Substances that initiate & Regulate inflammatory reactions.

← Mediators → 4 groups
- Vasoactive amines
- Arachidonic acid metabo
- Cytokins & Chemokins
- Complement System

Locally at the site of inflammation

(Resident cells)

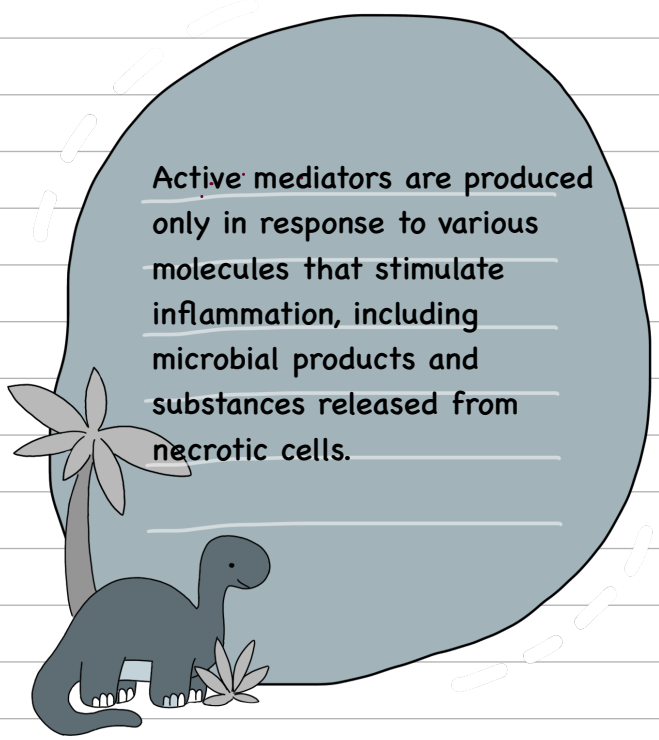
Cell-derived mediators are rapidly released from intracellular granules or synthesized de novo in response to a stimulus → They are most important for reactions against offending agents in tissues.

May be derived from circulation (Plasma derived mediators)

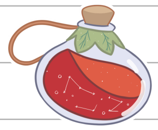
Plasma-derived mediators (e.g., complement proteins) are present in the circulation

→

They are produced mainly in the liver, are effective against circulating microbes



* Most of them are short lived.
* One mediator can stimulate others



Vasoactive amines

Histamine → acts on blood vessels

- Stored as preformed molecules (جاهز)
  - First mediator
- Released from mast cells (Degranulation)
  - physical injury
    - Cold
    - Trauma
    - Heat
  - Binding of AB to mast cells
    - Immediate Hypersensitivity Reaction (Allergic)
  - Anaphylatoxins (C3a & C5a)
- Also found
  - Basophils
  - Platelets
- Action → Binds to H1 Receptor
  - Vasodilation
  - ↑ Permeability by producing interendothelial gaps in post capillary venules
  - Contraction of smooth muscle
    - Autopsy of Asthma Patient ← خلي بالك

Antihistamine drugs are H1 Receptor Antagonist

→ Serotonin (5-hydroxytryptamine)

- Platelets & certain neuroendocrine cells (preformed)
  - such as in GIT → Neurotransmitter.
- Mast cells of RODENTS  Not human.
- Vaso Constrictor

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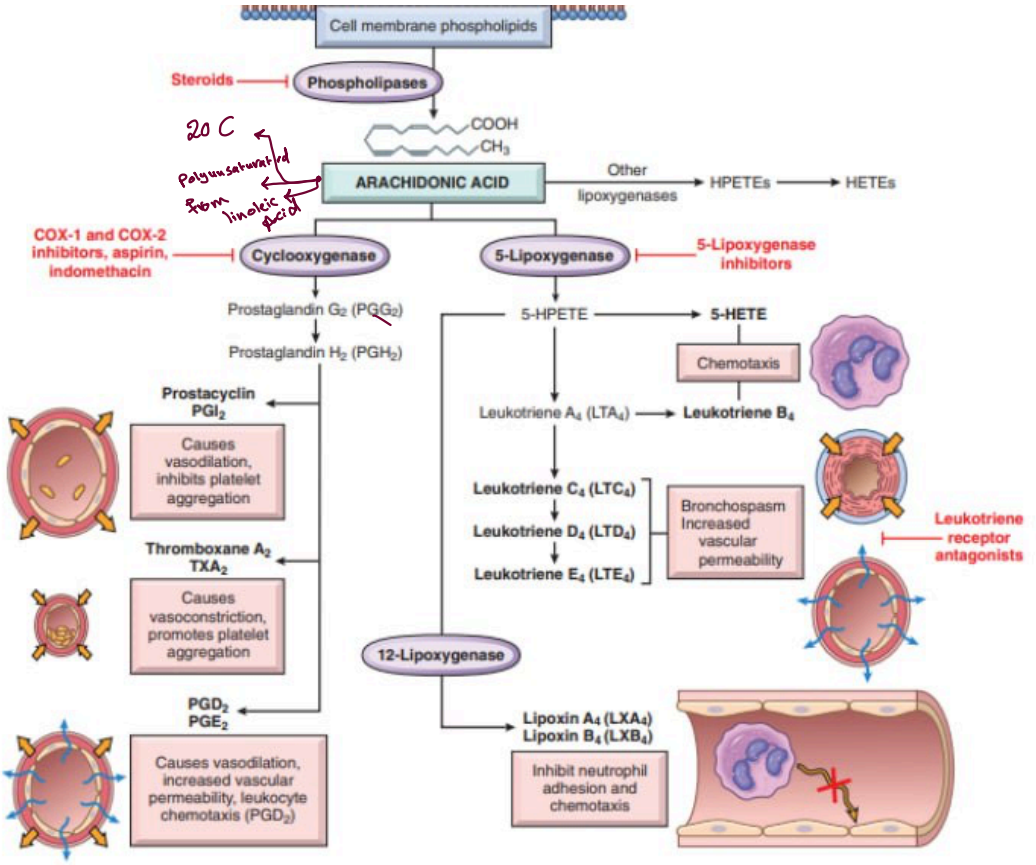


Type	Prostaglandins
• Produced by	✓ Mast cells, macrophages, endothelial cells, and many other cell types.
• Function	✓ Involved in the vascular and systemic reactions of inflammation.
• Subtypes	✓ The Inflammatory prostaglandins are PGE2, PGD2, PGF2a, PGI2 ✓ (prostacyclin), and TXA2 (thromboxane A2).
• Notes	✓ In addition to their local effects, prostaglandins are involved in the pathogenesis of pain and fever, two common systemic manifestations of inflammation. ✓ PGE2 makes the skin hypersensitive to painful stimuli, and causes fever during Infections
• Generated by	✓ Cyclooxygenase

Type	Leukotrienes
• **Produced by**	✓ Leukocytes and mast cells
• **Function**	
• **Subtypes**	✓ LTB4 →Produced by neutrophils and some macrophages. a) Potent chemotactic agent and activator of neutrophils, causing aggregation and adhesion of the cells to venular endothelium. b) Generation of ROS. c) Release of lysosomal enzymes. ✓ LTC4 ,LTD4 and LTE4 → Produced mainly in mast cells. a) Cause intense vasoconstriction, bronchospasm (important in asthma), and increased permeability of venules.
• **Notes**	
• **Generated by**	✓ lipoxygenase

Type	Lipoxins
• **Produced by**	✓ Leukocytes and mast cells
• **Function**	✓ Unlike prostaglandins and leukotrienes, the lipoxins suppress ✓ inflammation by inhibiting the recruitment of leukocytes. ✓ They inhibit neutrophil chemotaxis and adhesion to ✓ endothelium.
• **Subtypes**	✓ LXA4 ✓ LXB4
• **Notes**	
• **Generated by**	✓ Lipoxygenase

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	Leukotrienes B_4, HETE

HETE, Hydroxyeicosatetraenoic acid.

Characteristics comparison between COX-1 and COX-2

	COX-1	COX-2
Synthesis	intrinsic	induced
Functions	physiological: gastrointestinal protection platelet aggregation regulation vascular resistance regulation renal blood flow regulation	physiological: production of PG elevated during pregnancy pathological: producing proteinase, PG, and other inflammatory mediators

Inhibitors

1

Cox inhibitors

They inhibit both COX1 and COX2

Aspirin and buprofen

Thus it will inhibit all PGs synthesis

يعني المعدة حتاكل هوا

ليش؟

ولحل؟

Selective COX 2 inhibitors --> 200 - 300 fold block 2 than 1

كل شي بحسابه خلي بالك!!!

COX-1 is responsible for the production of prostaglandins that are involved in both inflammation and physiologic functions such as protecting gastric epithelial cells from acid-induced injury, whereas COX-2 generates prostaglandins that are involved only in inflammation.

Selective COX-2 inhibitors may increase the risk of cardiovascular and cerebrovascular events, possibly because they impair endothelial cell production of prostacyclin (PGI2), which prevents thrombosis, while leaving intact the COX-1–mediated production by platelets of TXA2, which induces platelet aggregation. Thus, selective COX-2 inhibition may tilt the balance toward vascular

Inhibitors

2. Lipoxygenase inhibitors --> Inhibit leukotrienes production, Used in Asthma (Zileuton)

3. Corticosteroids --> Broaaad spectrum, reduce the TRANSCRIPTION of genes encoding →
   A. COX 2
   B. Pospholipase A2
   C. Proinflammatory cytokines (IL-1 & TNF)
   D. iNOS

4. Leukotrienes receptor antagonists
   - It block leukotriene receptors and prevent the actions of the leukotrienes.
   - These drugs (e.g., Montelukast) are useful in the treatment of asthma

Cytokines

Are proteins secreted by many cell types (principally activated lymphocytes, macrophages, and dendritic cells, but also endothelial, epithelial, and connective tissue cells) that mediate and regulate immune and inflammatory reactions

TNF → Serve in Recruting leukocytes by promoting → Adhesion, Migration

→ Activated macrophages, Dendritic cells → Microbial products, Foreign bodies, Necrotic cells

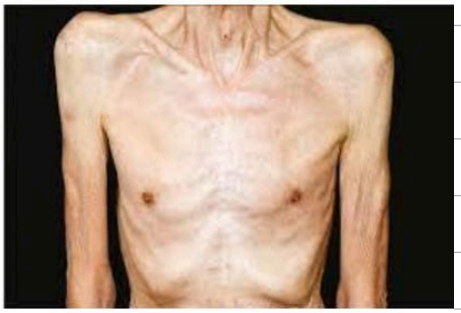
The most important roles of these cytokines in inflammation are the following:

1. Endothelial activation.
2. Activation of leukocytes and other cells.
3. Systemic acute-phase response.
4. TNF regulates energy balance by promoting lipid and protein catabolism and by suppressing appetite

Cachexia

- TNF antagonists have been remarkably effective in the treatment of chronic inflammatory diseases:

A. Rheumatoid arthritis.
B. Psoriasis.
C. Some types of inflammatory bowel disease.



✓ Sustained production of TNF contributes to cachexia, a pathologic state characterized by weight loss, muscle atrophy, and anorexia that accompanies some chronic infections and cancers

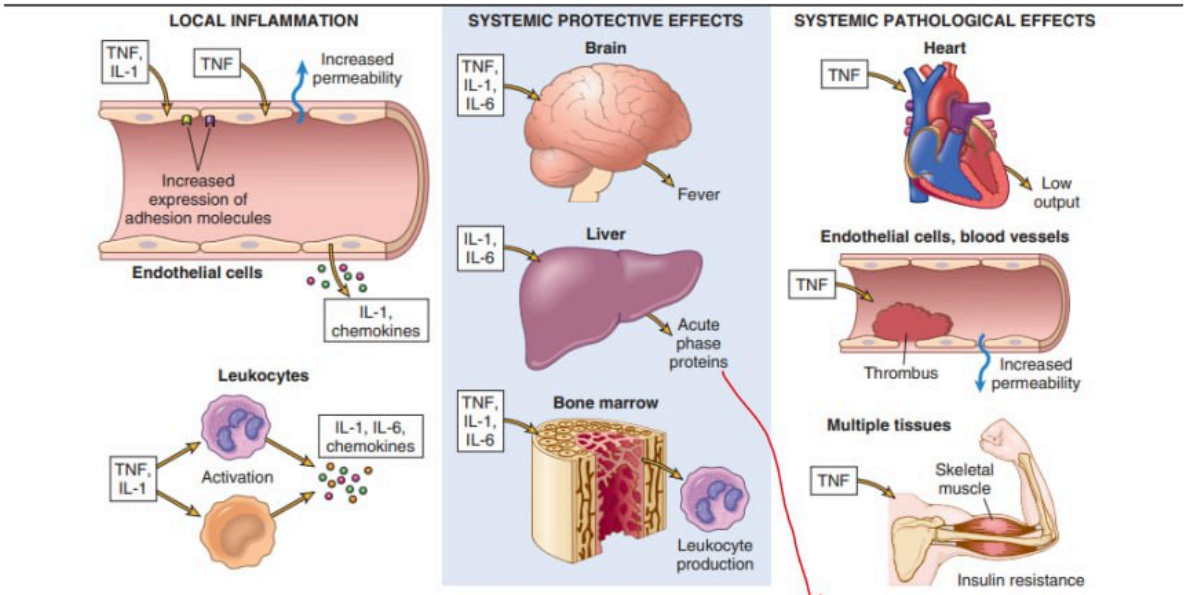


Figure 3.11 Major roles of cytokines in acute inflammation. *IL*, Interleukin; *TNF*, tumor necrosis factor.

ESR+CRP

Chemokines

-- Chemokines are a family of small proteins that act primarily as chemoattractants for specific types of leukocytes.

• Chemokines mediate their activities by binding to seven-transmembrane G protein-coupled receptors.

• They are classified into four major groups, according to the arrangement of cysteine (C) residues in the proteins:

Chemokines bind to proteoglycans and are displayed at high concentrations on the surface of endothelial cells and in the extracellular matrix.

• They have two main functions:

✓ Acute inflammation:

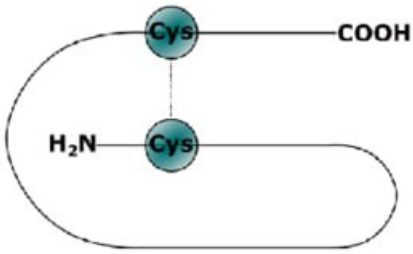
• Most chemokines stimulate leukocyte attachment to endothelium by acting on leukocytes to increase the affinity of integrins, and also serve as chemoattractants, thereby guiding leukocytes to sites of infection or tissue damage.

✓ Maintenance of tissue architecture:

• Organize various cell types in different anatomic regions of the tissues, such as T and B lymphocytes in discrete areas of the spleen and lymph node

Lack the first and third of the four conserved cysteines.
✓ The C chemokines (e.g., lymphotactin, XCL1) are relatively specific for lymphocytes.

C



Have the first two conserved cysteine residues adjacent.
Include monocyte chemoattractant protein (MCP-1, CCL2), eotaxin (CCL11), and macrophage inflammatory protein-1α (MIP-1α, CCL3).
✓ Mainly serve as chemoattractants for monocytes, eosinophils, basophils, and lymphocytes.

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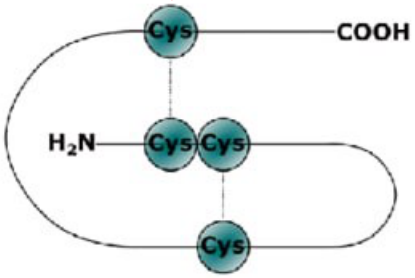
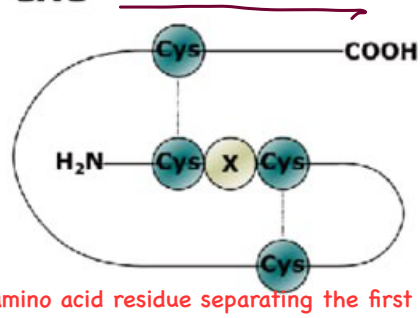
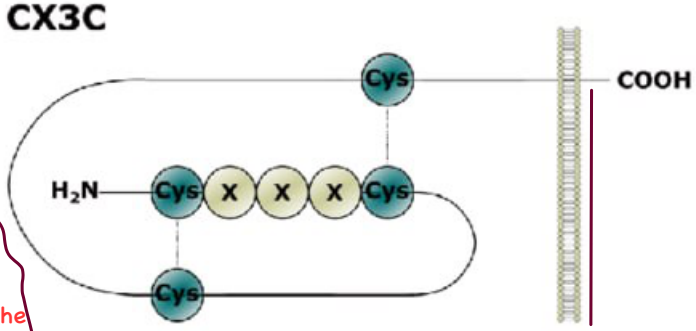


CXC



Have one amino acid residue separating the first two of the four conserved cysteines.
✓ These chemokines act primarily as neutrophils chemoattractant. IL-8 (now called CXCL8) is typical of this group.

CX3C



contain three amino acids between the first two cysteines

Complement System

- The complement system is a collection of soluble proteins and their membrane receptors that function mainly in host defense against microbes and in pathologic inflammatory reactions.
- There are more than 20 complement proteins, some of which are numbered C1 through C9.
- In the process of complement activation, several cleavage products of complement proteins are elaborated that cause increased vascular permeability, chemotaxis, and opsonization

- The critical step in complement activation is the proteolysis of the third (and most abundant) component, C3. Cleavage of C3 can occur by one of three pathways:

1. The classical pathway:
- Which is triggered by fixation of C1 to antibody (IgM or IgG) that has combined with antigen.

2. The alternative pathway:
- Which can be triggered by microbial surface molecules (e.g., endotoxin), complex polysaccharides, and other substances, in the absence of antibody.

3. The lectin pathway:
- In which plasma mannose-binding lectin binds to carbohydrates on microbes and directly activates C1.

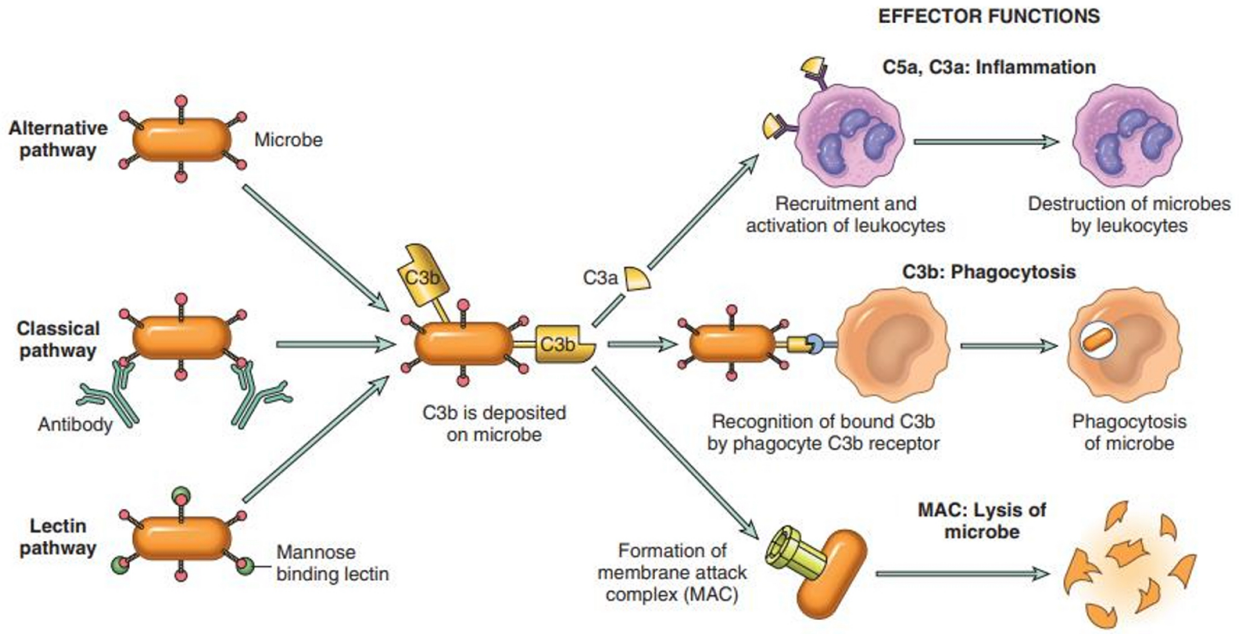


Figure 3.12 Activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins and by the membrane attack complex *(MAC)*.

- All three pathways of complement activation lead to the formation of an enzyme called the C3 convertase, which splits C3 into two functionally distinct fragments, C3a and C3b.

- C3a is released, and C3b becomes covalently attached to the cell or molecule where the complement is being activated.

- More C3b then binds to the previously generated fragments to form C5 convertase, which cleaves C5 to release C5a and leave C5b attached to the cell surface.

- C5b binds the late components (C6–C9), culminating in the formation of the membrane attack complex (MAC, composed of multiple C9 molecules).

- Complement proteins are present in inactive forms in the plasma, and many of them are activated to become proteolytic enzymes that degrade other complement proteins.

- The complement system has three main functions:

A. Inflammation:

- C5a, C4a and C3a are called **anaphylatoxins.**
- They stimulate histamine release from mast cells and thereby increase vascular permeability and cause vasodilation.

- C5a also is:

A. A chemotactic agent for neutrophils, monocytes, eosinophils, and basophils.

B. Activates the lipoxygenase pathway of arachidonic acid metabolism in neutrophils and monocytes, causing release of more inflammatory mediators.

B. Opsonization and phagocytosis:

- C3b and its cleavage product iC3b (inactive C3b) act as opsonins.
- Promote phagocytosis by neutrophils and macrophages, which bear cell surface receptors for these complement fragments.

B. Cell lysis:

- The deposition of the MAC on cells drills holes in the cell membrane, making the cells permeable to water and ions and resulting in their osmotic death (lysis).
- This function of complement is important mainly for the killing of microbes with thin cell walls, such as **Neisseria bacteria.**

- Regulatory proteins for complement system

A. C1 inhibitor → blocks the activation of C1.

- Inherited deficiency of this inhibitor is the cause of hereditary angioedema.

B. Decay accelerating factor (DAF) and CD59 :

- DAF prevents formation of C3 convertases.
- CD59 inhibits formation of the MAC.
- An acquired deficiency of these regulators and excessive complement activation and lysis of red cells This gives rise to a disease called paroxysmal nocturnal hemoglobinuria (PNH)

C. Factor H:

- Is a plasma protein that serves as a cofactor for the proteolysis of the C3 convertase.
- its deficiency results in excessive complement activation.
- Mutations in Factor H are associated with hemolytic uremic syndrome, as well as in wet macular degeneration of the eye

- The complement system contributes to disease in several ways:

1. The activation of complement by antibodies or antigen–antibody complexes deposited on host cells and tissues.
2. Inherited deficiencies of complement proteins cause increased susceptibility to infections.
3. Deficiencies of regulatory proteins cause a variety of disorders.