Foundation Block, Pathology

INFLAMMATION AND REPAIR
Lecture 4

Chemical mediator of inflammation
Systemic effect of inflammation

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Objectives

1. **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. **Describe the systemic manifestations of inflammation and their general physiology, including fever, leukocyte left shift, and acute phase reactants.**

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)**

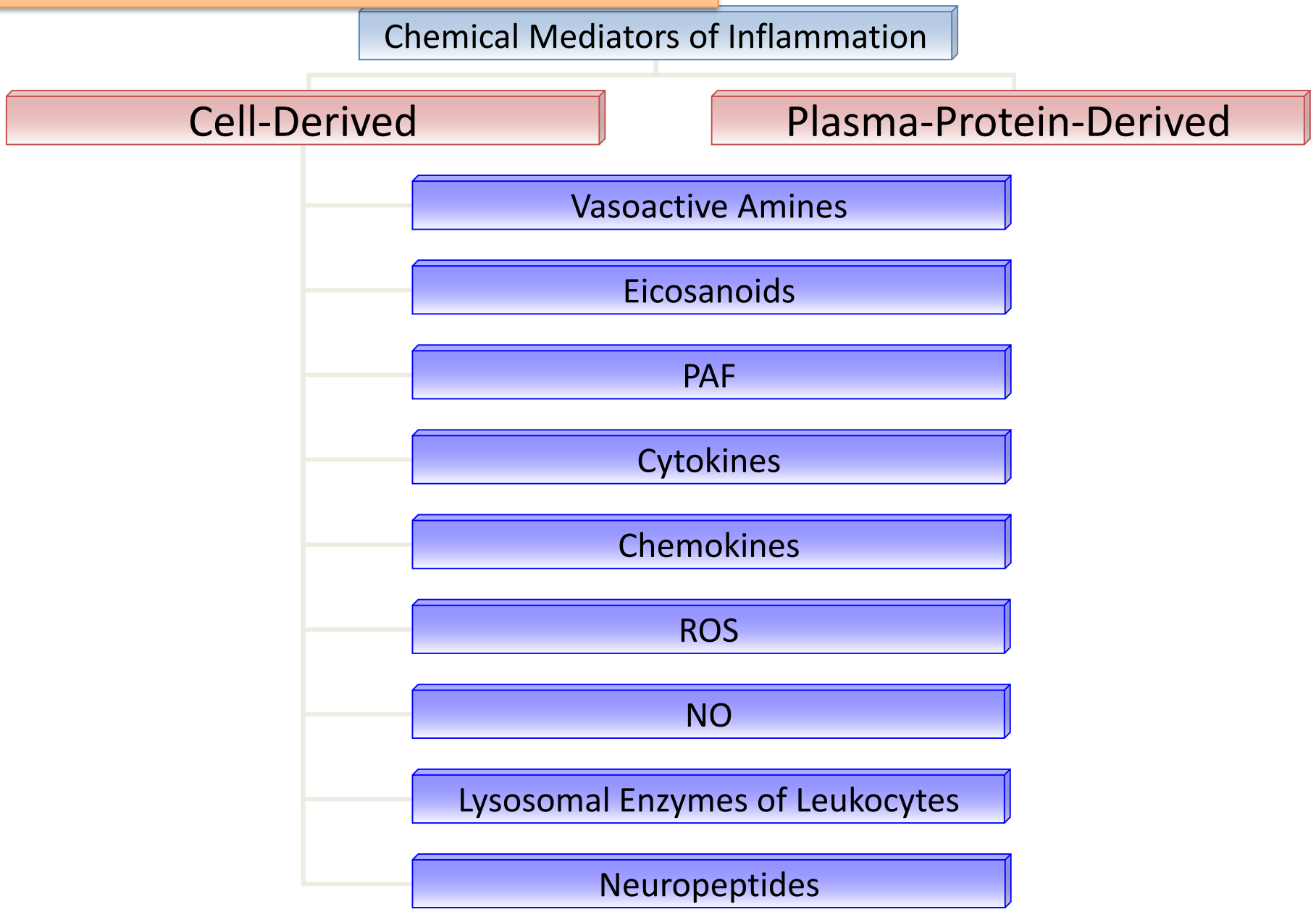
Source of Chemical mediators

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

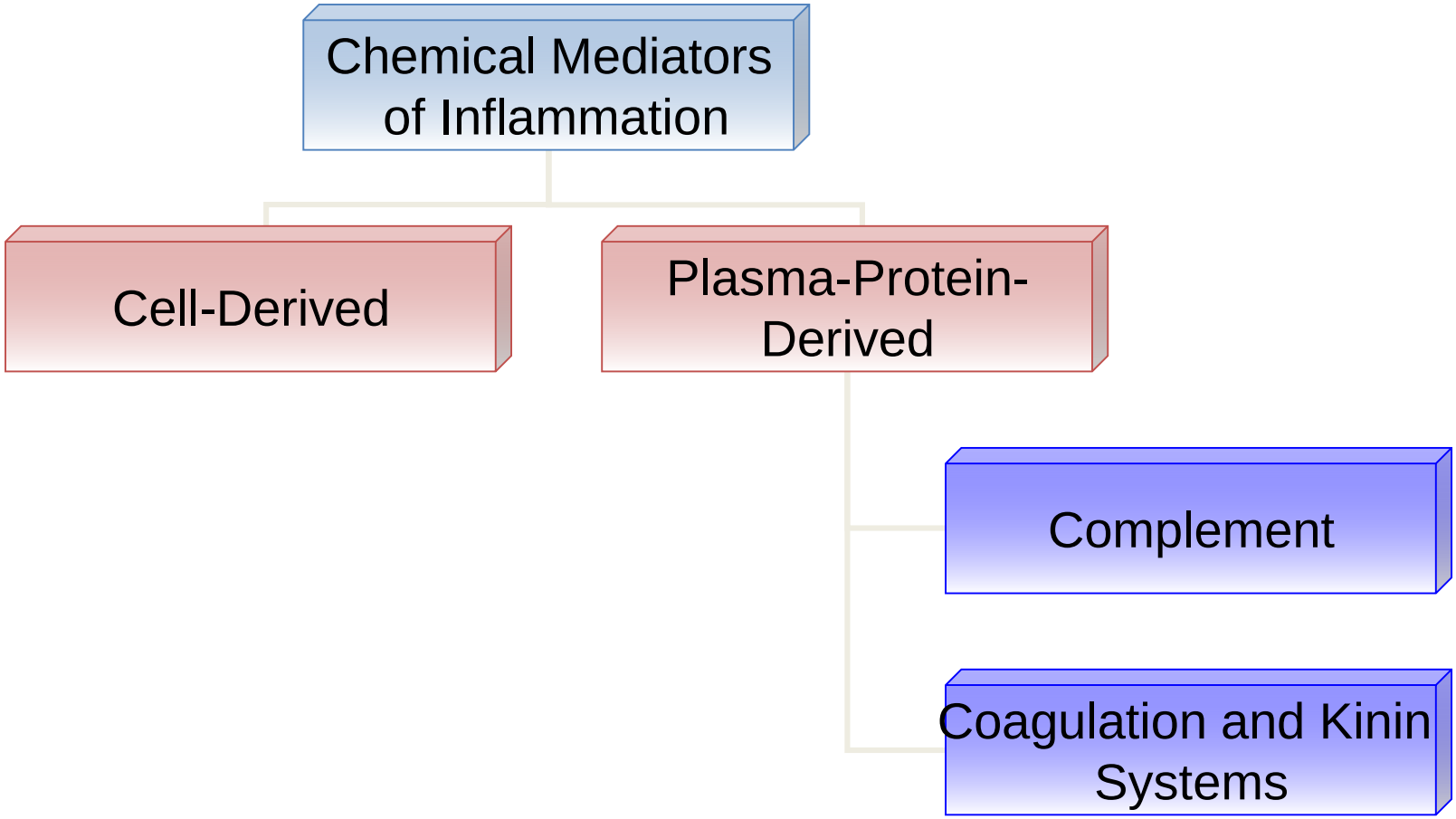
  – Many in “pro-form” requiring activation (enzymatic cleavage)

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

Chemical mediators of inflammation

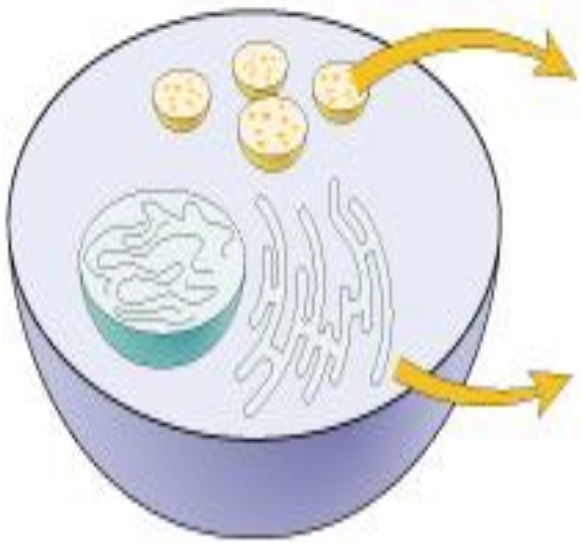


Chemical mediators of inflammation



Cell-Derived Mediators

Producing cells:



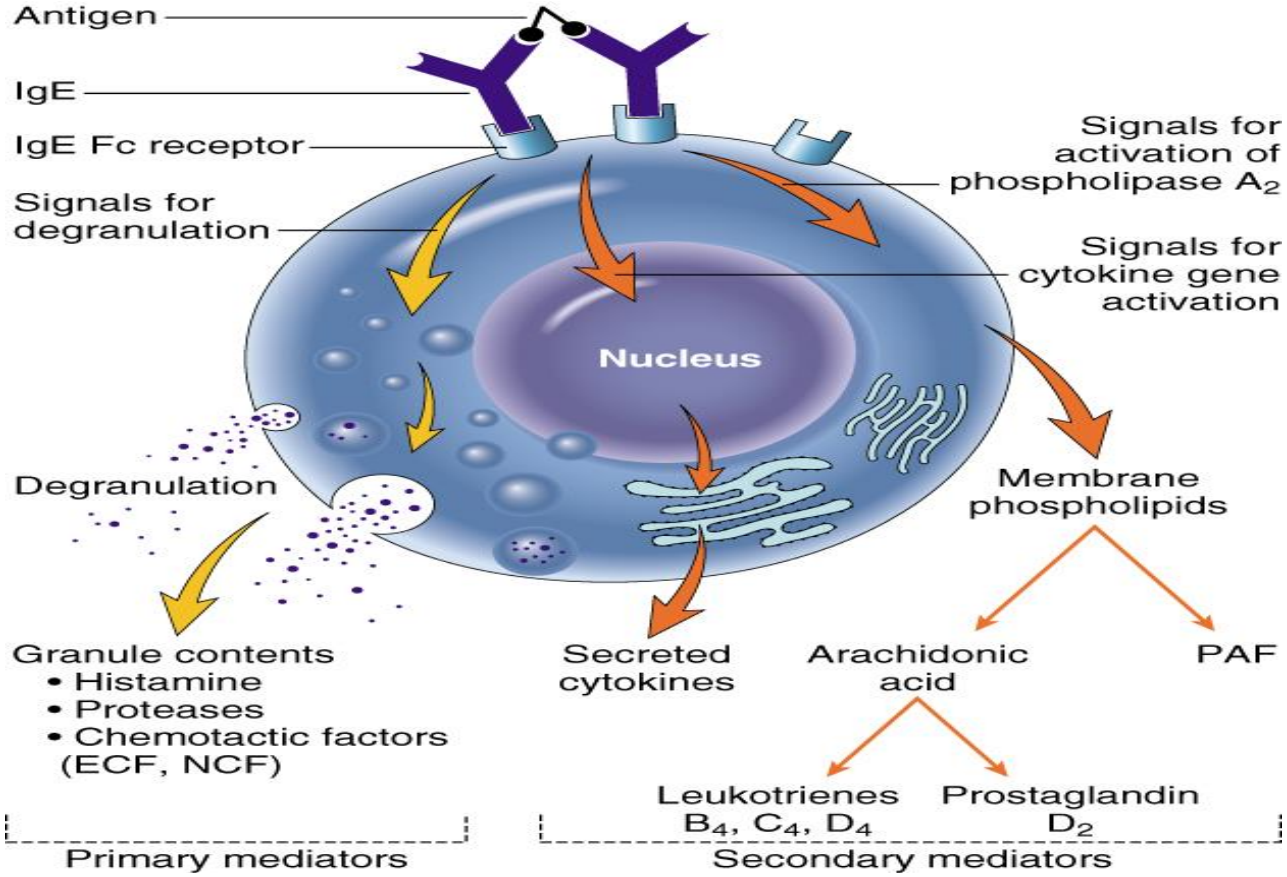
	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
	Lysosomal enzymes	Neutrophils, macrophages
Newly synthesized	Prostaglandins	All leukocytes, platelets, EC
	Leukotrienes	All leukocytes
	Platelet-activating factors	All leukocytes, 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 mediators in secretory granules



Histamine

Source:

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

Stimuli of Release:

Physical injury
Immune reactions
C3a and C5a fragments
Cytokines (e.g. IL-1 and IL-8)
Neuropeptides

Actions:

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

Inactivated by:
Histaminase

Serotonin (5-HT)

Source:

Platelets

Action:

Similar to histamine

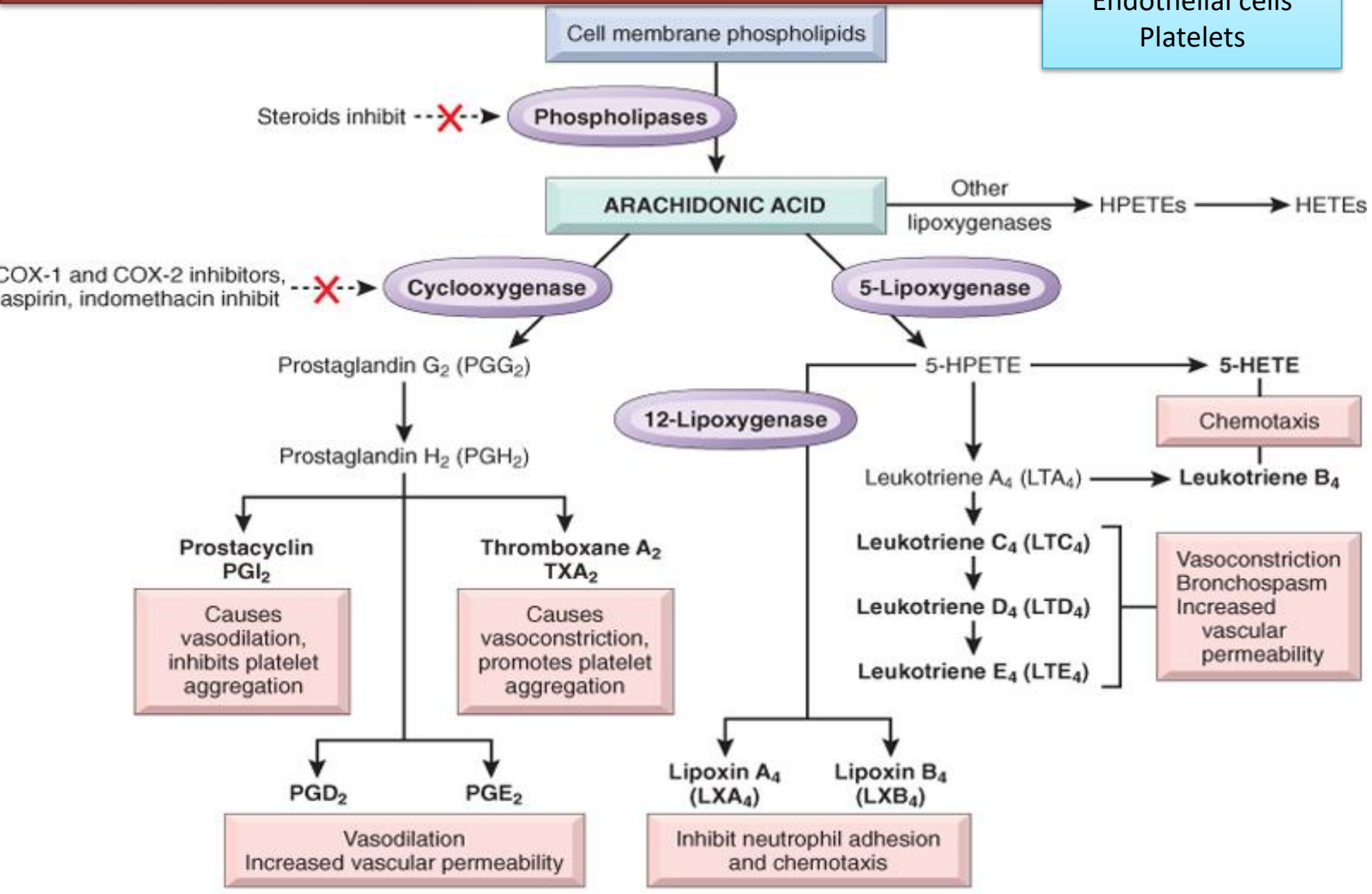
Stimulus:

Platelet aggregation

Chemical mediators of inflammation: cell derived

Arachidonic Acid Metabolites (*eicosanoids*)

Source:
Leukocytes
Mast cells
Endothelial cells
Platelets

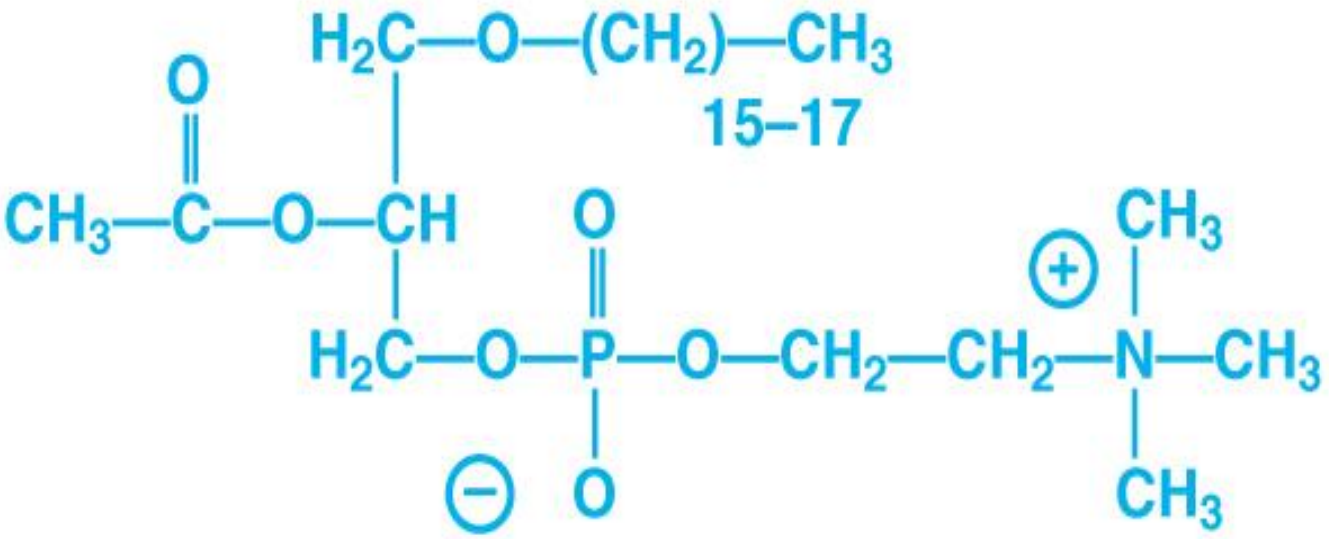


Arachidonic Acid Metabolites (*eicosanoids*)

Action	Eicosanoid
Vasodilation	Prostaglandins PGI_2 (prostacyclin), PGE_1, PGE_2, PGD_2
Vasoconstriction	Thromboxane A_2, leukotrienes C_4, D_4, E_4
Increased vascular permeability	Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte adhesion	Leukotriene B_4
Smooth muscle contraction	Prostaglandins PGC4, PGD4, PGE4

Chemical mediators of inflammation: cell derived

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

Chemical mediators of inflammation: cell derived

Chemical Mediators of Inflammation

Cell-Derived

Plasma-Protein-Derived

Cytokines

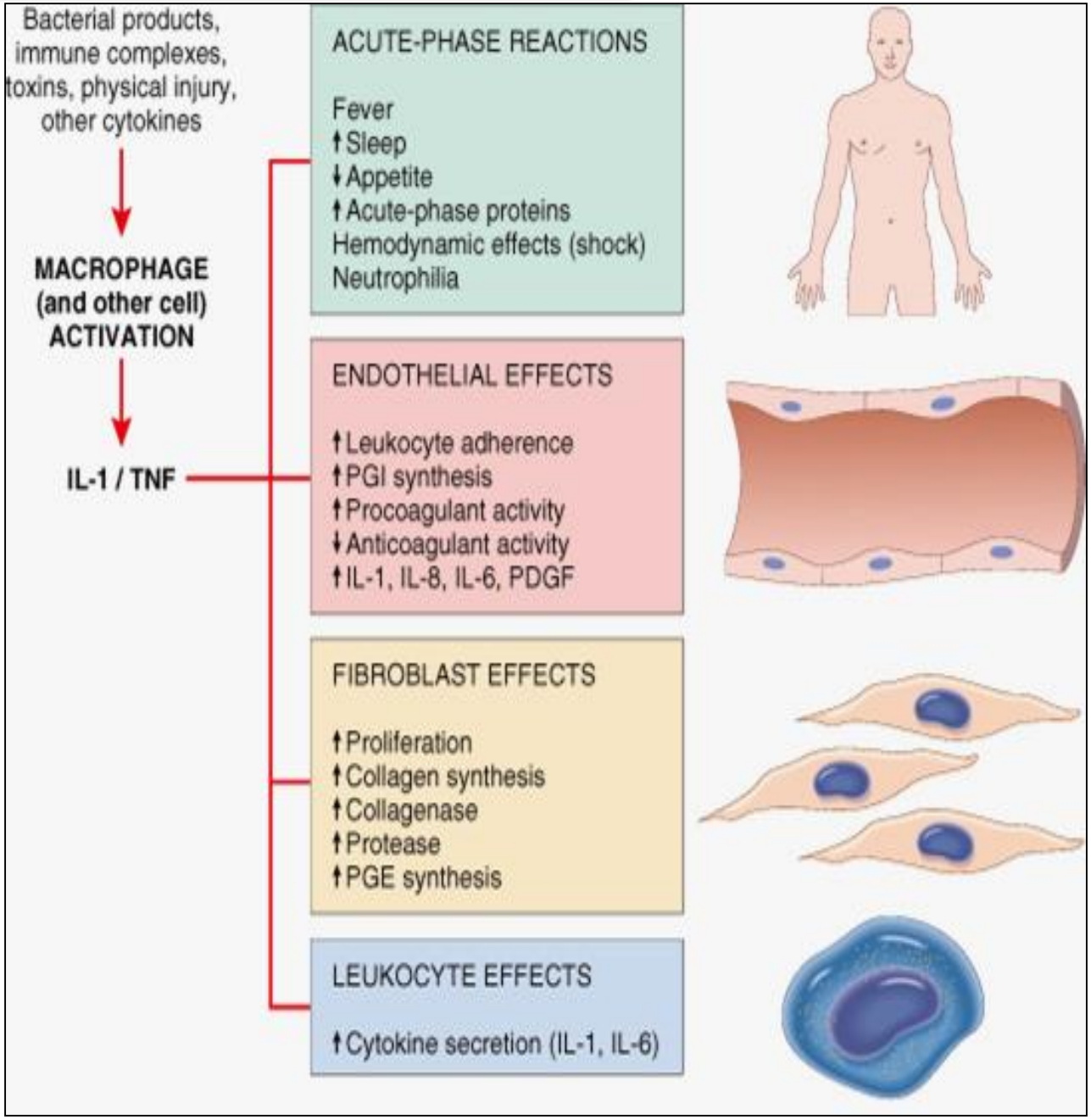
Polypeptides

Actions:

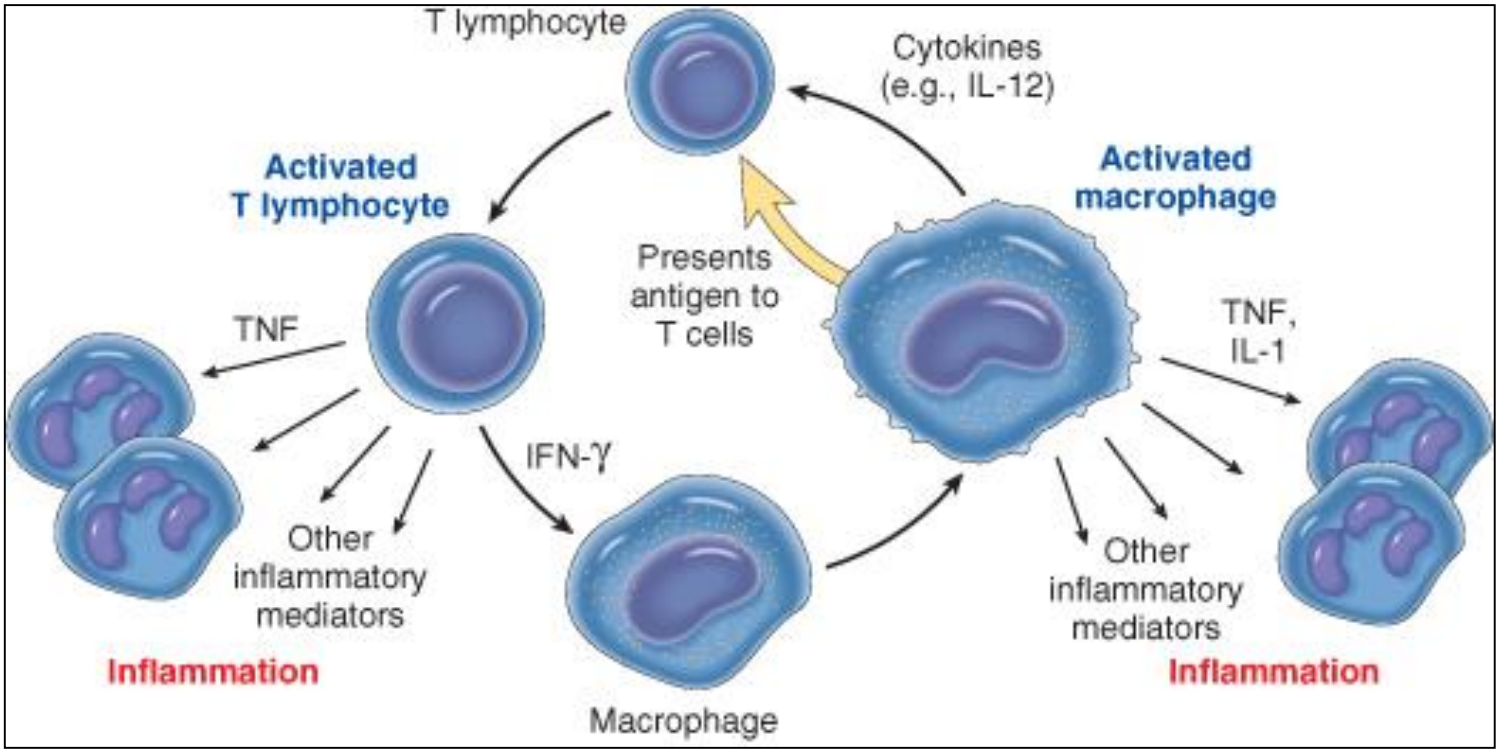
- Involved in early immune and inflammatory reactions
- Some stimulate bone marrow precursors to produce more leukocytes
- Have roles in acute and chronic inflammation

Chemical mediators of inflammation: cell derived

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



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.

Chemical mediators of inflammation: cell derived

Chemical Mediators of Inflammation

Cell-Derived

Plasma-Protein-Derived

Chemokines

Small proteins

They are chemoattractants for leukocytes

Main functions:

Leukocyte recruitment & activation in inflammation

Normal anatomic organization of cells in lymphoid and other tissues

Chemical mediators of inflammation: cell derived

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

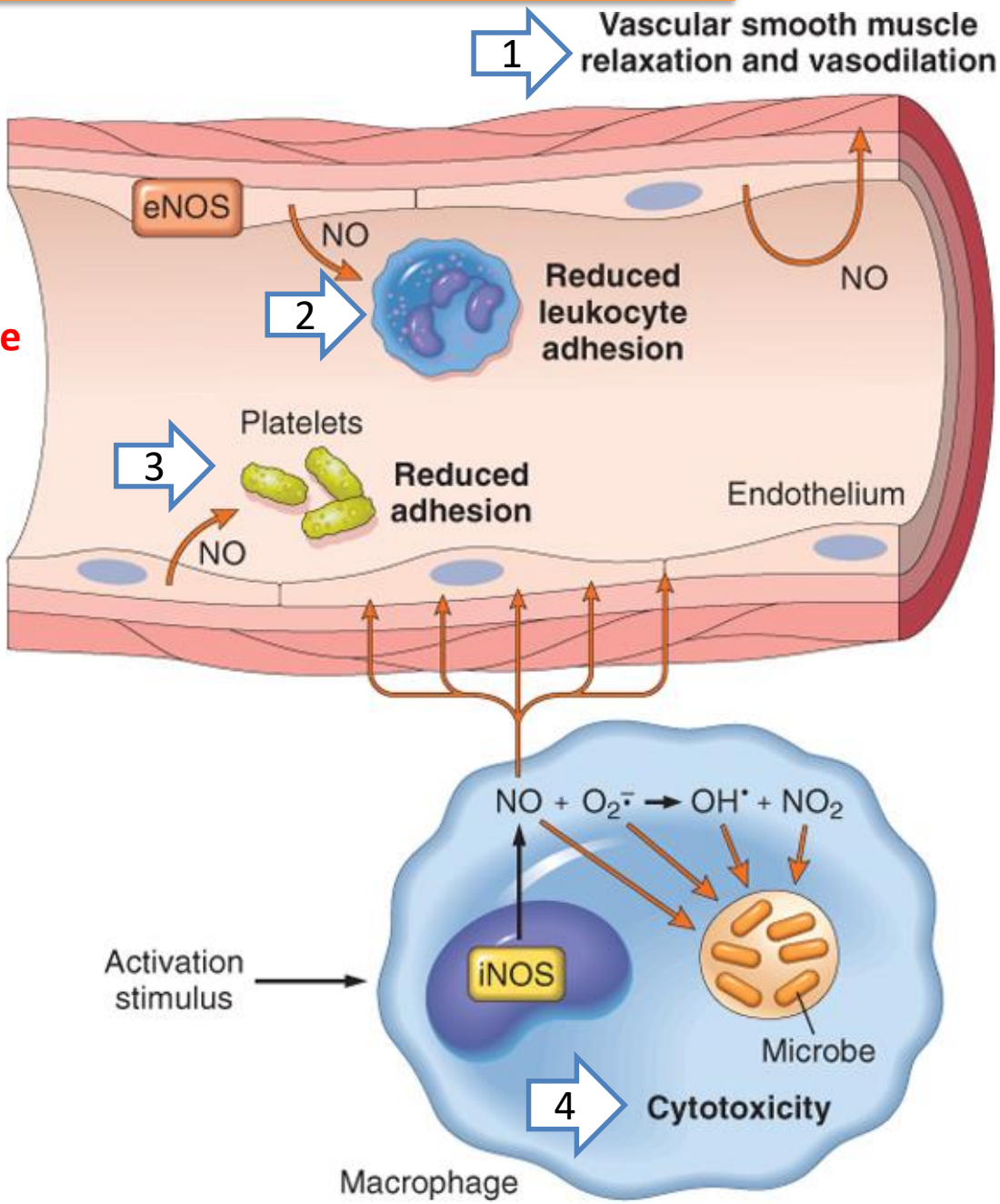
Soluble free-radical gas

Functions:

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

Chemical mediators of inflammation: cell derived

Actions of Nitric Oxide



Chemical mediators of inflammation: cell derived

Chemical Mediators of Inflammation

Cell-Derived

Plasma-Protein-Derived

Lysosomal Enzymes of Leukocytes

Neutrophils & Monocytes

<u>Enzymes:</u>

Acid proteases

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

<u>Their action is checked by:</u>

Serum antiproteases (e.g. α_1-antitrypsin)

Chemical mediators of inflammation: cell derived

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

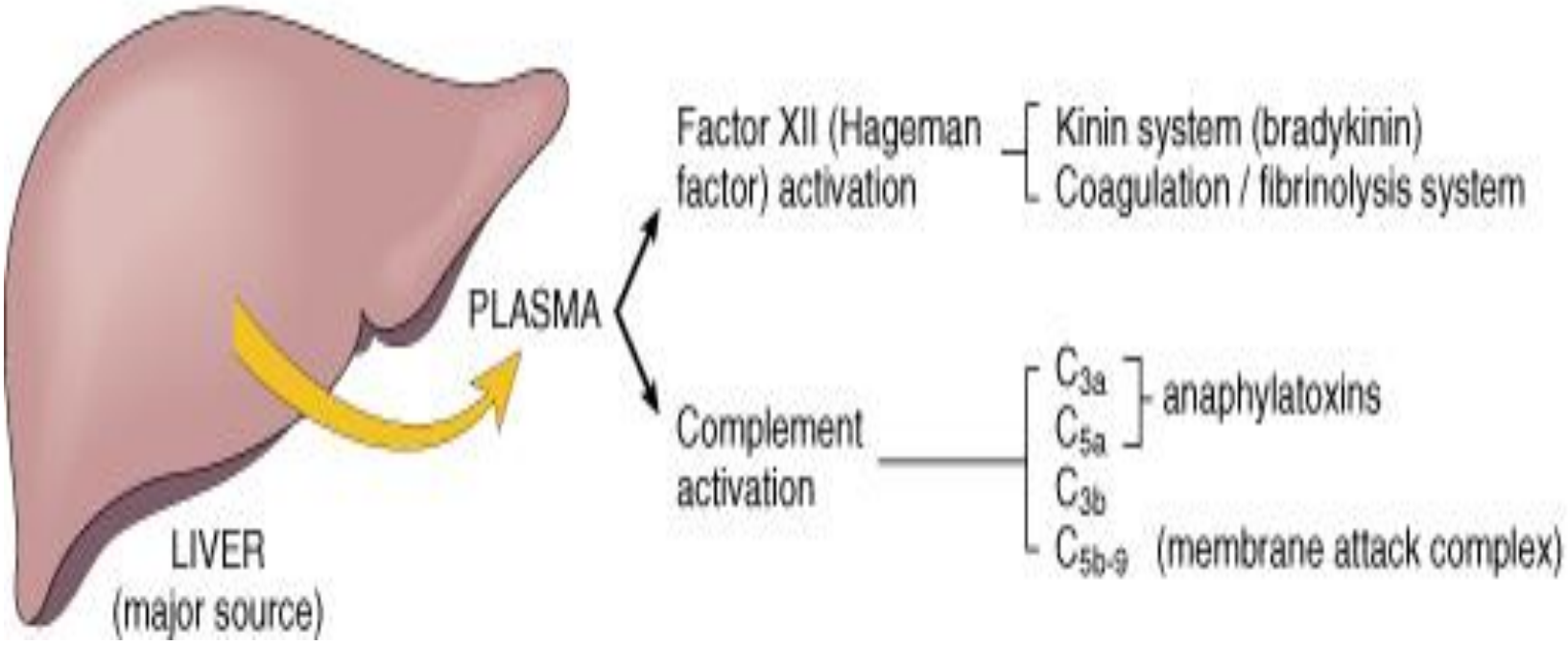
Regulates vessel tone

Modulates vascular permeability

Chemical mediators of inflammation: Plasma protein derived

Chemical Mediators of Inflammation

- Cell-Derived
- Plasma-Protein-Derived



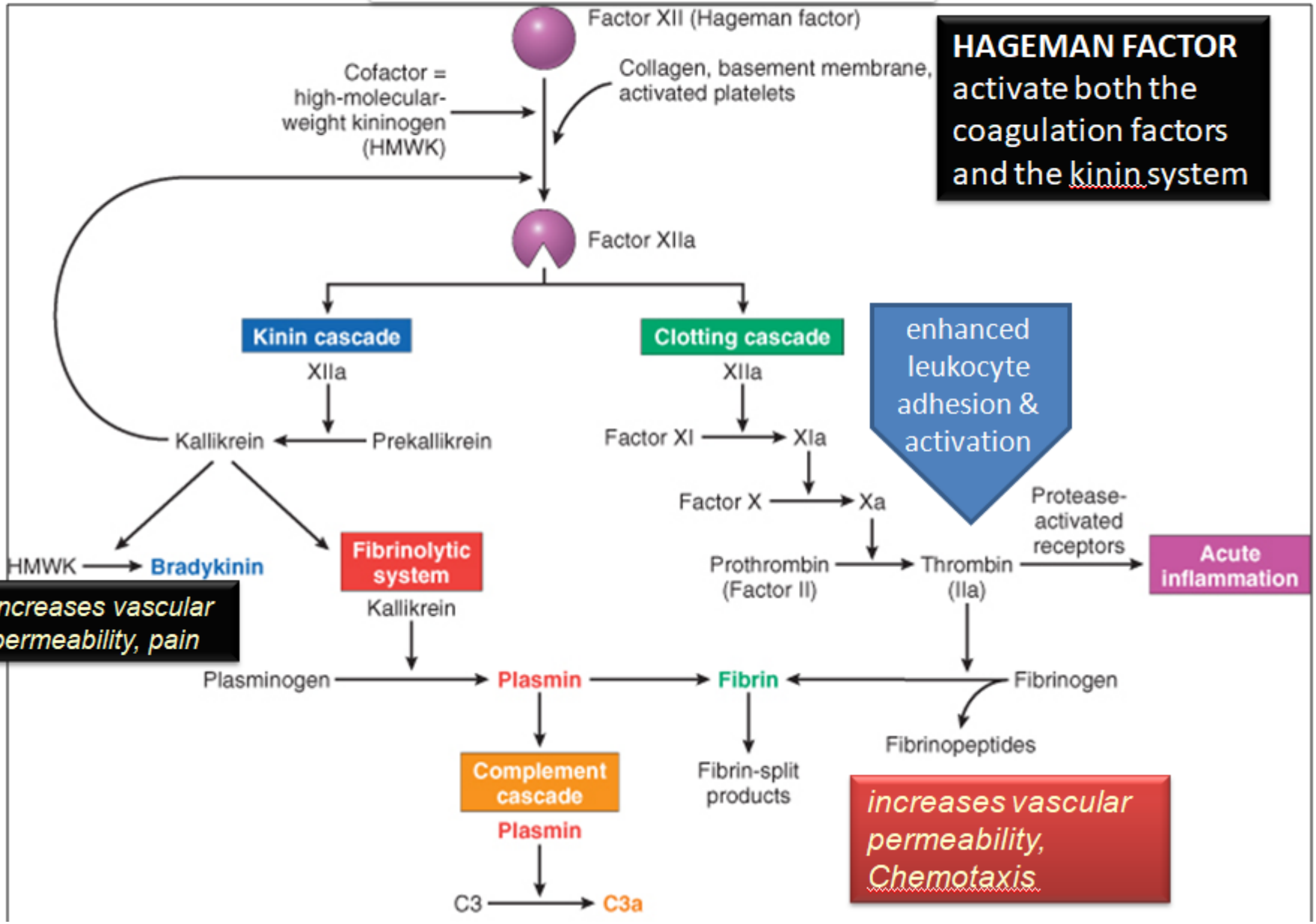
PLASMA PROTEASES

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

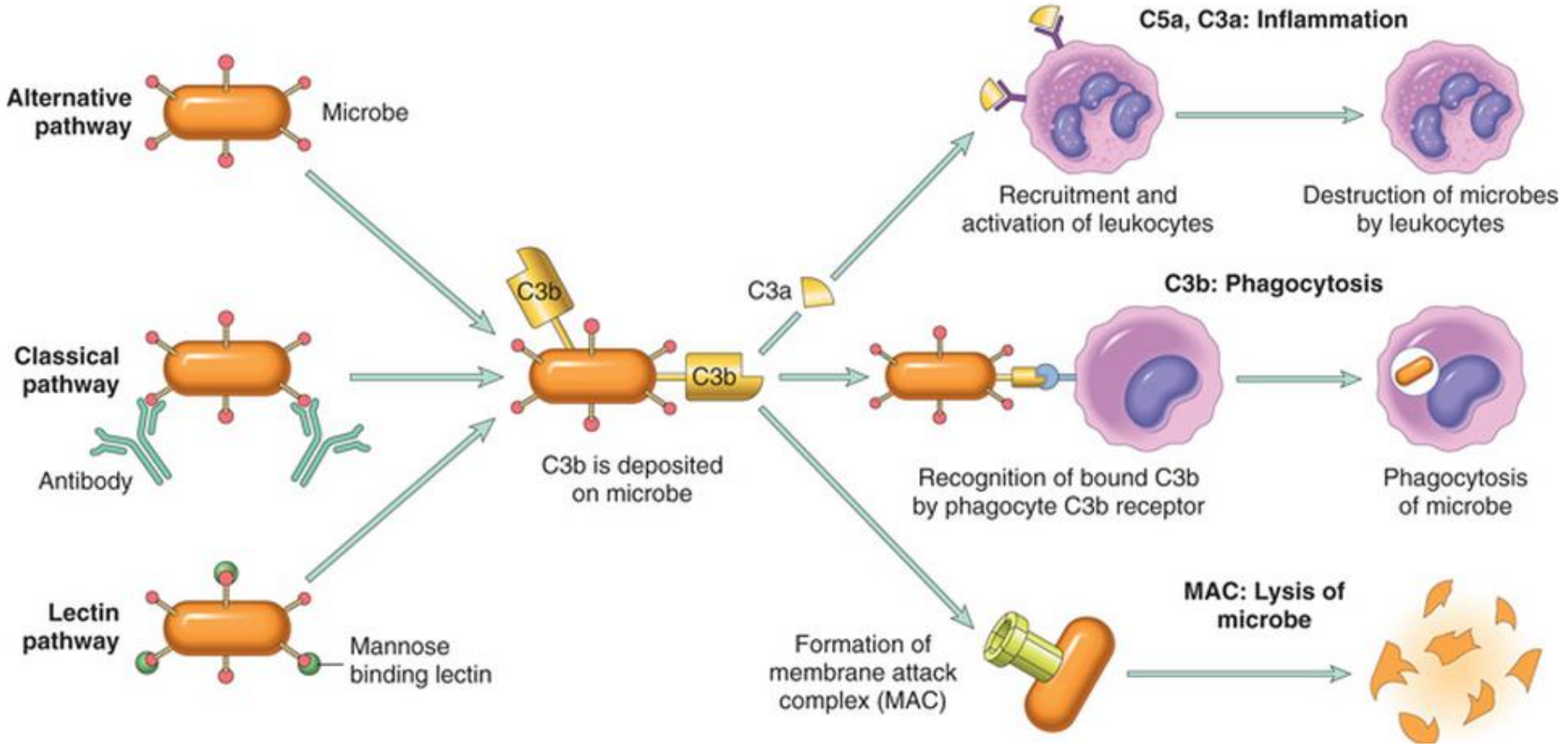
1. Kinin
2. Complement
3. Clotting systems

Chemical mediators of inflammation: Plasma protein derived

Kinin & clotting systems



Complement System



Complement protein

C3a & C5a → Increase vascular permeability
(anaphylatoxins)

C5a → Chemotaxis

C3b → Opsonization

C5-9 → membrane attack complex

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

Systemic effects of Inflammation

- Acute phase reaction/response
  - IL-1 and TNF
    - Fever
    - Malaise
    - Anorexia
- Bone marrow
  - IL-1 + TNF
    - Leukocytosis
- Lymphoid organs
- Liver
  - IL-6, IL-1, TNF
    - Acute phase proteins
      - C-reactive protein
      - Lipopolysaccharide binding protein
      - Serum amyloid A
      - a-2 macroglobulin
      - Haptoglobin
      - Ceruloplasmin
      - fibrinogen

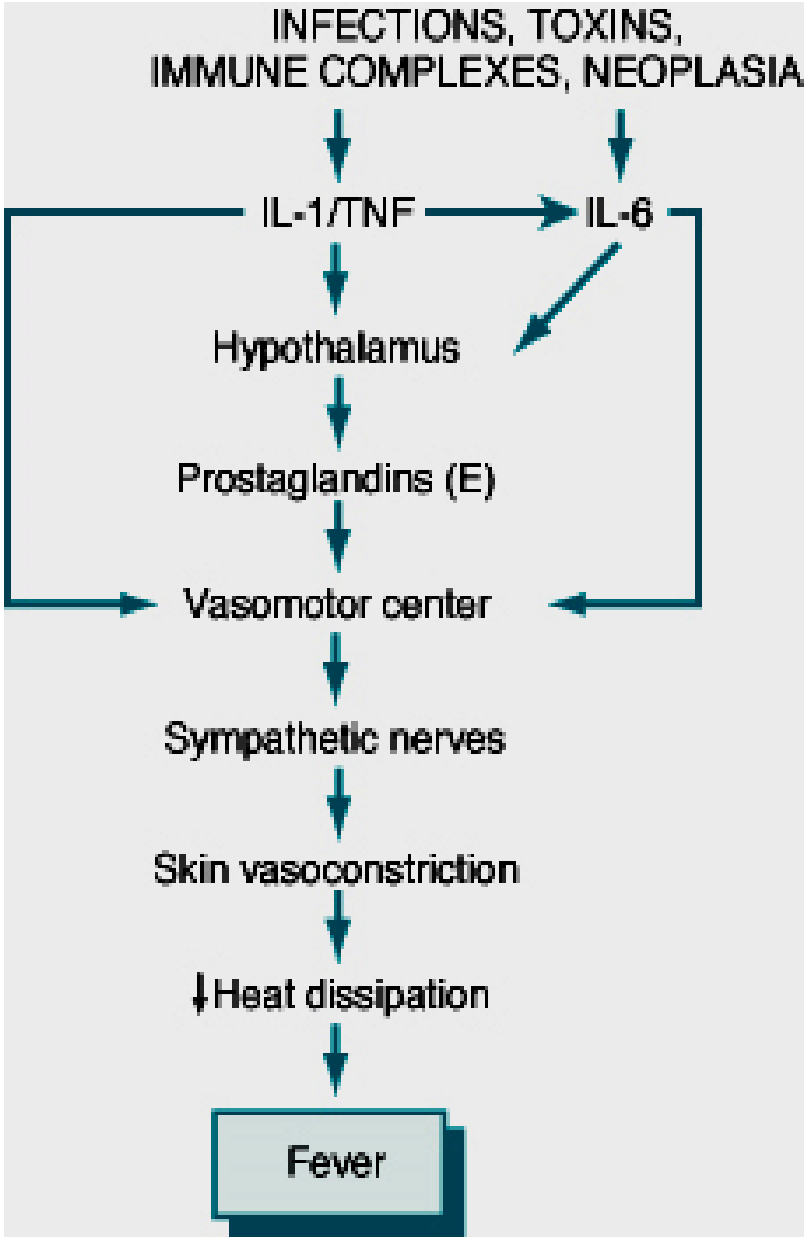
Fever
Produced in response to Pyrogens

- Types of Pyrogens:
  - **Exogenous pyrogens:**
    Bacterial products
  - **Endogenous pyrogens:**
    IL-1 and TNF
- Bacterial products stimulate leukocytes to release cytokines such as IL-1 and TNF that increase the enzymes (cyclooxygenases) that convert AA into prostaglandins.

Fever

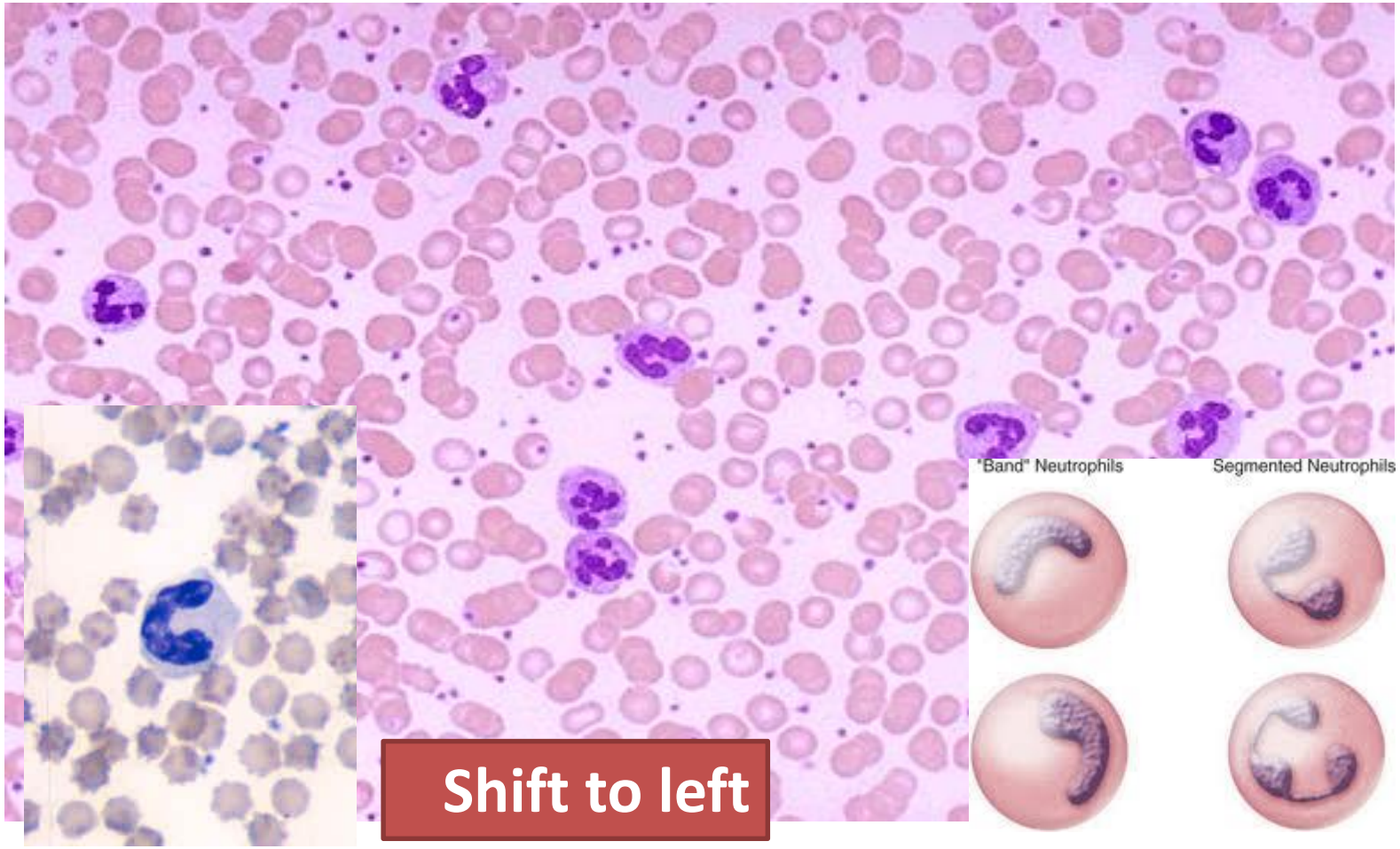
- In the hypothalamus, the prostaglandins, especially PGE_2, stimulate the production of neurotransmitters such as cyclic AMP, which function to reset the temperature set-point at a higher level.

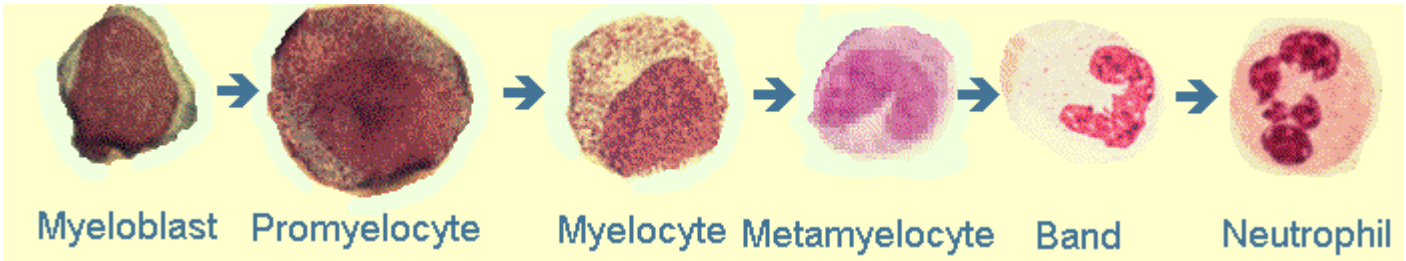
- NSAIDs, including aspirin , reduce fever by inhibiting cyclooxygenase and thus blocking prostaglandin synthesis.



Systemic manifestations of inflammation

Leukocytosis





Inflammation
Systemic Manifestations

Leukocytosis:

WBC count climbs to 15,000 or 20,000 cells/µl

most bacterial infection (Neutrophil)

Lymphocytosis:

Infectious mononucleosis, mumps, German measles

Eosinophilia: **bronchial asthma, hay fever, parasitic infestations**

Leukopenia: **typhoid fever, infection with rickettsiae/protozoa**

Systemic manifestations of inflammation

Acute Phase Proteins

Acute Phase Proteins are normally found in the blood at low concentrations, but following hepatic stimulation by IL-6 their concentration increases

Detection of elevated levels of acute phase proteins is an indication of an inflammatory response

- C-reactive protein (CRP)
- Lipopolysaccharide binding protein
- Serum amyloid A (SAA)
- a-2 macroglobulin
- Haptoglobin
- Ceruloplasmin
- fibrinogen

CRP and SAA, bind to microbial cell walls, and they may act as opsonins and fix complement

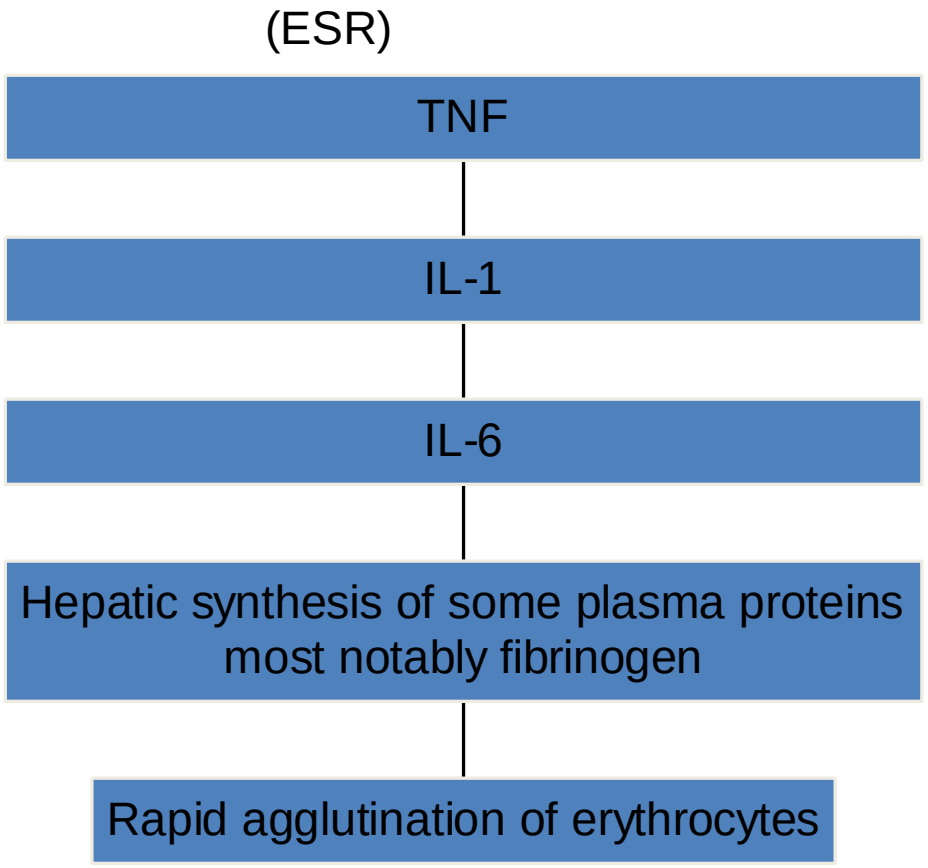
Acute phase proteins

- Elevated serum levels of CRP serve as a marker for acute inflammation and increased risk of myocardial infarction in patients with coronary artery disease.

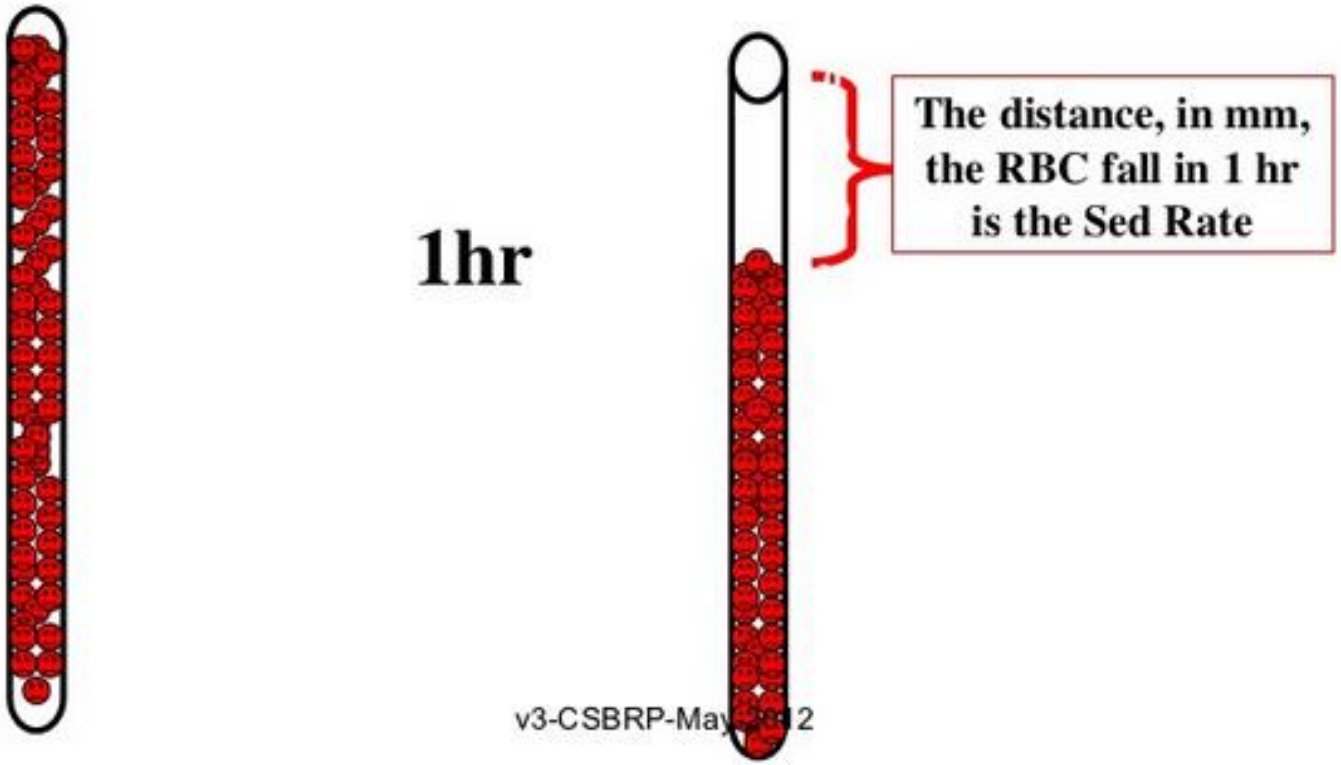
Prolonged production of these proteins (especially SAA) in states of chronic inflammation can cause:
secondary amyloidosis

Increased erythrocyte sedimentation rate (ESR)

- The rise in fibrinogen causes erythrocytes to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual erythrocytes.

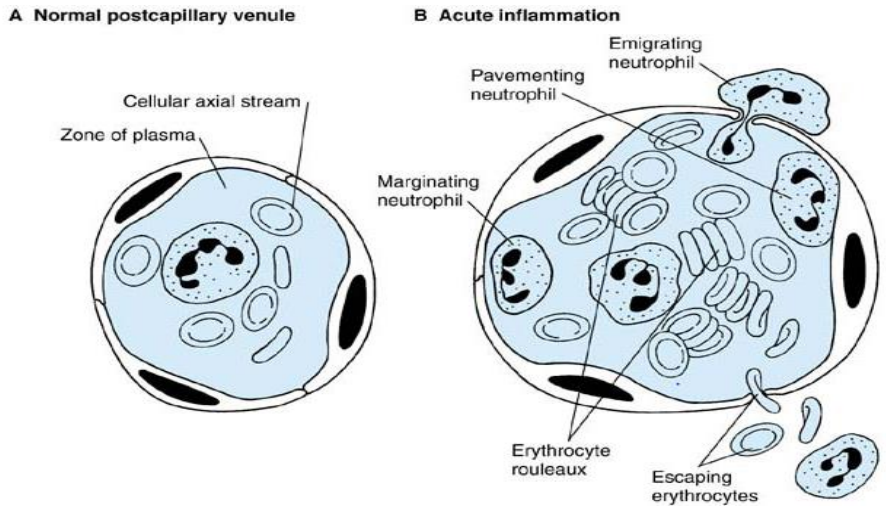


Erythrocyte Sedimentation Rate (ESR)



Erythrocyte sedimentation rate (ESR)

This is a simple test for an inflammatory response caused by any stimulus.



Fibrinogen binds to red cells and causes them to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual red cell

Summary

1. **Chemical mediator of inflammation**
2. **The systemic manifestations of inflammation include fever, leukocyte left shift, and acute phase reactants.**