

PATHOLOGY TEAMWORK


MED 444





Chemical mediators in inflammation and patterns of acute inflammation

OBJECTIVES

Editing file

-  **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**

-  **Recognize the different patterns of inflammation**

-  **List and describe the outcome of acute inflammation.**

COLOR INDEX:

MAIN TEXT (BLACK)

FEMALE SLIDES (PINK)

MALE SLIDES (BLUE)

IMPORTANT (RED)

DR'S NOTE (GREEN)

EXTRA INFO (GREY)

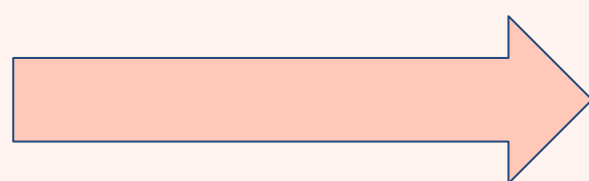
Chemical mediators of inflammation

we Really recommend you to watch this [Playlist](#) to Understand All of the Inflammation Chapters Perfectly

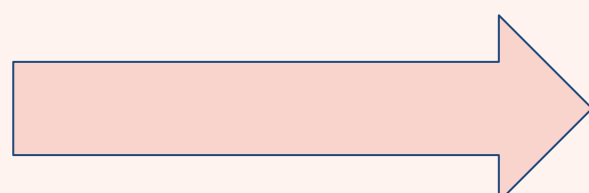
Mediators:

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

production of active mediators is triggered by:



microbial products



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

Mediator function is tightly regulated by:

Most mediators have the potential to cause harmful effects.
- **Therefore**, there should be a mechanism to checks and balances their action.

Decay
(e.g. AA metabolites)

inactivated by enzymes
(e.g. kininase inactivates bradykinin)

eliminated
(e.g. antioxidants scavenge toxic oxygen metabolites)

Source of chemical mediators

cell-derived:

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

against offending agents in **tissue**

Plasma-derived:

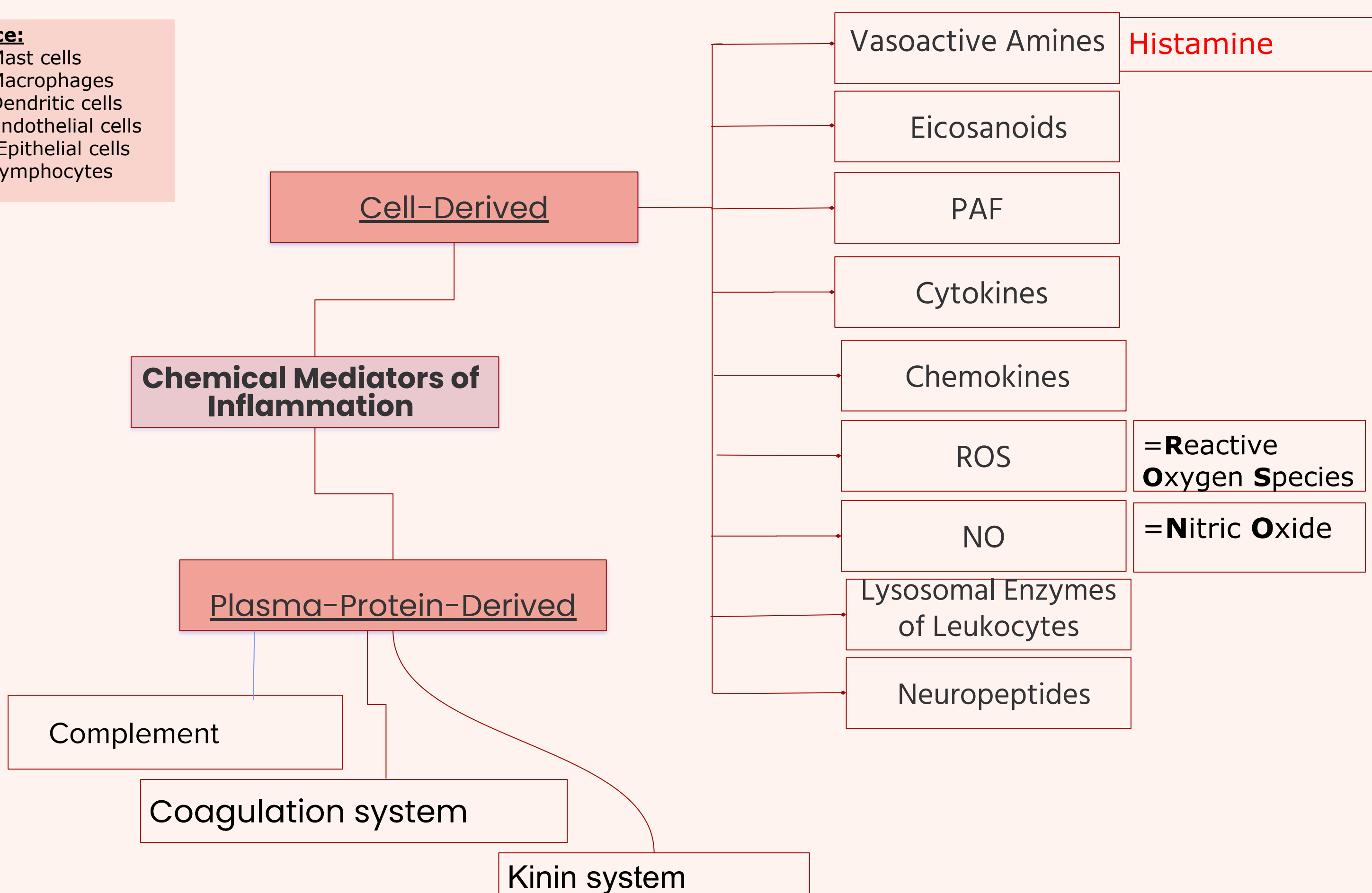
- 1- Complement
- 2- kinins
- 3-coagulation factors

Many in "pro-form" inactive requiring activation (enzymatic cleavage)

against circulating **microbes**

Source:

1. Mast cells
2. Macrophages
3. Dendritic cells
4. Endothelial cells
5. Epithelial cells
6. Lymphocytes



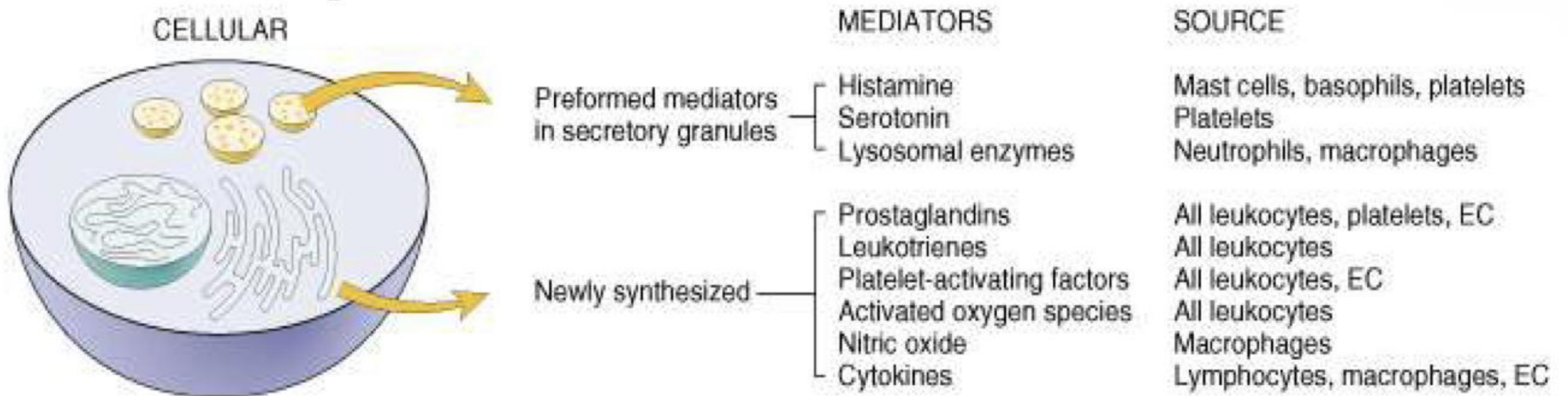
Chemical mediators of inflammation: cell derived



Cell-Derived Mediators

Girls slides have
 "Tissue macrophages
 Mast cells
 Endothelial cells
 Leukocytes"

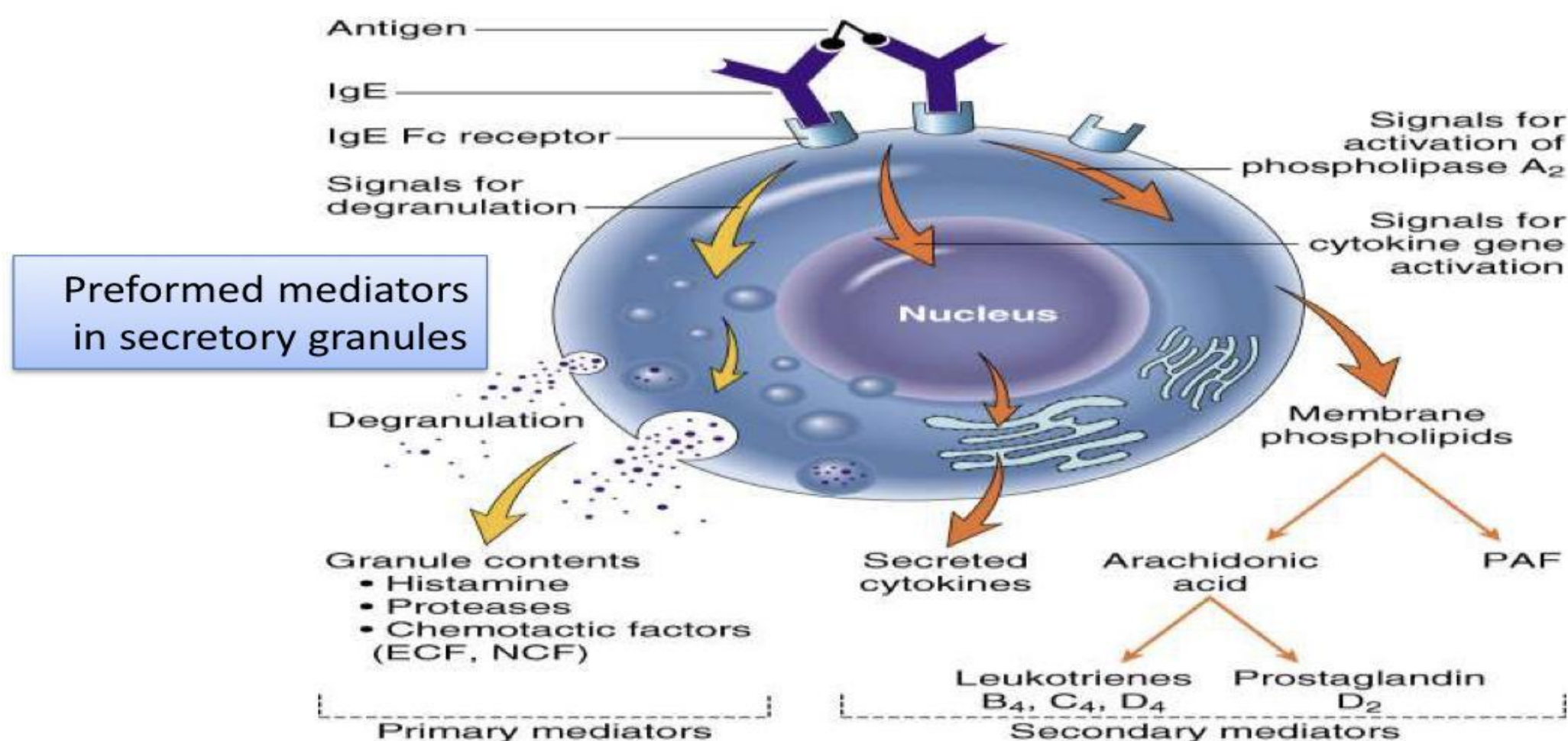
Producing cells:



Vasoactive Amines

Immune reaction involves linking of: Antigen IgE IgE Fc receptor. 439

Histamine & Serotonin Among first mediators in acute inflammatory reactions



Chemical mediators of inflammation: cell derived- preformed

Histamine

plays a major role in the early phase of acute inflammation and increases vascular permeability

Source:

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

Stimuli of Release:

- **Physical injury**
- **Immune reactions** (cross-linking of cell-surface IgE by antigen)
- **C3a and C5a fragments**
- **Cytokines** (e.g. IL-1 and IL-8) - **Neuropeptides**

Actions:

- 1-**ARTERIOULAR DILATION**
- 2-**INCREASED VASCULAR PERMEABILITY** (venular gaps)
- 3-**ENDOTHELIAL ACTIVATION**

Inactivated
by:
Histaminase

The **antihistamine** drugs that are commonly used to treat some inflammatory reactions e.g. **allergies** are **H 1 receptor antagonists** that bind to and **block the receptor**.

Serotonin (its function not really known).441 **(5-HT)**

Source: Platelets

Action:

- Neurotransmitter in the gastrointestinal tract
- a vasoconstrictor (the importance of this action in inflammation is unclear)

Stimulus: **Platelet aggregation**

5-HT receptors, 5-hydroxytryptamine receptors, or serotonin receptors, are a group of G protein-coupled receptor. 441

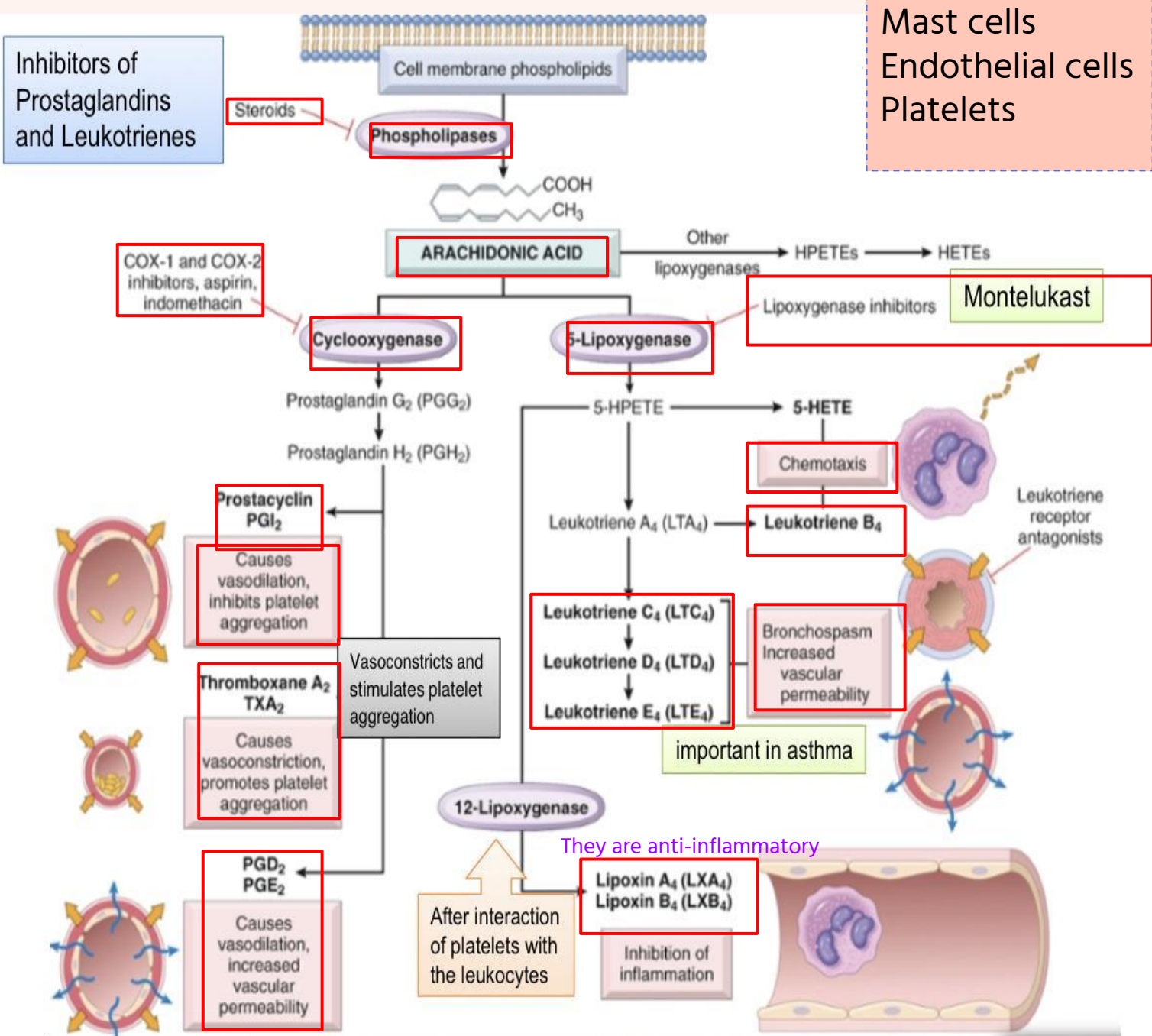
Note 439:

It is important to know things that are only synthesized by one source

Chemical mediators of inflammation: cell derived- newly synthesized

Arachidonic Acid Metabolites (eicosanoids)

Source:
Leukocytes
Mast cells
Endothelial cells
Platelets



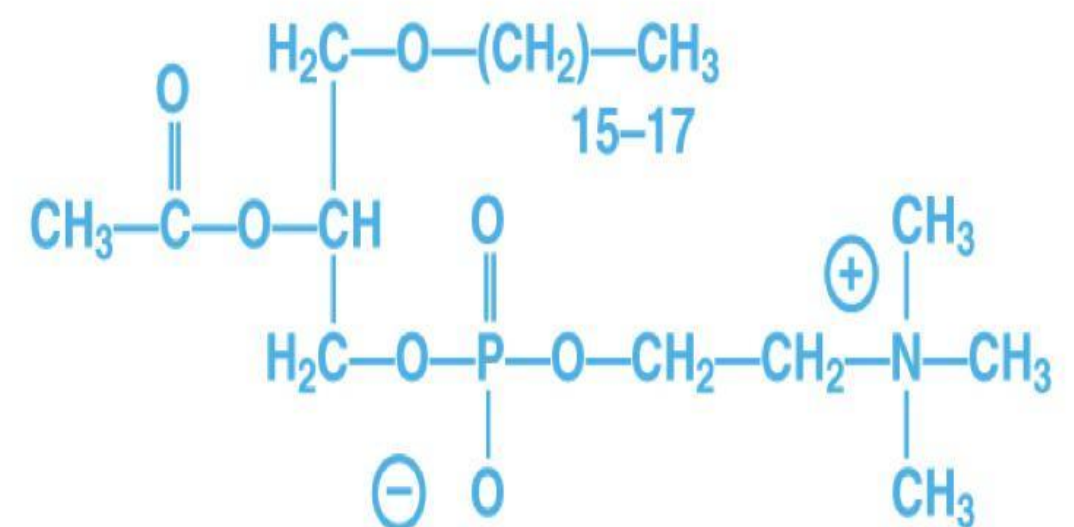
Platelet-Activating Factor (PAF)

SOURCES

Mast cells/basophils
Neutrophils
Monocytes/macrophages
Endothelium
Platelets
Others

MAJOR INFLAMMATORY ACTIONS

Increased vascular permeability
Leukocyte aggregation
Leukocyte adhesion
Leukocyte priming/chemotaxis
Platelet activation
Stimulation of other mediators (LT, O₂⁻)



PLATELET-ACTIVATING FACTOR

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 , HETE
Smooth muscle contraction	Prostaglandins PGC ₄ , PGD ₄ , PGE ₄

Prostaglandins affect thermoregulatory center of CNS in hypothalamus and cause fever. Note:441

Chemical mediators of inflammation: cell derived- newly synthesized

Cytokines Polypeptides

Source:
Lymphocytes
Macrophages
Dendritic cells
Endothelial cells
Epithelial cells

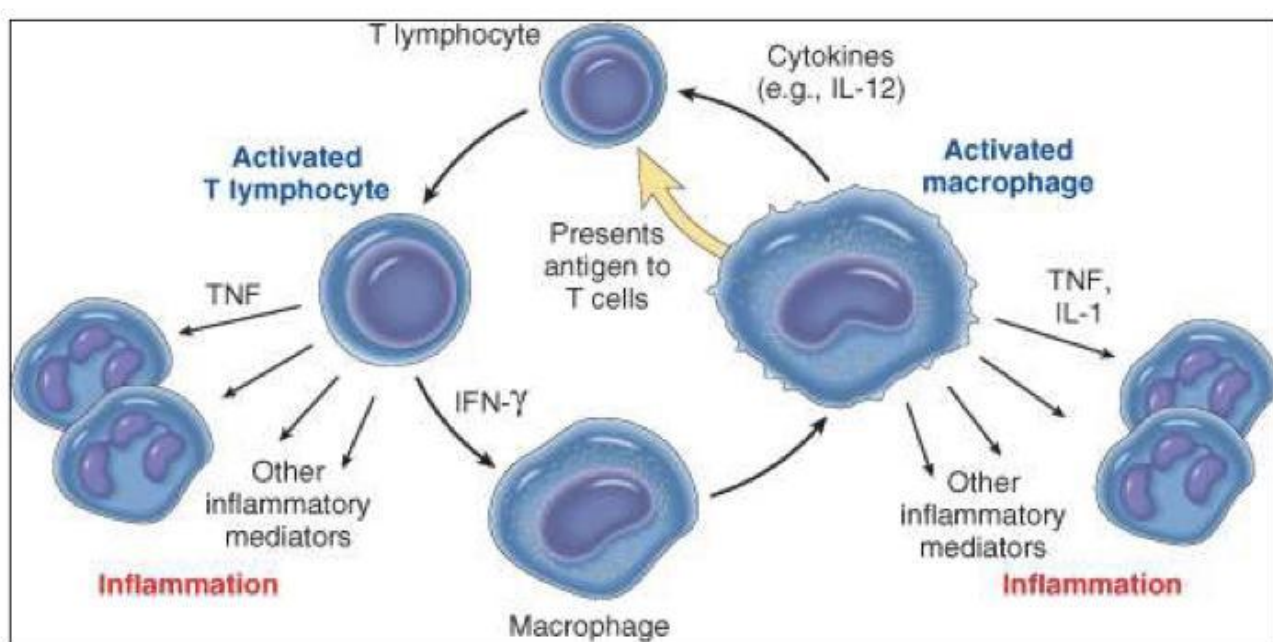
Actions:

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

Interferons have many uses in medicine especially in hepatitis. Note:441

Cytokines of Chronic Inflammation:
Interferon- γ (INF- γ) & Interleukin (IL-12)

Cytokine of Acute inflammation:
Interleukin (IL-1 and IL-6) & tumor necrosis factor (TNF)



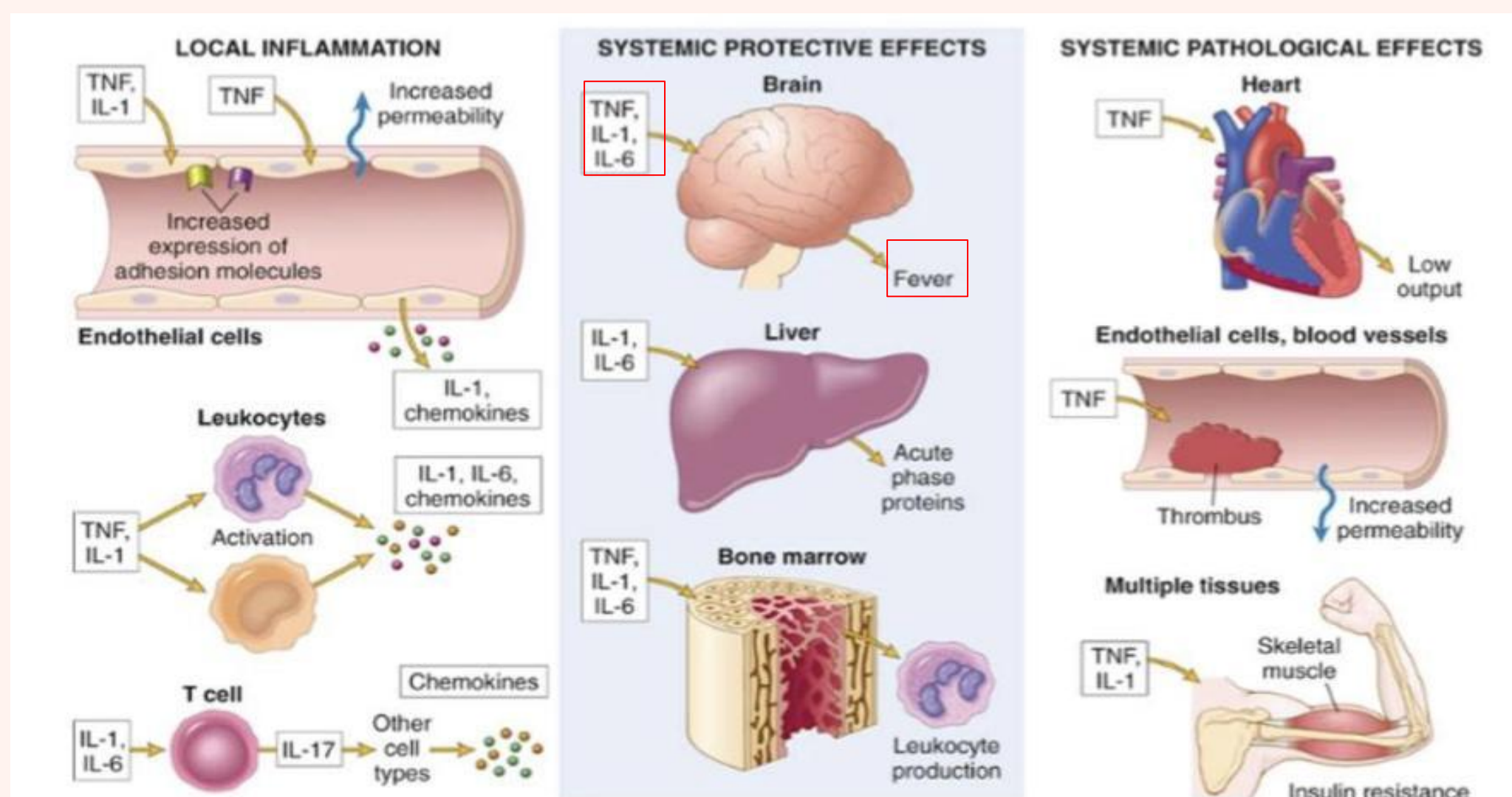
Activated lymphocytes and macrophages influence each other and also release inflammatory mediators that affect other cells.

Action:

- Local Stimulates expression of endothelial adhesion molecules and secretion of other cytokines;
- systemic effects (ex, fever)

Major roles of cytokines in acute inflammation

TNF antagonists is effective in the treatment of rheumatoid arthritis



Chemical mediators of inflammation: cell derived- newly synthesized

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

Chemokines play major role in chemotaxis and leukocyte activation. No chemotaxis no defense against inflammation no migration of leukocyte from blood vessels to the tissue.441

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)

Reactive Oxygen Species

Synthesized via:

NADPH oxidase pathway

Source:

Neutrophils and Macrophages

Stimuli of release:

- Microbes
- Immune complexes
- Cytokines

Action:

Microbicidal (cytotoxic) agent

Oxidative action make tissue injury but kill the bacteria. Note:441

1

2

3

4

Nitric Oxide (NO)

Short-lived Soluble free-radical gas

Functions:

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

Neuropeptides

Small proteins

Secreted by nerve fibers mainly in lung & GIT

Initiate inflammatory response

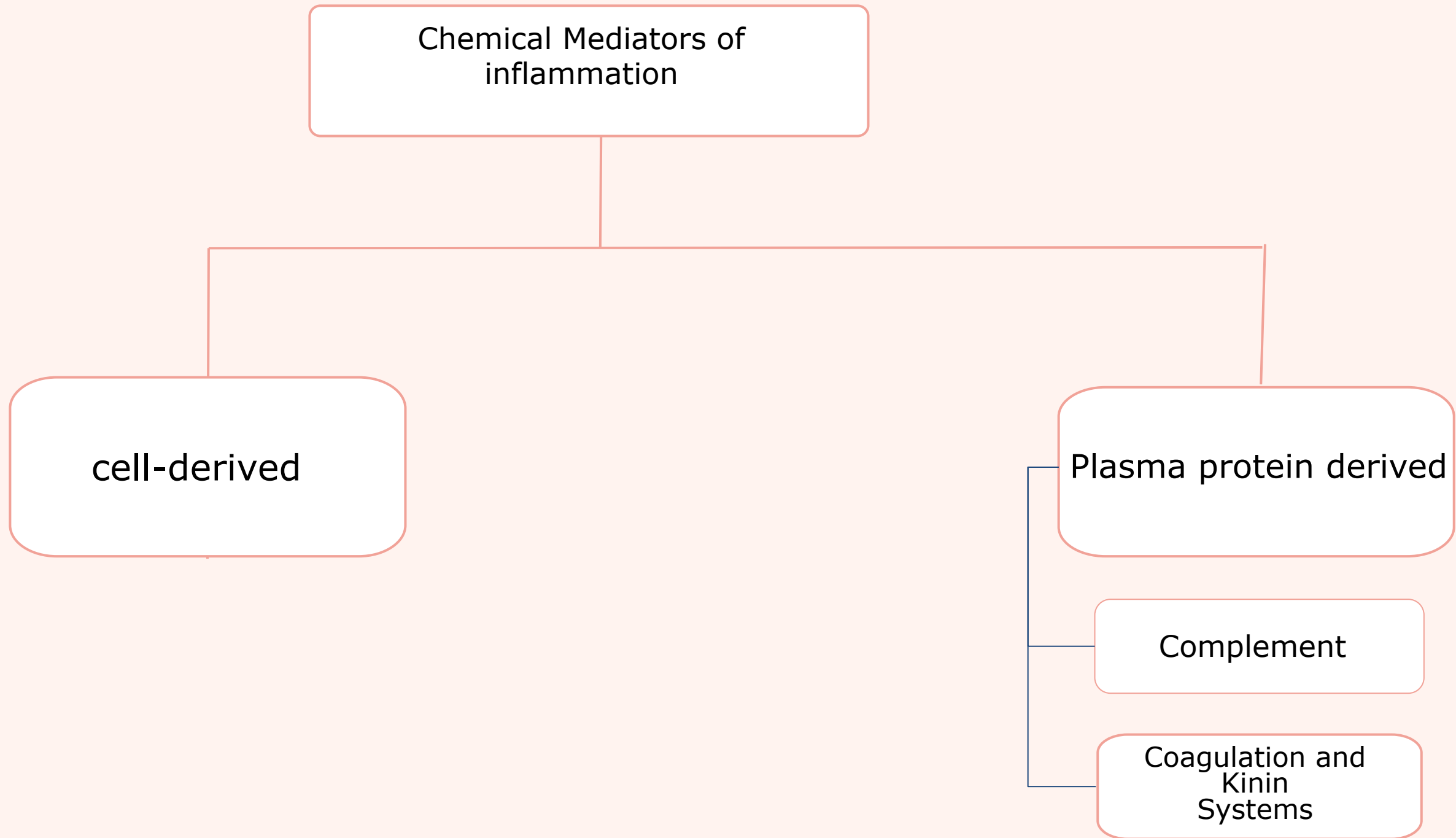
e.g. Substance P :

Transmits pain signals

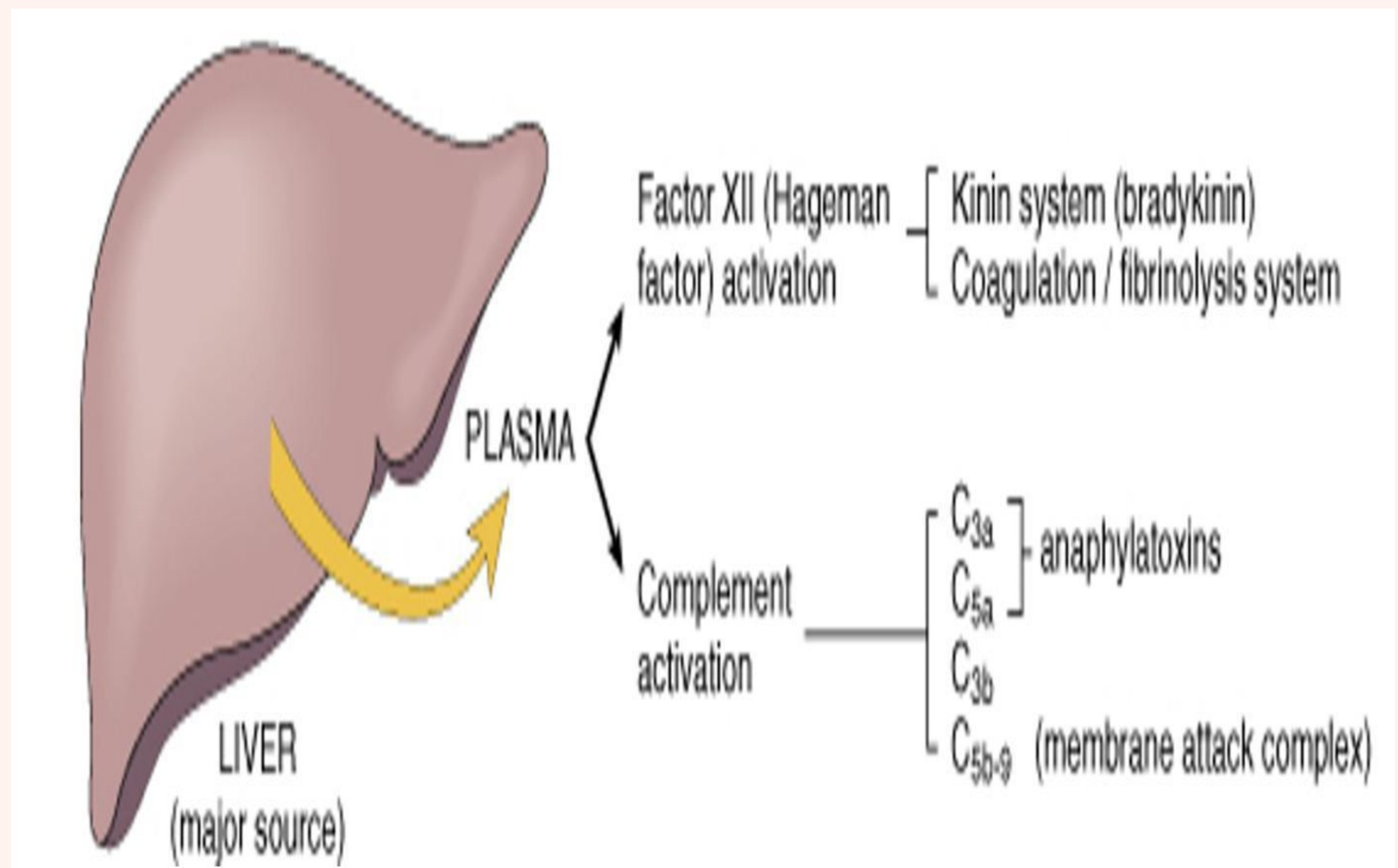
Regulates vessel tone

Modulates vascular permeability

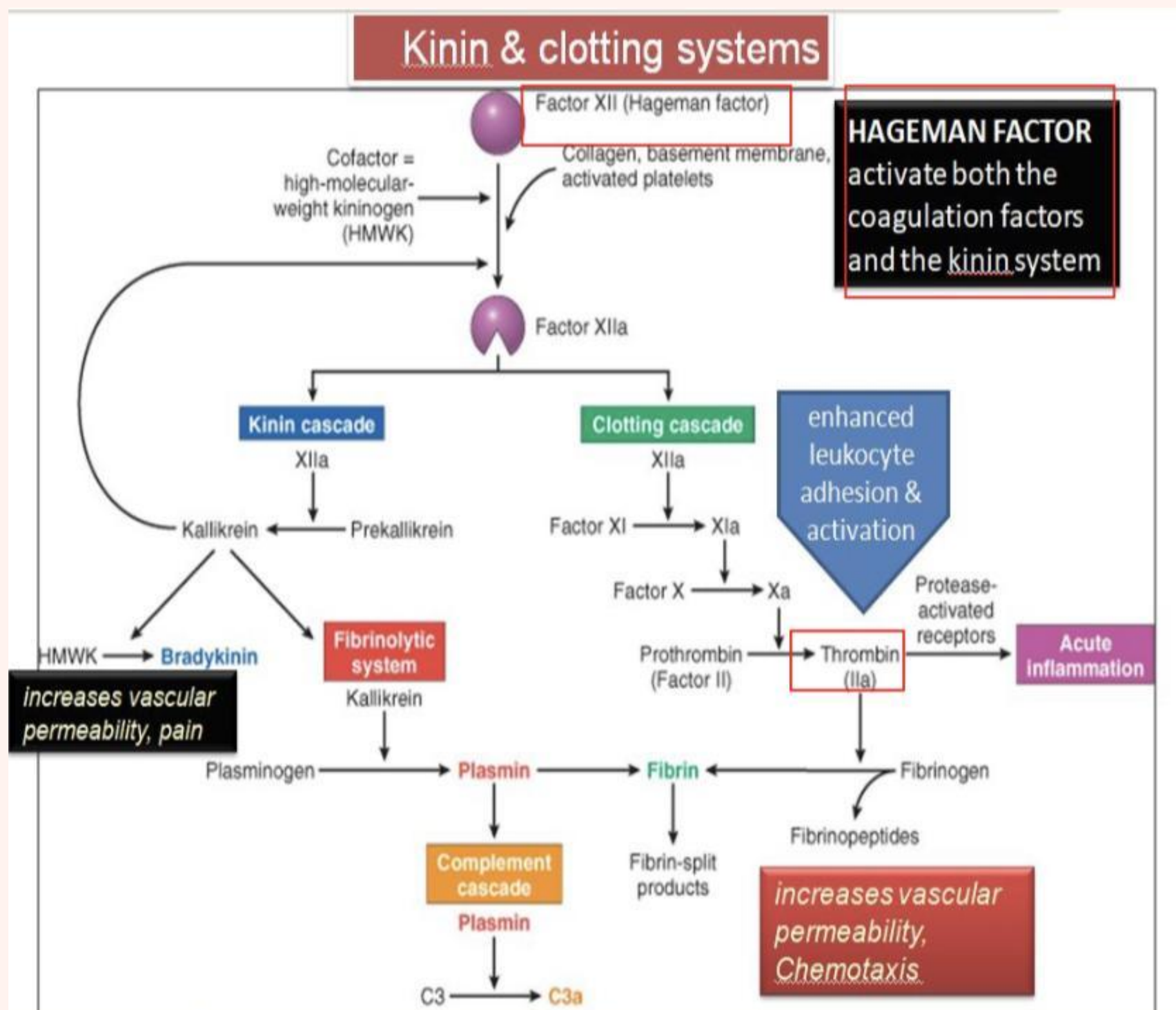
Chemical mediators of inflammation



1. Clotting systems
2. Kinin
3. Complement

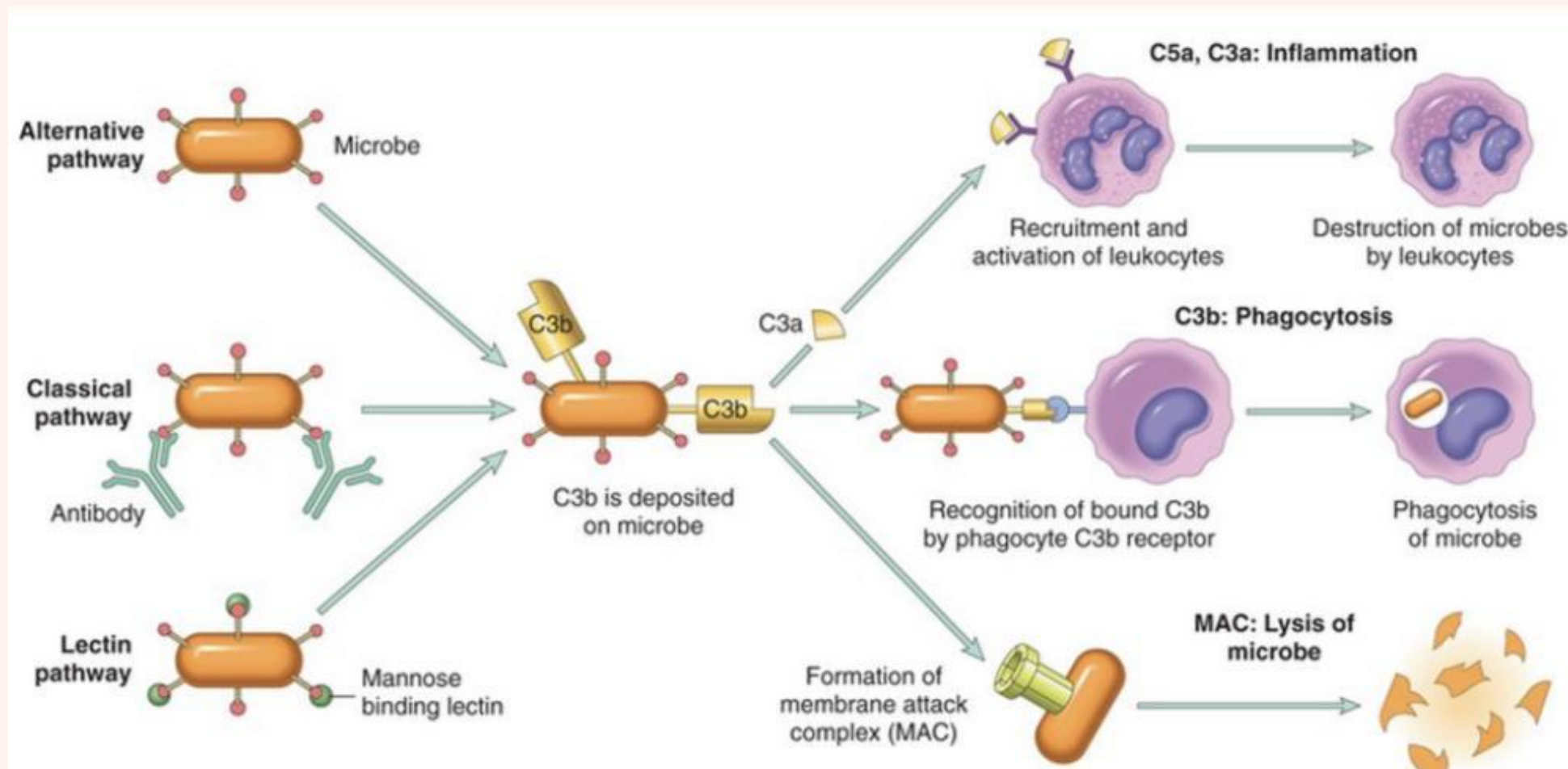


Kinin and Clotting systems



For more info: Kinin-kallikrein system is a hormonal system that plays a major role in inflammation, blood pressure control, coagulation, pain and cellular proliferation. Bradykinin Increases Vascular Permeability (Pain)

Complement System



C3a & C5a → Increase vascular Permeability (anaphylatoxins)
C5a → Chemotaxis

C3b → Opsonization
C5-9 → membrane attack complex (MAC), lead to bacterial lysis

Role Mediators in Different Reactions of Inflammation

Vasodilation	Prostaglandins Histamine (vasoactive amine) Nitric oxide
Increased vascular permeability	Vasoactive amines Bradykinin - Leukotrienes C4, D4, E4 PAF - Substance P
Chemotaxis, leukocyte recruitment and activation Important	C3a, C5a - Leukotriene B4 Chemokines (IL-1, TNF)
Opsonization	IgG, C3b
Fever	IL-1, TNF - Prostaglandins
Pain	Prostaglandins - Bradykinin
Tissue damage	Neutrophil and macrophage lysosomal enzymes Oxygen metabolites and Nitric oxide

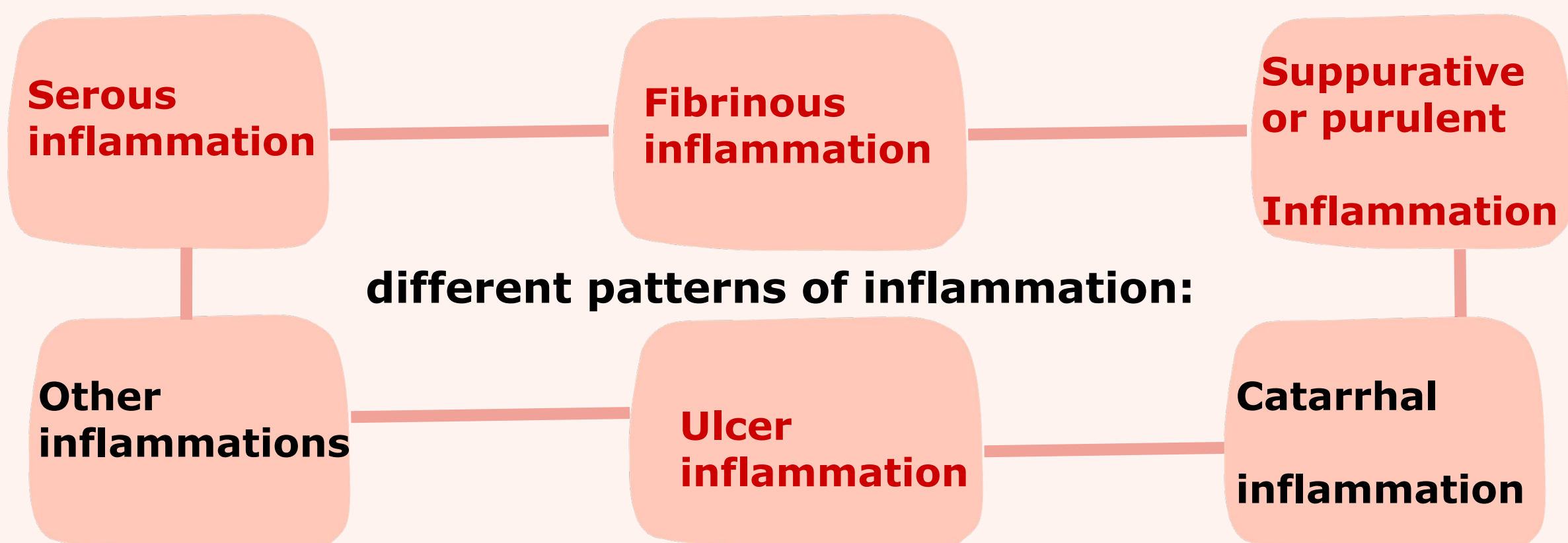
very important

Bold highlighted are very important as doctor said but memorize all of them

Morphologic Patterns of Acute Inflammation

Several types of inflammation vary in their morphology and clinical correlates. Why?

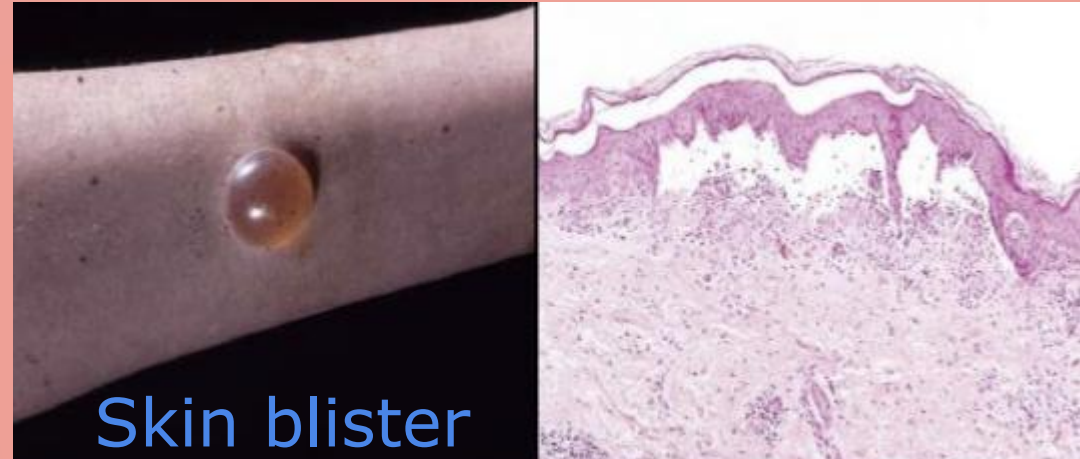
- The severity of the reaction
- The particular tissue
- Specific cause
- Site involved



different patterns of inflammation

Sites:

- Body cavities (peritoneum, pleura, or pericardium)
- Skin

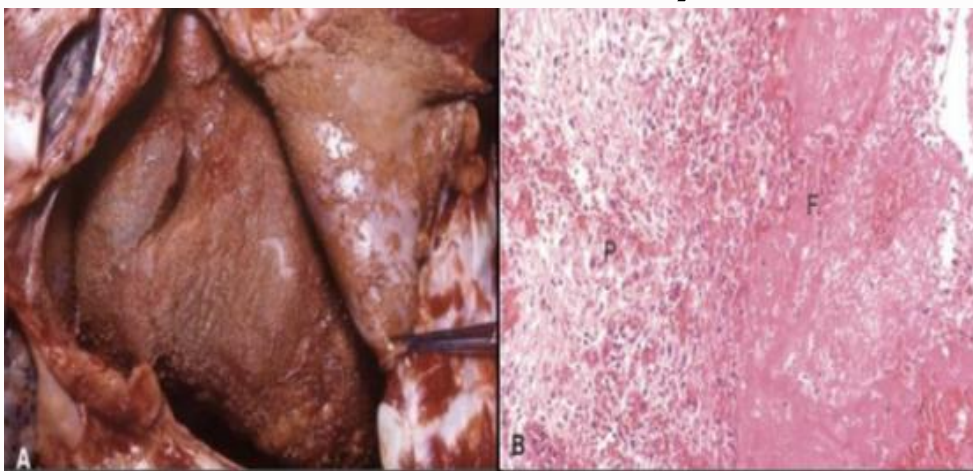


Skin blister

Serous inflammation

marked by the outpouring of a thin fluid

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)



Fibrinous inflammation

- Fibrinous exudates may be removed by fibrinolysis.
- if not: it may stimulate the ingrowth of granulation tissue (organization)



Catarrhal inflammation

Inflammation Affects Mucosa-lined surfaces with the outpouring of watery mucus.

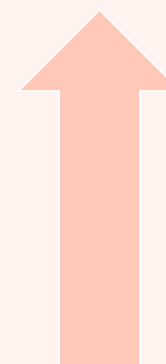
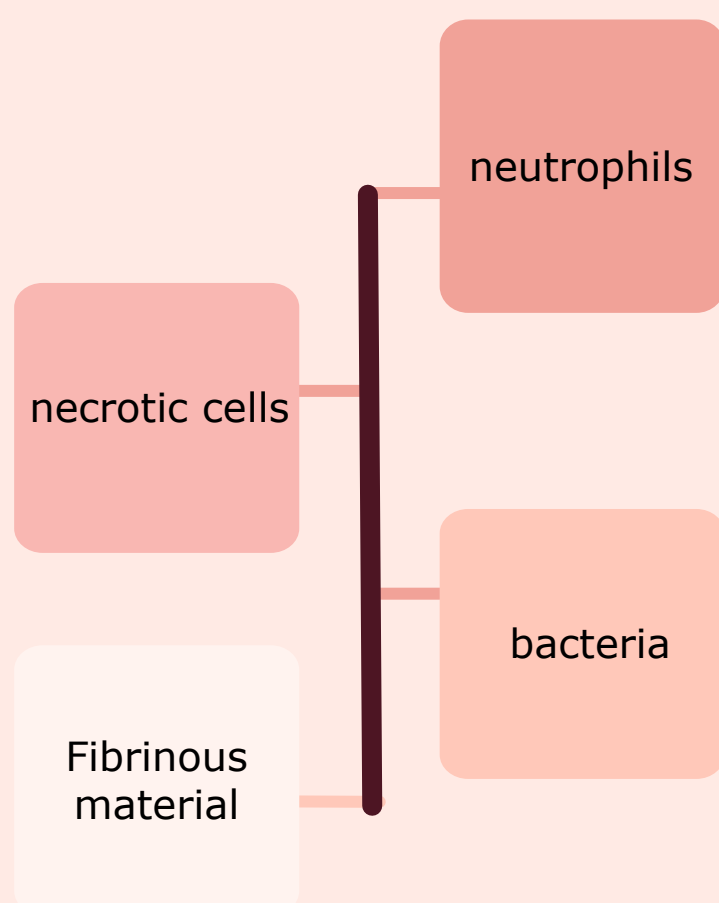
different patterns of inflammation

Suppurative or Purulent inflammation

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

Purulent inflammation is characterized by the production of pus, an exudate consisting of neutrophils, the liquefied debris of necrotic cells, and edema

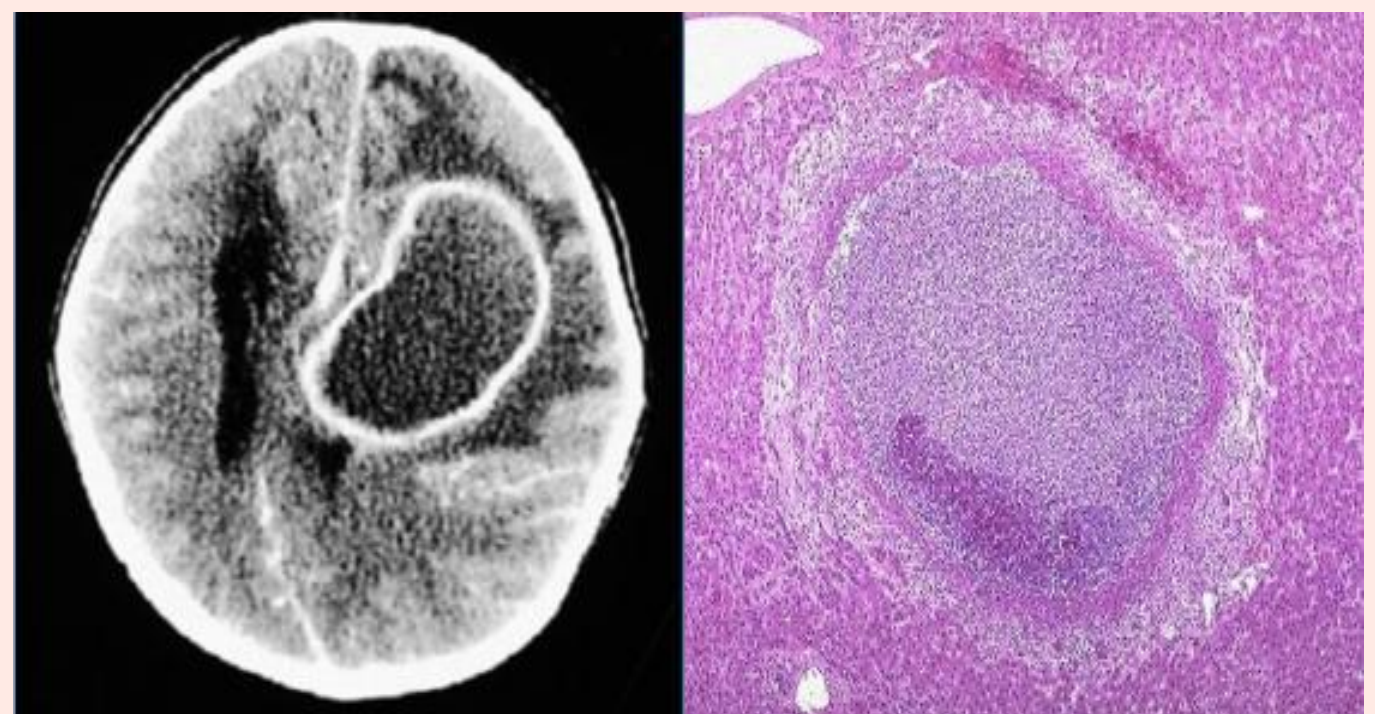
An abscess is a cavity lined by granulation tissue and containing:



An enclosed collection of pus consists of a mixture of neutrophils and necrotic debris

Morphologic Patterns of Acute Inflammation:

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



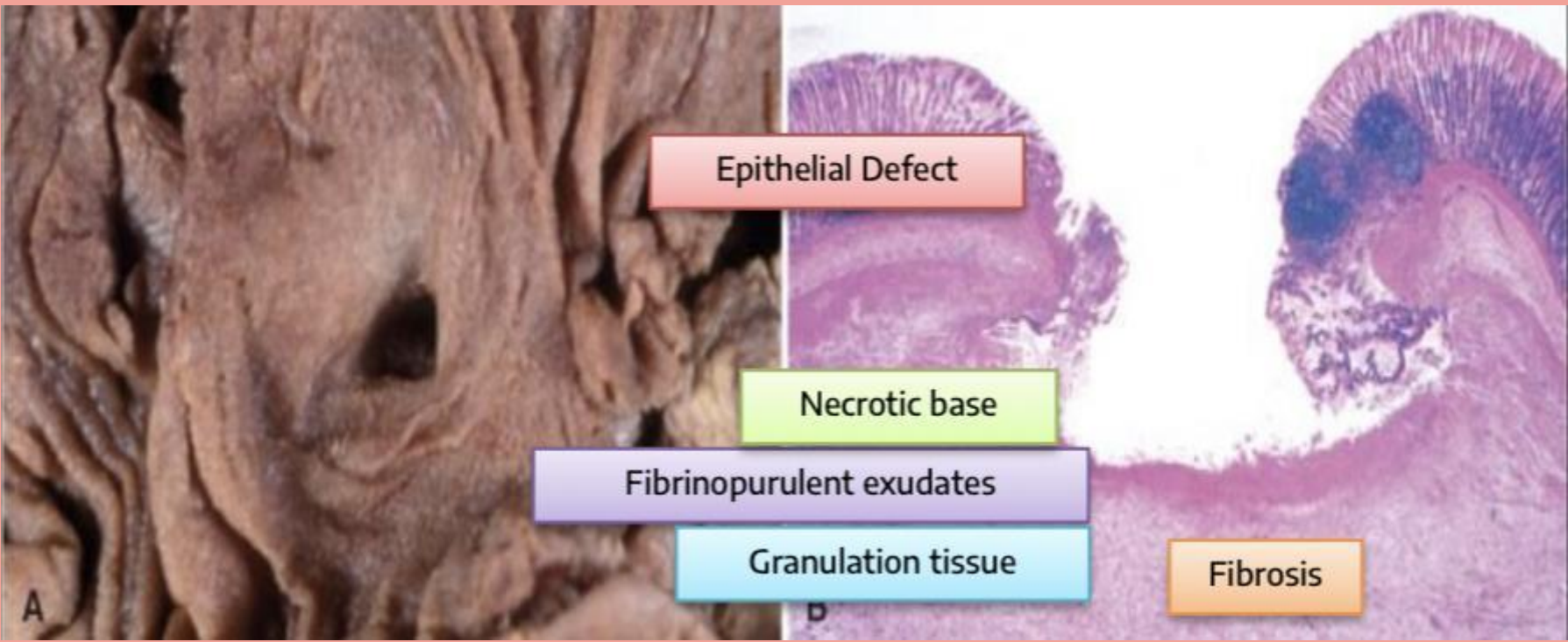
consisting of, containing, or discharging pus
صدید أو خراج



different patterns of inflammation

Ulcer inflammation

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.



Other inflammations

Sinus

A tract between the abscess and a surface (skin).

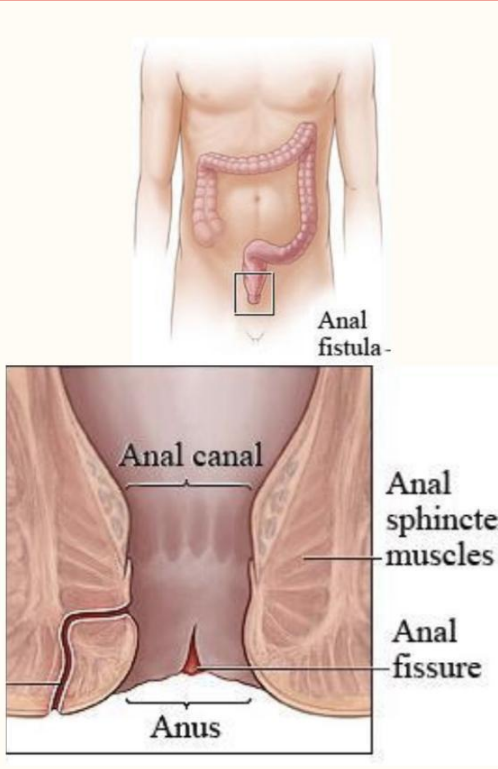
has one channel, and drains outside. (Team439)



Fistula

A tract between two surfaces.

has two channels (Team439)



Cellulitis

denotes a spreading of acute inflammation through interstitial tissues.

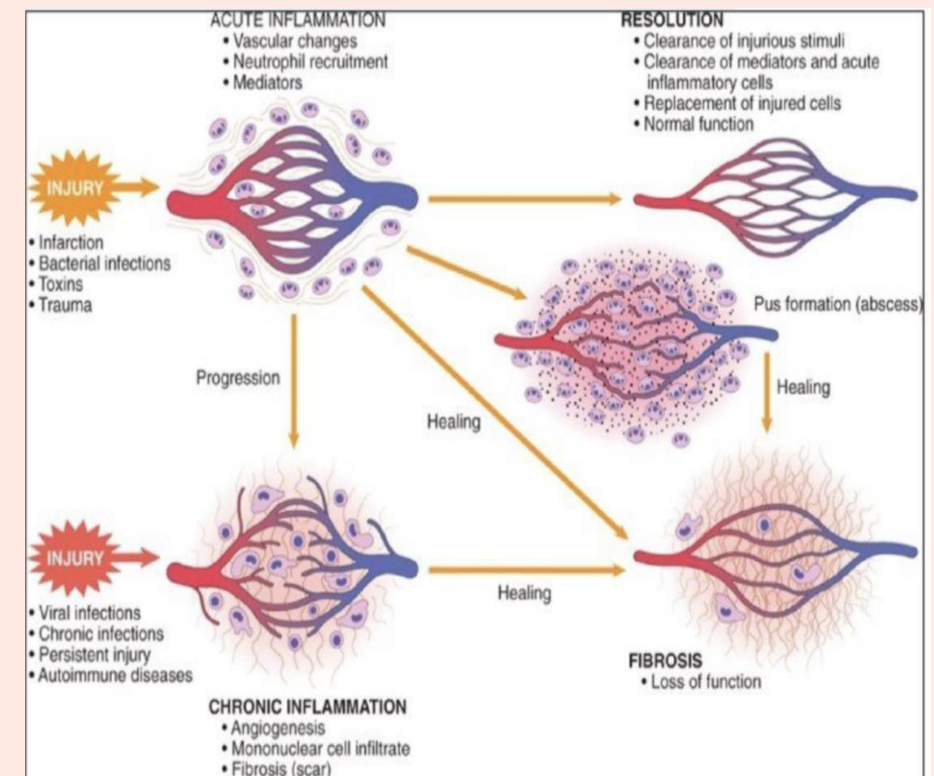


*to separate in the form of dead tissue from living tissue.

different patterns of inflammation

Acute inflammation may have one of the four outcomes:

1. Complete **resolution** (شفاء كامل)
2. Healing by connective tissue replacement (**fibrosis**) (تليف)
3. **Progression** of the tissue response to chronic inflammation (التطور إلى التهاب مزمن)
4. **Abscess** formation (تكون خراج)



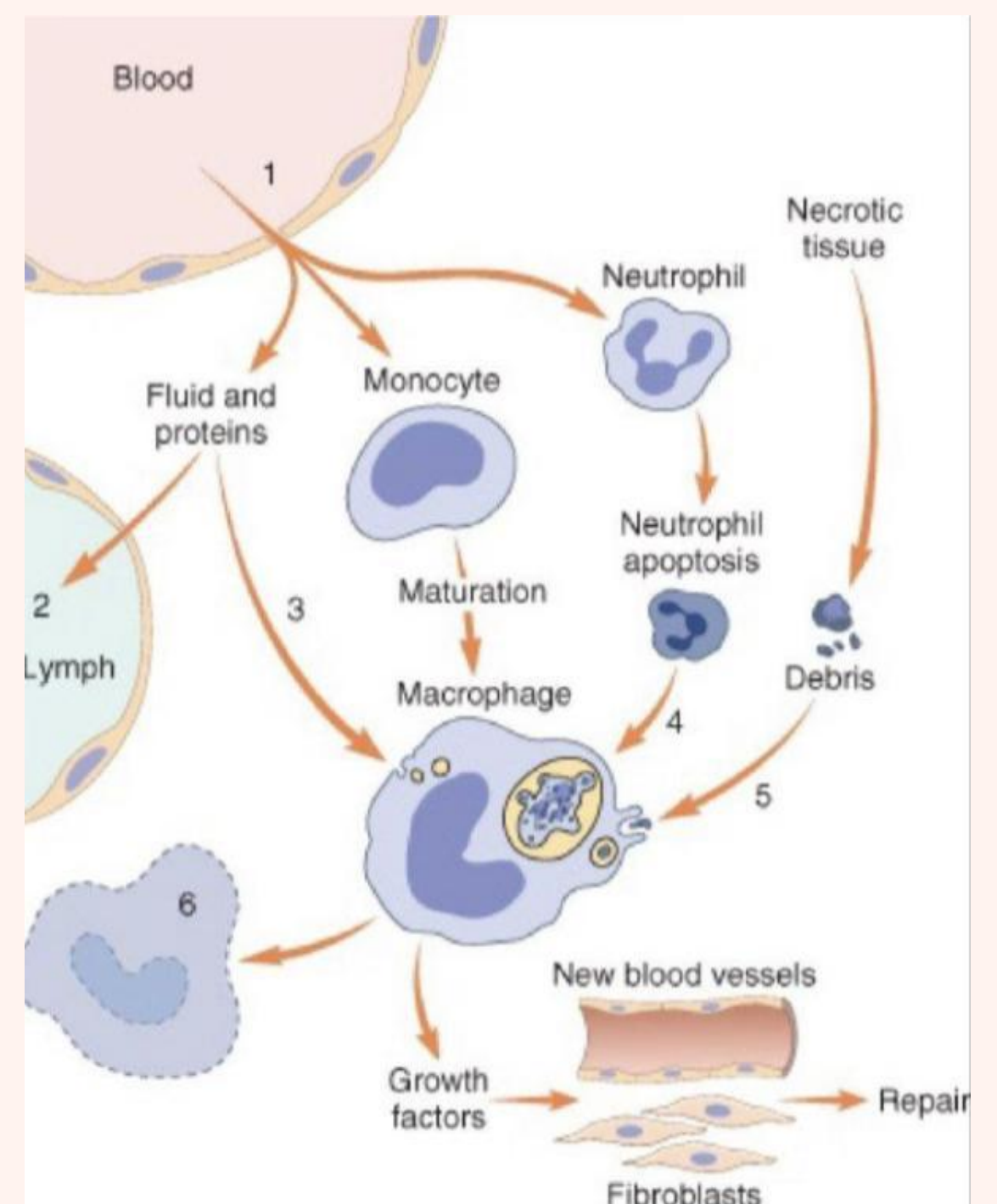
Events in the resolution of inflammation:

2. The necrotic debris, edema fluid, and inflammatory cells are cleared by phagocytes and lymphatic drainage.

- 1
- 2
- 3

1. Neutralization, decay, or enzymatic degradation of the various chemical mediators: normalization of vascular Permeability, and cessation* of leukocyte emigration and apoptosis.

3. Lymph node become enlarged and inflamed



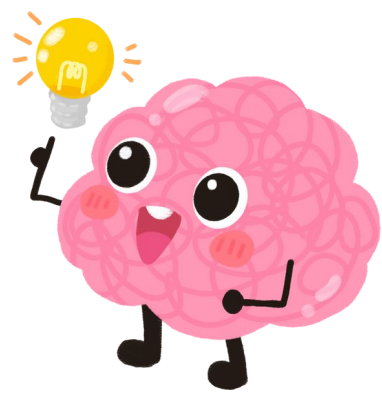
*process of ending or being brought to an end

Chemical Mediators

Chemical mediator	Source	Function
Histamine	Mast cells, circulating basophils, and platelet	-Arteriolar Dilation -Increased vascular permeability -Endothelial Activation
Serotonin	Platelets	Platelet aggregation
arachidonic acid	Released from the cell membrane	Pro-Inflammatory Mediator
Cytokines (TNF, IL-1...)	Lymphocytes Macrophages Dendritic cells Endothelial cells Epithelial cells	inflammatory reactions
Chemokine	-	Leukocyte recruitment & activation
Reactive Oxygen Species.	Neutrophils and Macrophages	Microbicidal (cytotoxic) agent
Nitric Oxide (NO)	-	Vasodilation Antagonism of platelet activation
Neuropeptides	Secreted by nerve fibers	Initiate inflammatory response

Take home message

- 1. Chemical mediators of inflammation are substances produced during inflammation inducing a specific events in acute inflammation including vasodilation, increased vascular permeability, chemotaxis, leukocyte recruitment and activation, opsonization, fever, pain and tissue damage.**
- 1. There are different patterns of inflammation such are serous inflammation, suppurative inflammation, fistula formation , etc...**



KEYWORDS

Suppurative or Purulent inflammation	Characterized by the production of large amounts of pus (خراج) or purulent exudate consisting of neutrophils, necrotic cells, and edema fluid caused by pyogenic (pus-producing) bacteria.
Abscesses	A localized collections of purulent* inflammatory tissue caused by suppuration buried in a tissue, an organ, or a confined space
Ulcer inflammation	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.
eicosanoids	arachidonic-acid metabolites signaling molecules that play a unique role in innate immune responses
Chemotaxis	the directed movement of cells with the direction and guidance of Chemoattractants
Cytokines	are signaling proteins that help control inflammation in your body.
Endothelium	a thin membrane that lines the inside of the heart and blood vessels.

1- Which one of the following is NOT a cell-derived chemical mediator?

A) PAF	B) Kinins	C) Chemokines	D) ROS
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2- Immunoglobulin responsible for allergic reactions?

A) IgE	B) IgA	C) IgG	D) IgM
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3- Acute inflammation can be caused by:

A) infarction	B) Drugs	C) Trauma	D) All of them
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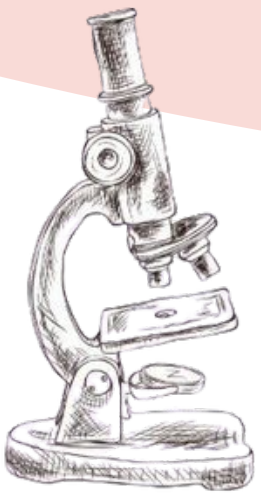
4- What is the source of serotonin?

A) Mast cells	B) Platelets	C) Lymphocytes	D) Epithelial cells
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5- Which of the following is cytokines of chronic inflammation ?

A) IL-6	B) IL-2	C) TNF	D) INF-γ
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6- Which of the following cause Fever?			
A)bradykinin	B)TNF	C)IgG	D)C3a
7- What is the responsible protein for chemotaxis			
A)c9	B)c3b	C)c5A	D)Mac
8- fibrinous exudate may be removed by			
A)nitric oxide	B)fibrinolysis	C)hemolysis	D)antibiotics
9- An enclosed collection of pus consists of a mixture of neutrophils and necrotic debris			
A)suppurative abcess	B)Ulcers	C)Catarrhal inflammation	D)cellulitis
10- if the acute inflammation progresses it could lead to:			
A)fibrosis	B)chronic inflammation	C)resolution	D)pus formation



PATHOLOGY TEAM₄₄₄

PATHOLOGY TEAMWORK

MED444

Ritaj Alsubaie

LEADER

Manar Alqahtani

LEADER

Abdulaziz Nasser

LEADER



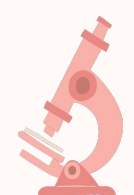
Shaden Alotaibi



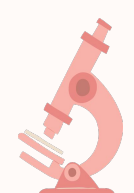
Rahaf Al turki



Layal Alkhalifah



Norah Alnoشان



Noor Altalag



Aram Alzahrani



Nisreen Alotaibi



Lana Alfouzan



Seeta bin aqeel



Lujain Darraj



Hessa Alamer



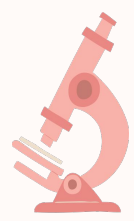
Sahar Alfallaj



Nora Albahily



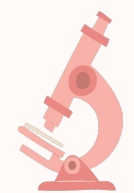
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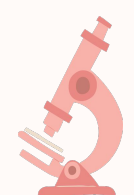
Abdulmalik Aldafs



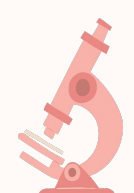
Abdumohsen Alrahaimi



Ibrahim Abdallah



Ibrahim Al Bin Ali



Lubna Alamri



Fahad Albalawi



Jana Alrumaihi



Hmood Alsehali



Osama Alotaibi



Ziyad BuKhari



Abdullah Alzoom



Khalid Alkanhal



Mazen Alzahrani



Rakan Alarifi



Abdullah khalid



Sulaiman Abdulkarim



Mohammed Alsheeban



pathology.444ksu@gmail.com