platelets	Platelet activation
Others	Stimulation of other mediators (LT, $O_2^{\bullet-}$)



PLATELET-ACTIVATING FACTOR

3. Chemical mediators of inflammation

Chemical Mediators of Inflammation

Cell-Derived

Plasma-Protein-Derived

Cytokines

Polypeptides

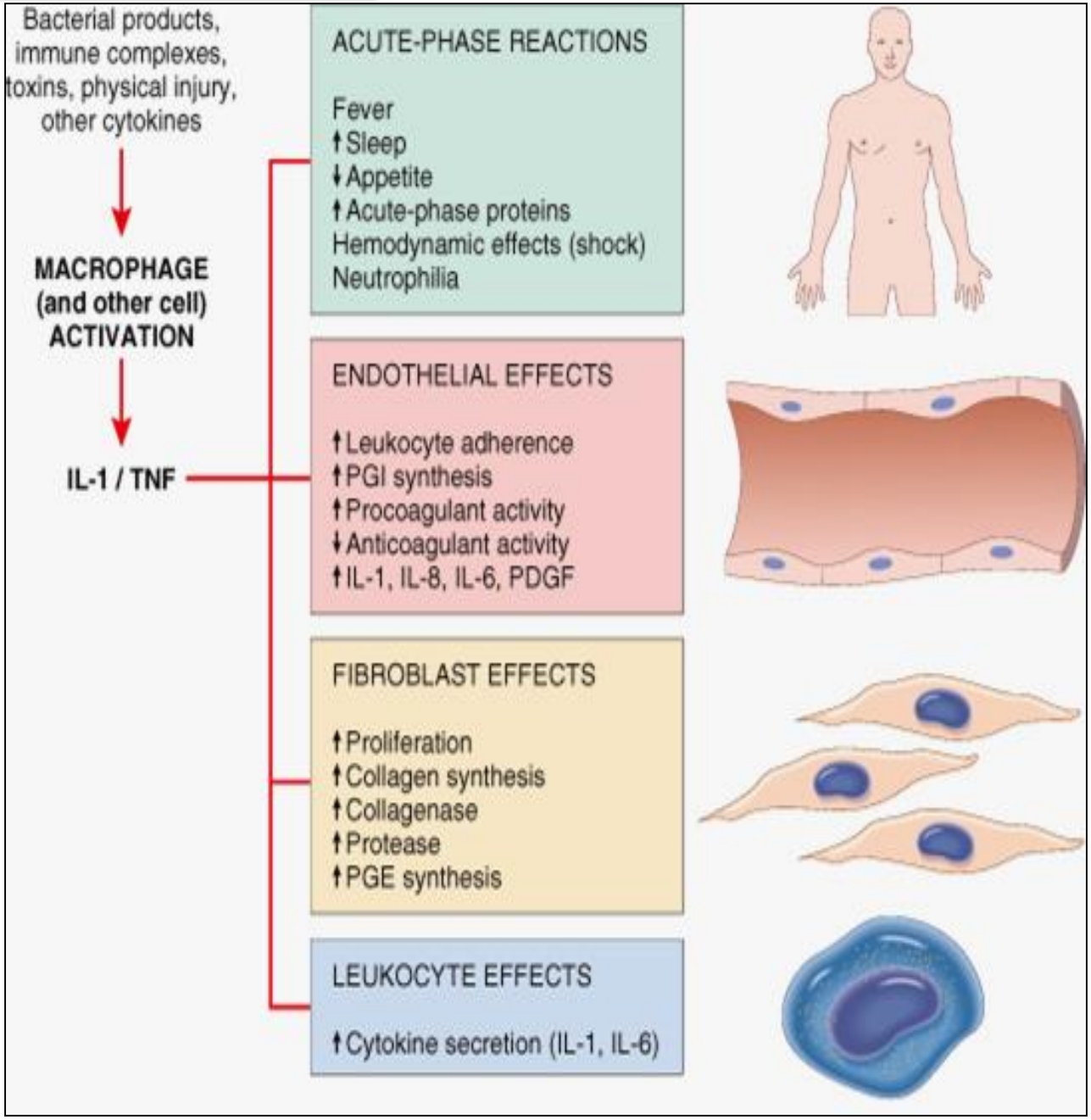
Actions:

Involved in early immune and inflammatory reactions

Some stimulate bone marrow precursors to produce more leukocytes

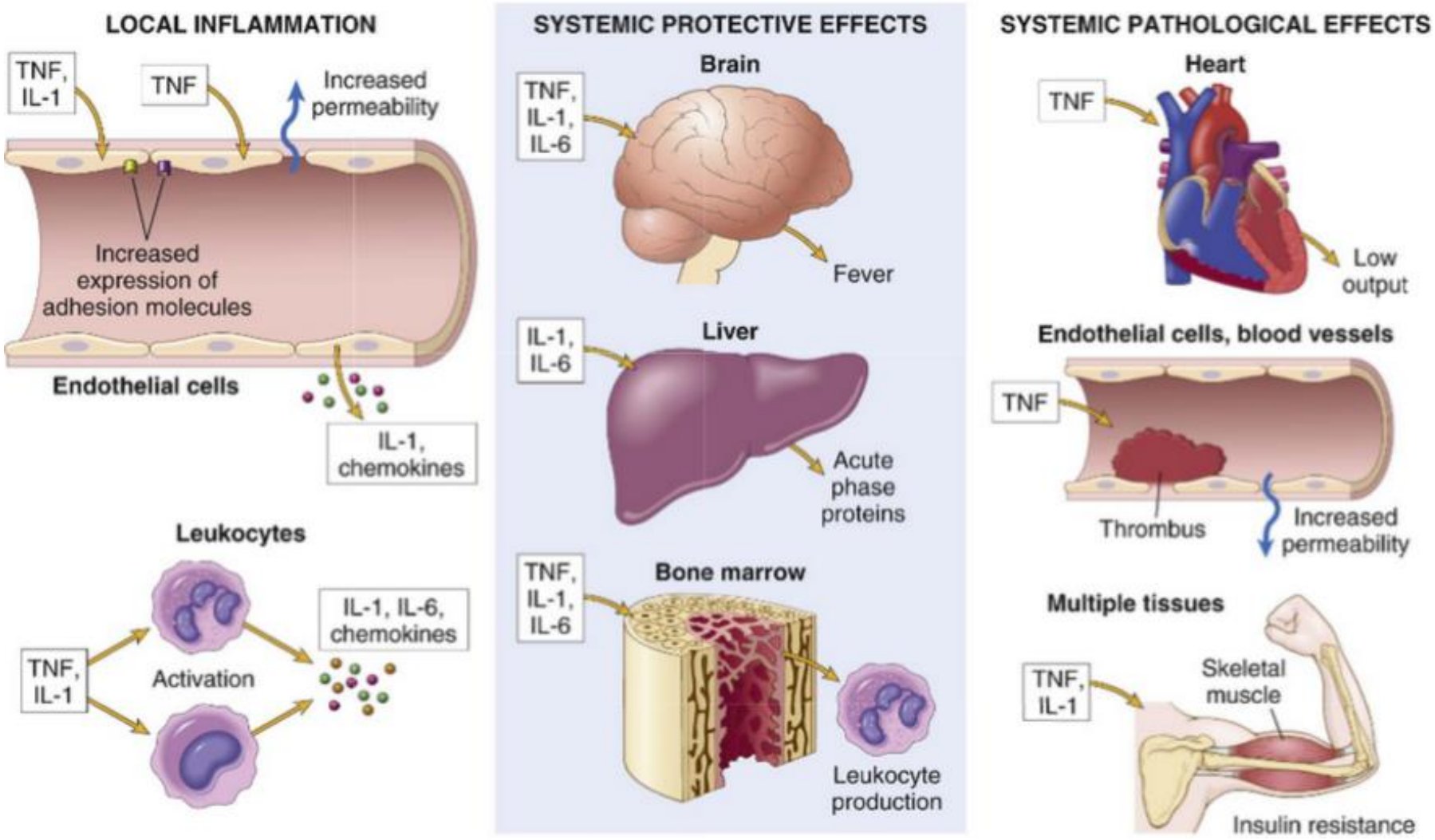
3. Chemical mediators of inflammation

Cytokine of
Acute inflammation:
Interleukin (IL-1) & TNF



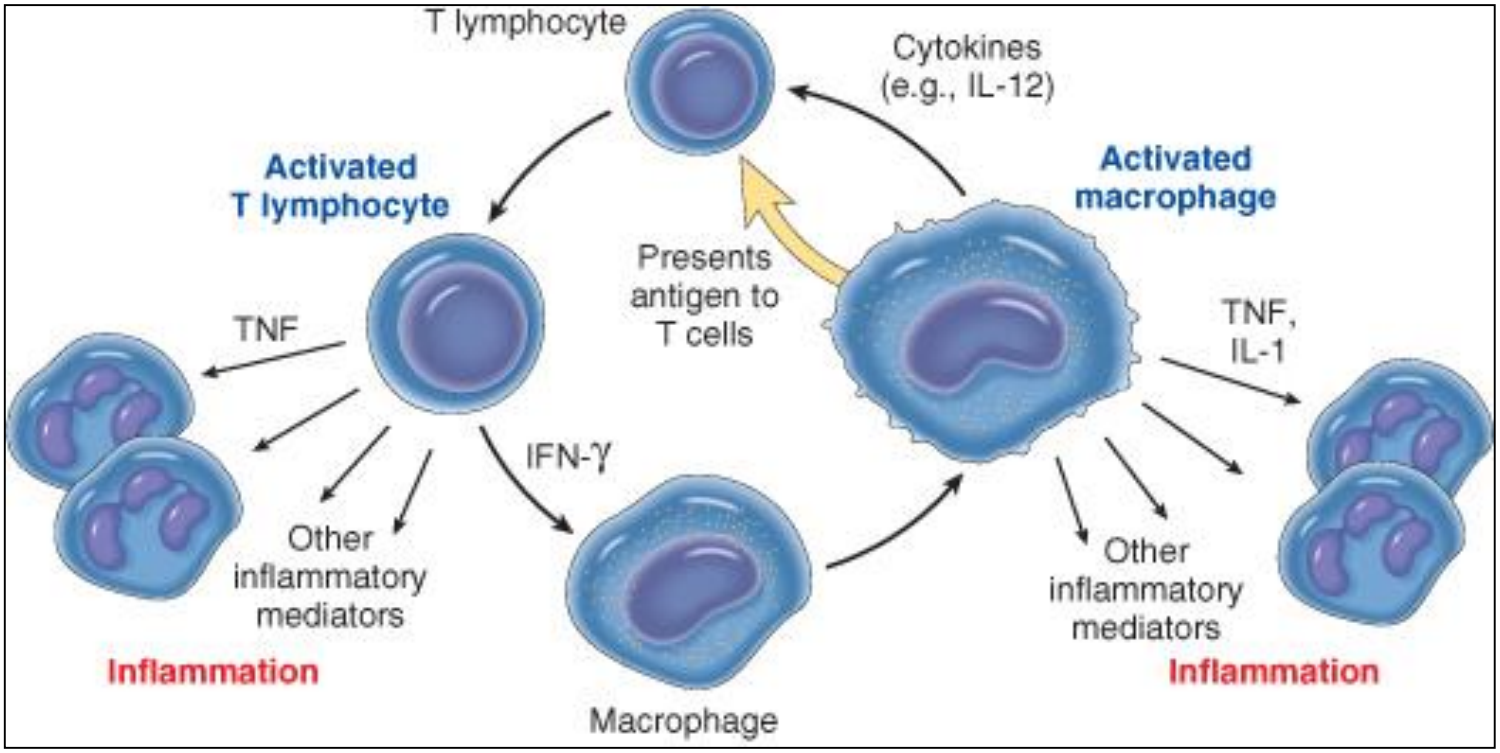
3. Chemical mediators of inflammation

Major roles of cytokines in acute inflammation



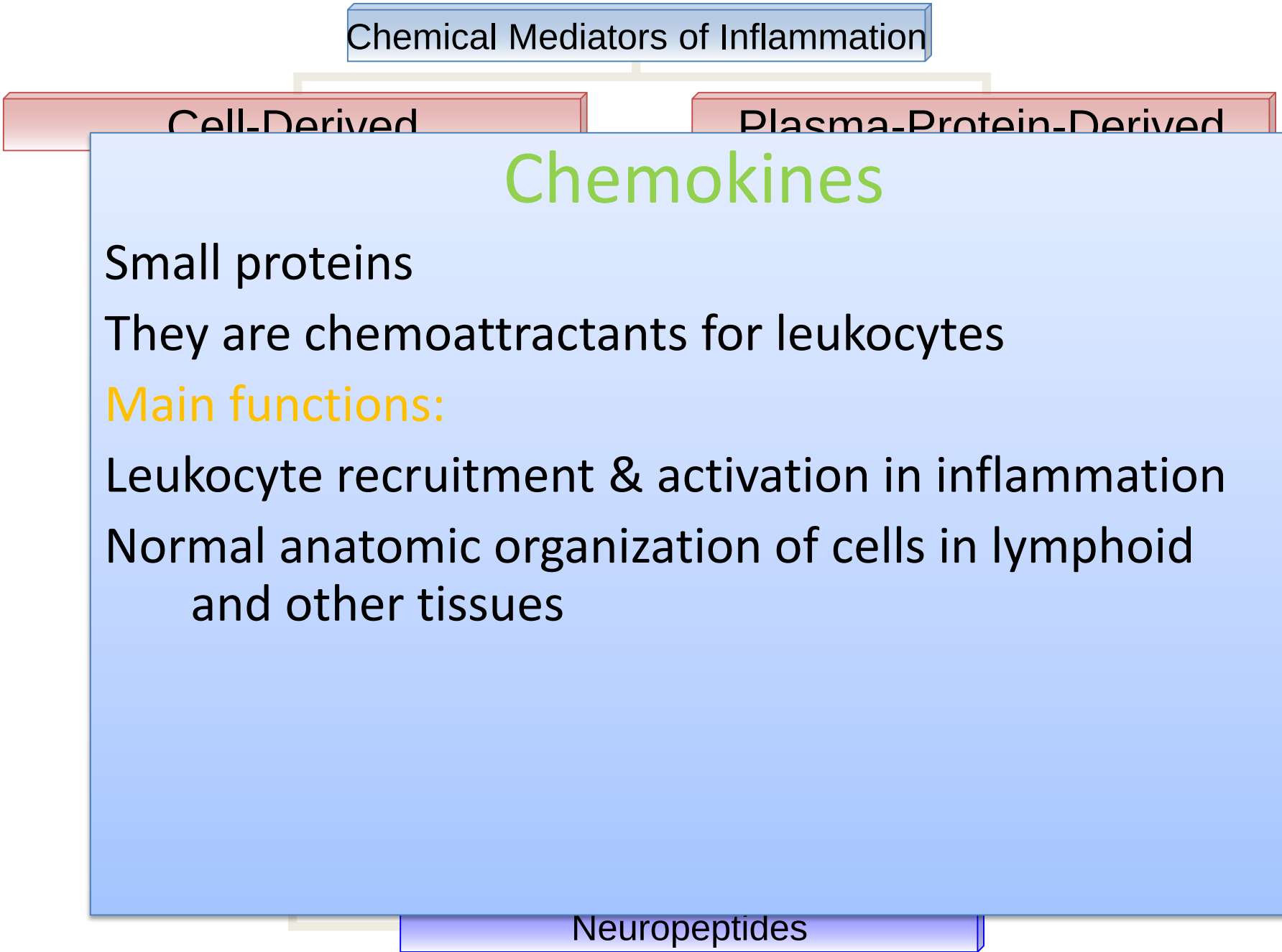
Cytokines of Chronic Inflammation:

Interferon-γ (INF- γ) & Interleukin (IL-12)



Activated lymphocytes and macrophages influence each other and also release inflammatory mediators that affect other cells.

3. Chemical mediators of inflammation



3. Chemical mediators of inflammation

Chemical Mediators of Inflammation

Cell-Derived

Plasma-Protein-Derived

Reactive Oxygen Species

Synthesized via

NADPH oxidase pathway

Source:

Neutrophils and Macrophages

Stimuli of release:

Microbes

Immune complexes

Cytokines

Action:

Microbicidial (cytotoxic) agent

3. Chemical mediators of inflammation

Chemical Mediators of Inflammation

Cell-Derived

Plasma-Protein-Derived

Nitric Oxide (NO)

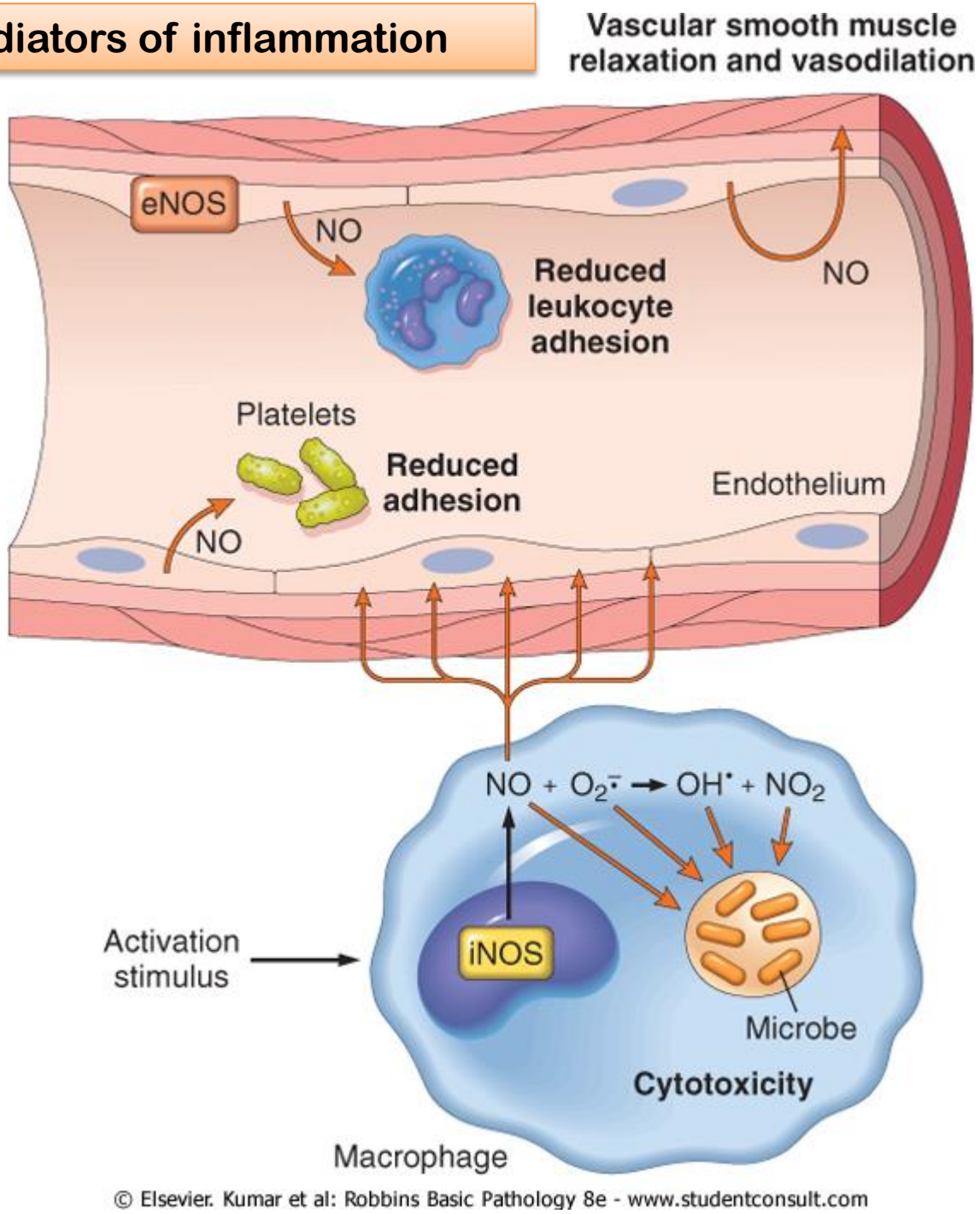
Short-lived

Soluble free-radical gas

Functions:

- Vasodilation
- Antagonism of platelet activation (adhesion, aggregation, & degranulation)
- Reduction of leukocyte recruitment
- Microbicidial (cytotoxic) agent (with or without ROS) in activated macrophages

3. Chemical mediators of inflammation



3. Chemical mediators of inflammation

Chemical Mediators of Inflammation

Lysosomal Enzymes of Leukocytes

Neutrophils & Monocytes

Enzymes:

Acid proteases

Neutral proteases (e.g. elastase, collagenase, & cathepsin)

Their action is checked by:

Serum antiproteases (e.g. α_1-antitrypsin)

3. Chemical mediators of inflammation

Chemical Mediators of Inflammation

Cell-Derived

Plasma-Protein-Derived

Neuropeptides

Small proteins

Secreted by nerve fibers mainly in lung & GIT

Initiate inflammatory response

e.g. Substance P :

Transmits pain signals

Regulates vessel tone

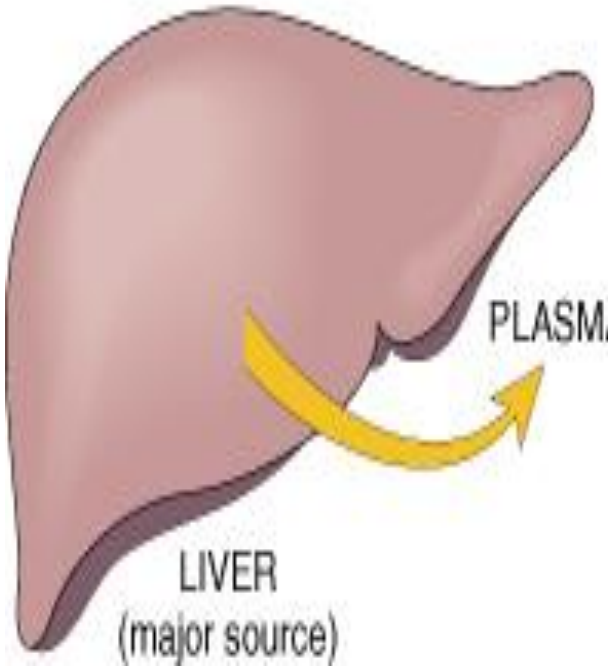
Modulates vascular permeability

Neuropeptides

3. Chemical mediators of inflammation

Chemical Mediators of Inflammation

- Cell-Derived
- Plasma-Protein-Derived



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

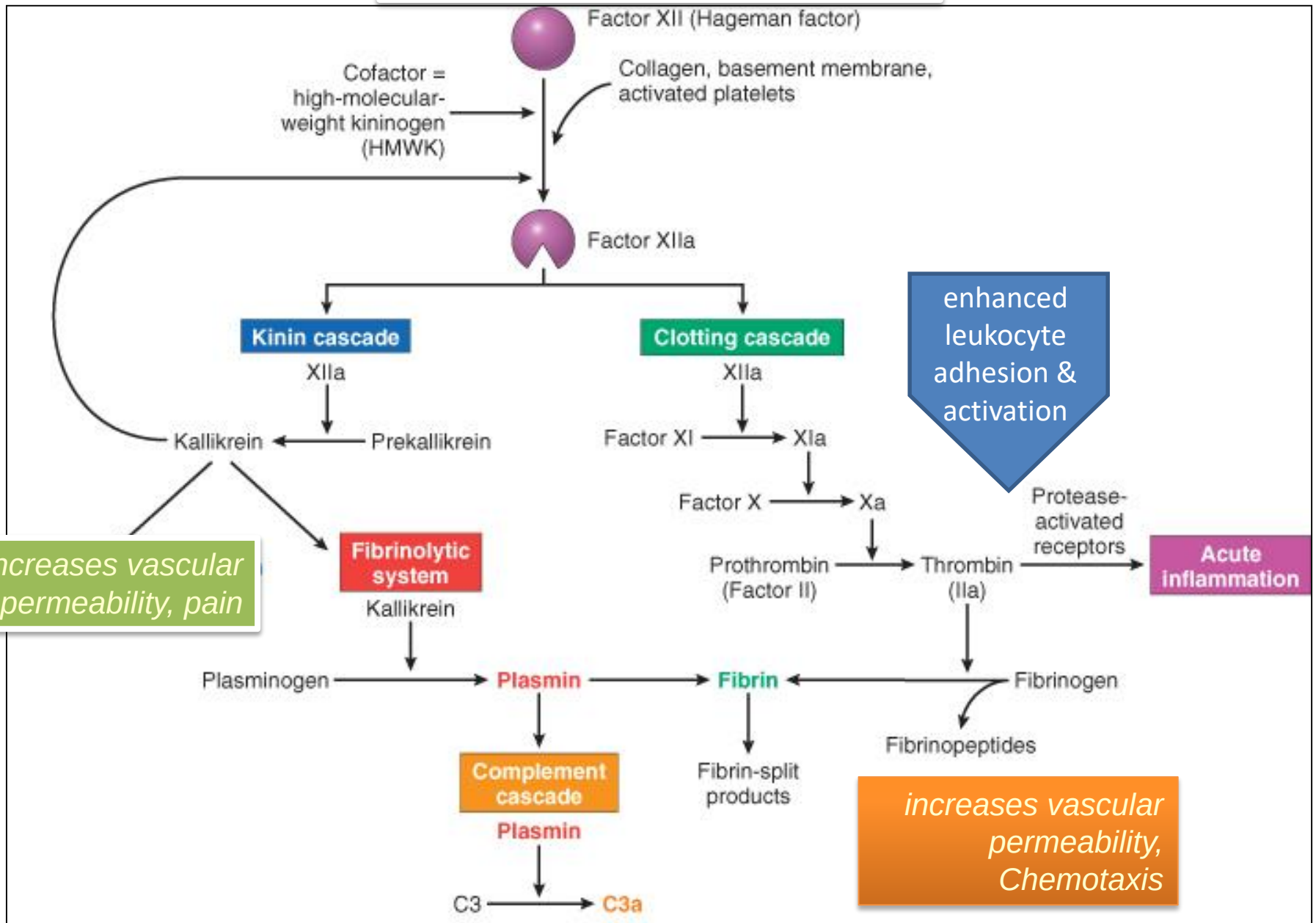
PLASMA PROTEASES

- A variety of phenomena in the inflammatory response are mediated by plasma proteins that belong to three interrelated systems

1. Kinin
2. the complement
3. clotting systems

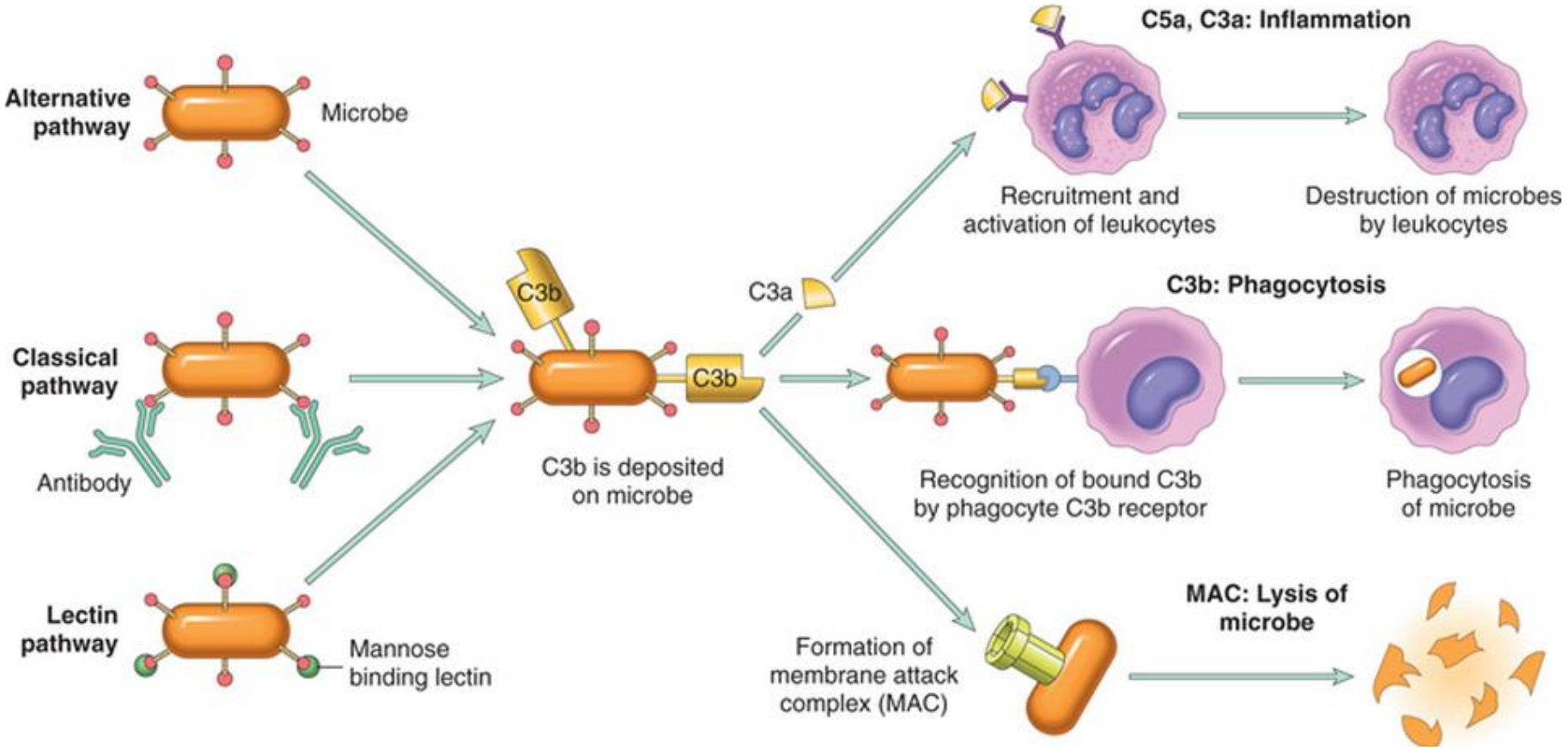
3. Chemical mediators of inflammation

Kinin & clotting systems



3. Chemical mediators of inflammation

Complement System



Complement protein

C3a & C5a → Increase vascular permeability
(anaphylatoxins)

C5a → Chemotaxis

C3b → Opsonization

C5-9 → membrane attack complex

3. Chemical mediators of inflammation

Role of Mediators in Different Reactions of Inflammation

Vasodilation	Prostaglandins Histamine Nitric oxide
Increased vascular permeability	Vasoactive amines Bradykinin Leukotrienes C4, D4, E4 PAF Substance P
Chemotaxis, leukocyte recruitment and activation	C5a Leukotriene B4 Chemokines IL-1, TNF Bacterial products
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Neutrophil and macrophage lysosomal enzymes Oxygen metabolites Nitric oxide

Mediators	Source	Principal Actions
Cell-Derived:		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Serotonin	Platelets	Vasodilatation, increased vascular permeability.
Prostaglandins	Mast cells, leukocytes	Vasodilatation, pain, fever.
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation.
Platelet-activating factor	Leukocytes, endothelial cells	Vasodilatation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage
Nitric oxide	Endothelium, macrophages	Vascular smooth muscle relaxation; killing of microbes
Cytokines (e.g. TNF, IL-)	Macrophages, lymphocytes Endothelial cells, mast cells	Local endothelial activation (expres-sion of adhesion molecules), systemic acute-phase response in severe infections, septic shock