Pathophysiology
College of Pharmacy
Mustaqbal university
3rd stage

Inflammation

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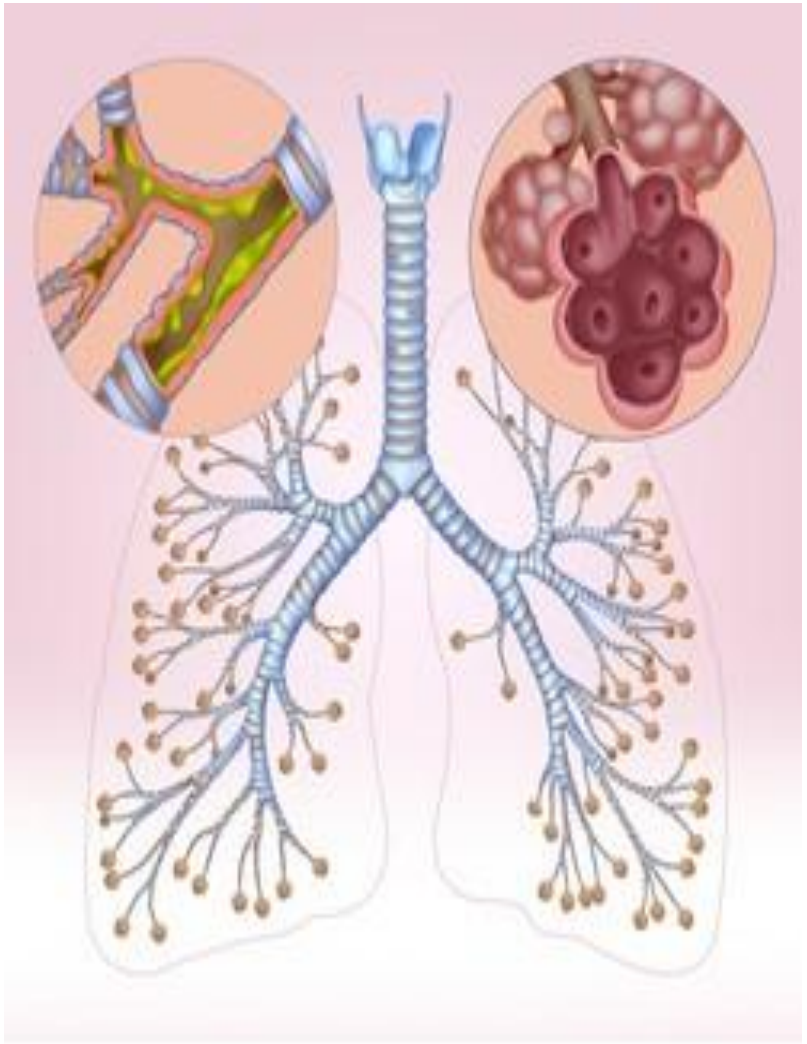

Cellular Events of Acute Inflammation

- **2- Cellular Phase:** the cellular phase of acute inflammation involves the delivery of leukocytes, mainly neutrophils, to the site of injury so they can perform their normal functions of host defense.
- The delivery and activation of leukocytes can be divided into the following steps:
- **Adhesion and margination, transmigration, and chemotaxis:**
- The recruitment of leukocytes to the precapillary venules, where they exit the circulation, is facilitated by the slowing of blood flow and margination along the vessel surface.
- Leukocyte adhesion and transmigration from the vascular space into the extravascular tissue is facilitated by complementary adhesion molecules (e.g., selectins, integrins) on the leukocyte and endothelial surfaces.
- After extravasation, leukocytes migrate in the tissues toward the site of injury by chemotaxis, or locomotion oriented along a chemical gradient.

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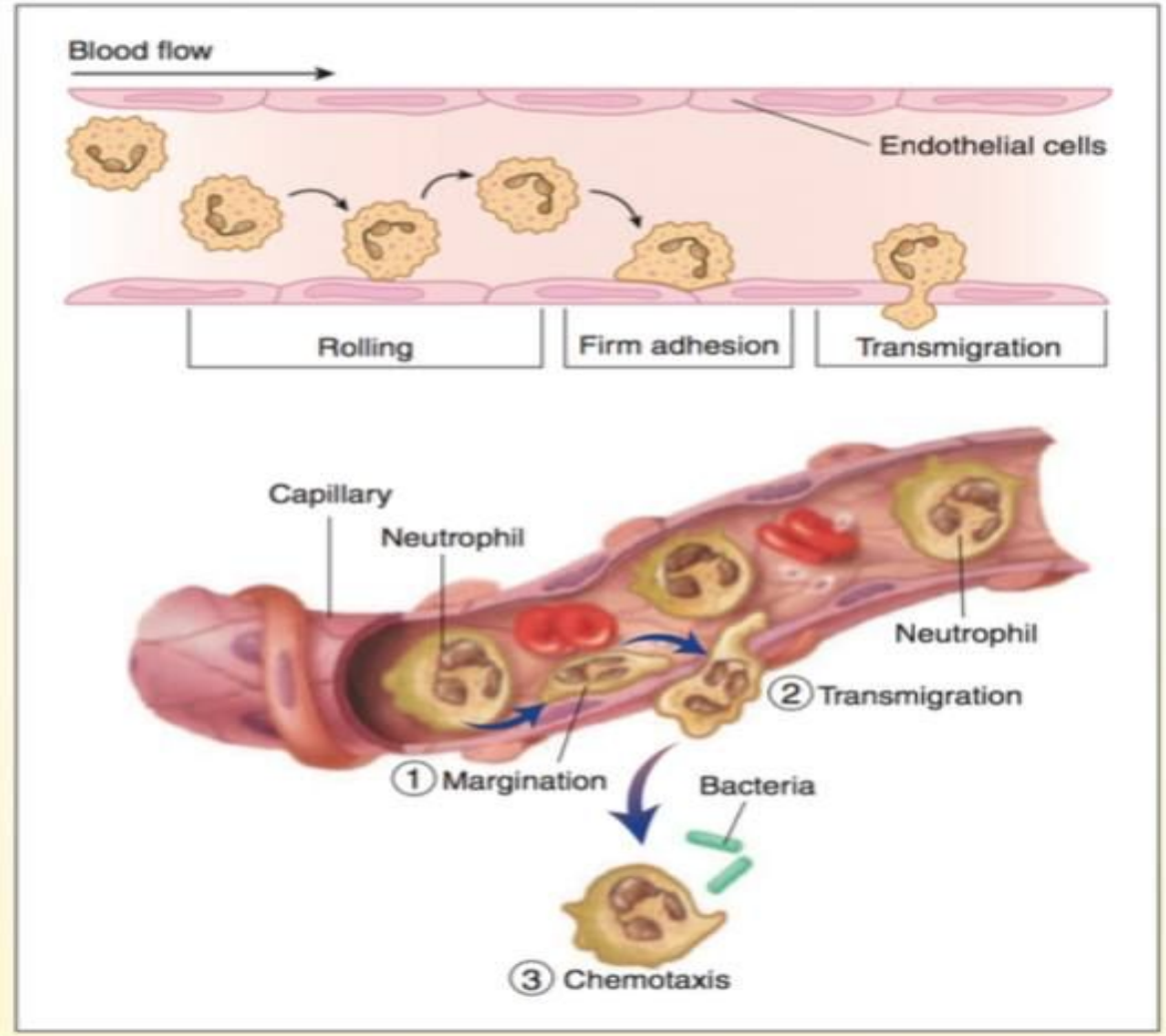
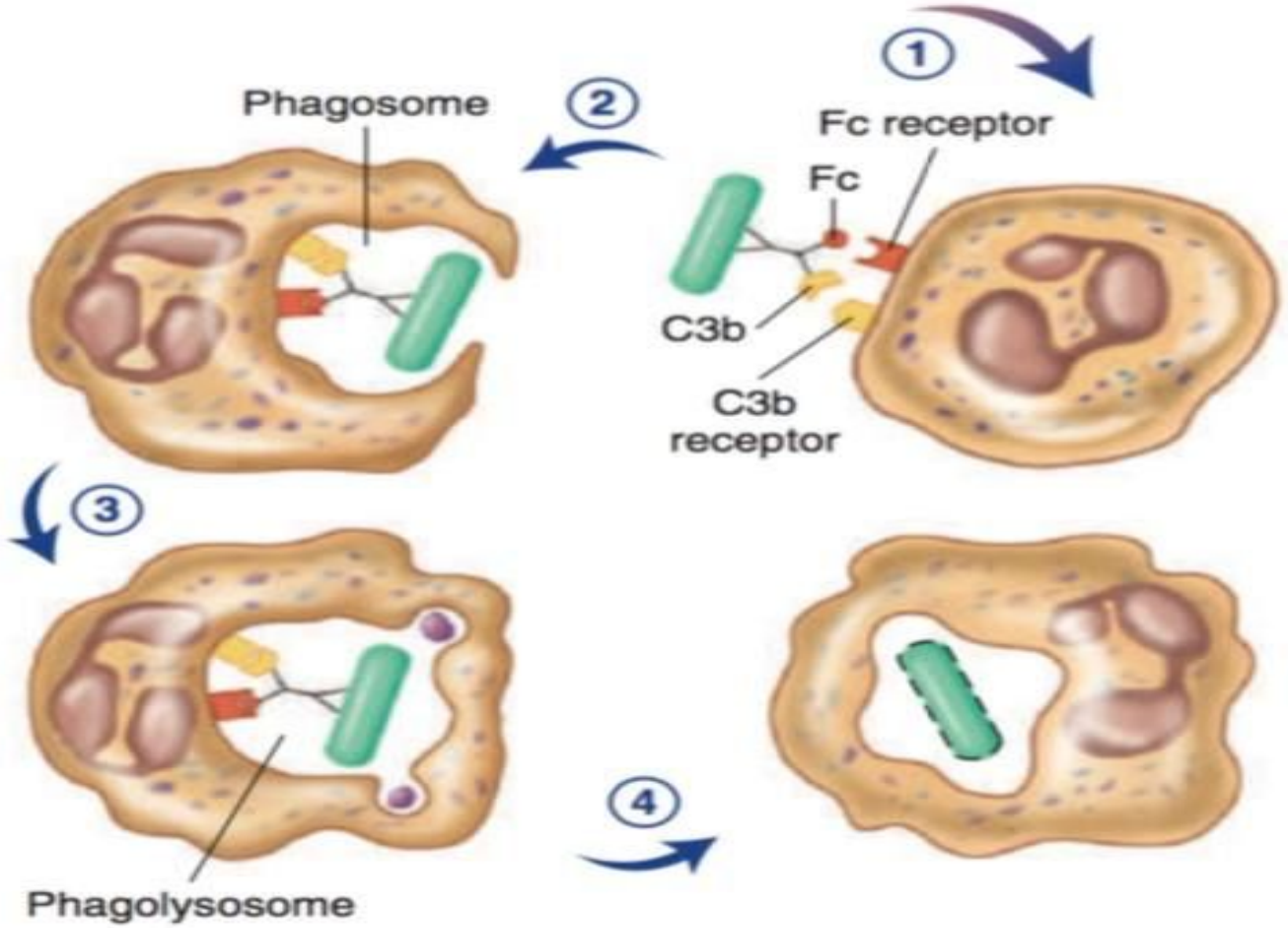
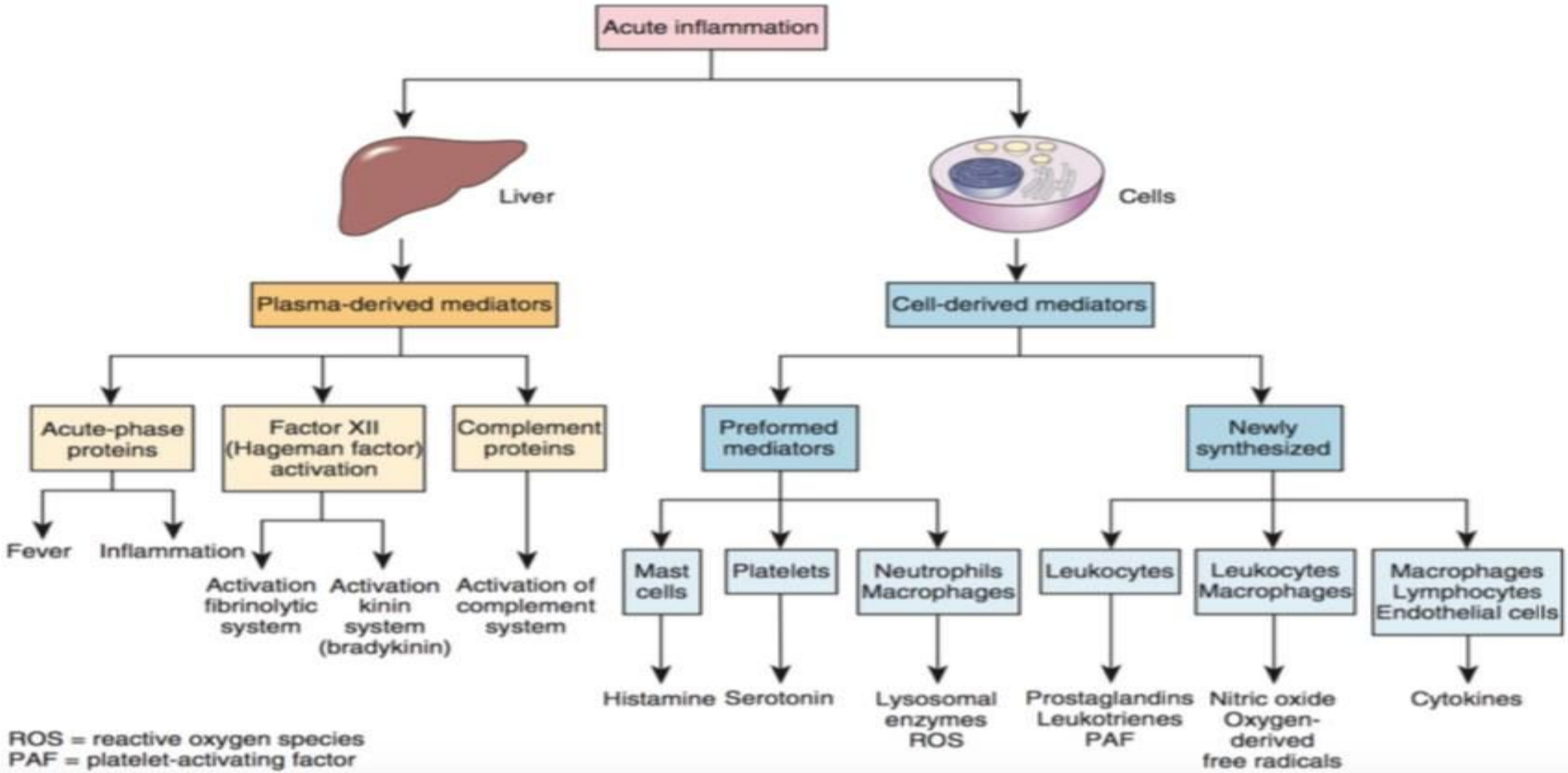


- **Leukocyte Activation and Phagocytosis:**
- Once at the sight of injury, the products generated by tissue injury trigger a number of leukocyte responses, including phagocytosis and cell killing.
- (1) Opsonization of microbes by complement factor C3b and antibody facilitates recognition by neutrophil C3b and the antibody Fc receptor.
- (2) Receptor activation triggers intracellular signaling and actin assembly in the neutrophil, leading to formation of pseudopods that enclose the microbe within a phagosome.
- (3) killing: phagosome then fuses with an intracellular lysosome to form a phagolysosome into which lysosomal enzymes and oxygen radicals are released to kill and degrade the microbe.

Leukocyte activation and phagocytosis



- **Inflammatory Mediators:**
- **chemical mediators responsible for the events. Inflammatory mediators may be derived from the plasma or produced locally by cells at the site of inflammation .**
- **The *plasma- derived mediators*: which are synthesized in the liver, include the acute-phase proteins, coagulation (clotting) factors, and complement proteins . These mediators are present in the plasma in a precursor form that must be activated by a series of proteolytic processes to acquire their biologic properties.**
- ***Cell-derived mediators :* are normally sequestered in intracellular granules that need to be secreted (e.g., histamine from mast cells) or newly synthesized (e.g., cytokines) in response to a stimulus. The major sources of these mediators are platelets, neutrophils, monocyte/macrophages, and mast cells, but most endothelial cells, smooth muscle cells, and fibroblasts can be induced to produce some of the mediators.**

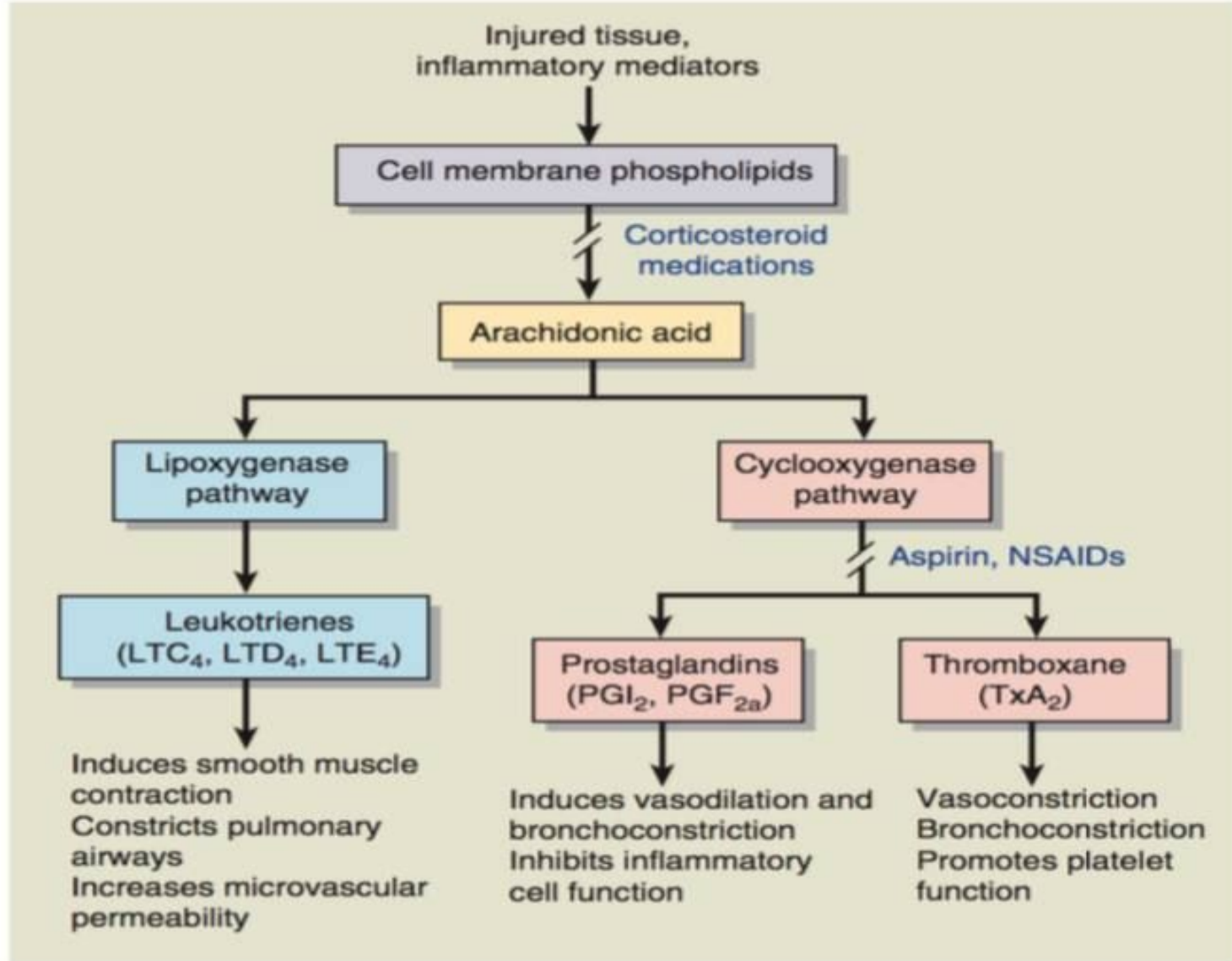

Acute inflammation
Liver
Cells
Plasma-derived mediators
Cell-derived mediators
Acute-phase proteins
Factor XII (Hageman factor) activation
Complement proteins
Preformed mediators
Newly synthesized
Fever
Inflammation
Activation fibrinolytic system
Activation kinin system (bradykinin)
Activation of complement system
Mast cells
Platelets
Neutrophils Macrophages
Leukocytes
Leukocytes Macrophages
Macrophages Lymphocytes Endothelial cells
Histamine
Serotonin
Lysosomal enzymes ROS
Prostaglandins Leukotrienes PAF
Nitric oxide Oxygen-derived free radicals
Cytokines
ROS = reactive oxygen species
PAF = platelet-activating factor

- **Plasma-Derived Mediators:**
- The plasma is the source of inflammatory mediators that are products of three major protein cascades or systems: the kallikrein–kininogen system, which generates kinins; the coagulation system, which includes the important fibrin end product; and the complement system that includes the various complement proteins.
- Kinins are products of the liver. kinin, bradykinin, causes increased capillary permeability and pain.
- The coagulation system also contributes to the vascular phase of inflammation mainly through formation of the fibrin mesh formed during the final steps of the clotting process.
- The complement system consists of a cascade of plasma proteins that play important roles in both immunity and inflammation. These proteins contribute to the inflammatory response by (1) causing vasodilation and increasing vascular permeability; (2) promoting leukocyte activation, adhesion, and chemotaxis; and (3) augmenting phagocytosis.

- **Cell-Derived Mediators**
- The cell-derived mediators are released from cells that are present at sites of inflammation. Tissue macrophages, mast cells, endothelial cells, as well as leukocytes that are recruited to the site from the blood are all capable of releasing the different mediators of inflammation:
- **Histamine and Serotonin: Both histamine and serotonin are stored as preformed molecules in mast cells and other cells and are among the first mediators to be released in acute inflammatory reactions.**
- **Histamine: produces dilation of arterioles and increases the permeability of venules. It acts at the level of the microcirculation by binding to histamine1 (H1) receptors on endothelial cells and is considered the principal mediator of the immediate transient phase of increased vascular permeability in the acute inflammatory response.**
- **Serotonin : has an effects similar to histamine. It is found primarily within platelet granules and is released during platelet aggregation.**

- **Arachidonic Acid Metabolites:**
- Arachidonic acid is a 20-carbon unsaturated fatty acid found in the phospholipids of cell membranes.
- Release of arachidonic acid by phospholipases initiates a series of complex reactions that lead to the production of the *eicosanoid* family of inflammatory mediators (prostaglandins, leukotrienes, and related metabolites).
- Eicosanoid synthesis follows one of two pathways: the cyclooxygenase pathway, which culminates in the synthesis of prostaglandins; and the lipoxygenase pathway, which culminates in the synthesis of the leukotrienes .
- The corticosteroid drugs block the inflammatory effects of both pathways by inhibiting phospholipase activity and thus preventing the release of arachidonic acid.

The cyclooxygenase and lipoxygenase pathways and sites where the corticosteroid and nonsteroidal anti-inflammatory drugs (NSAIDs) exert their action.

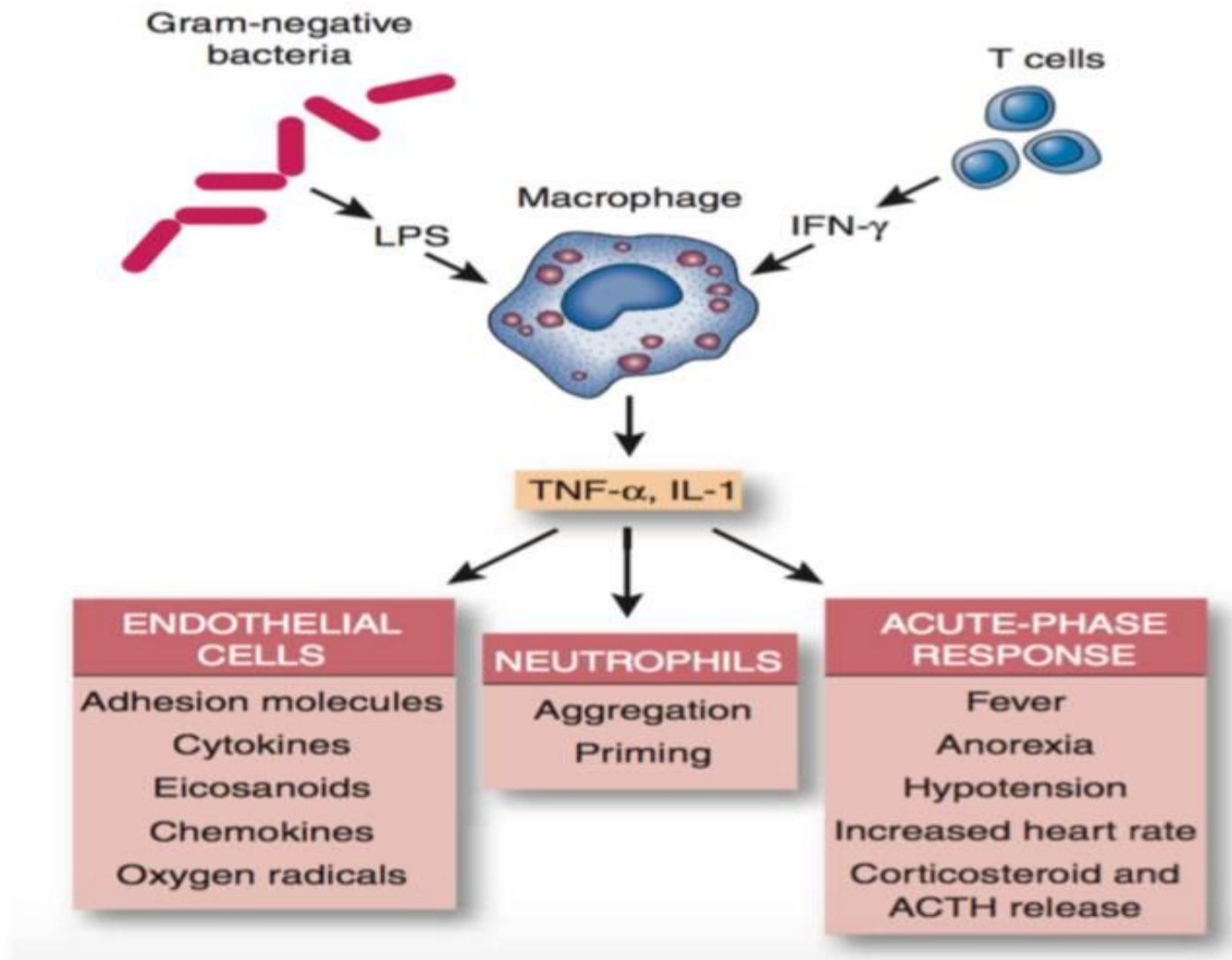


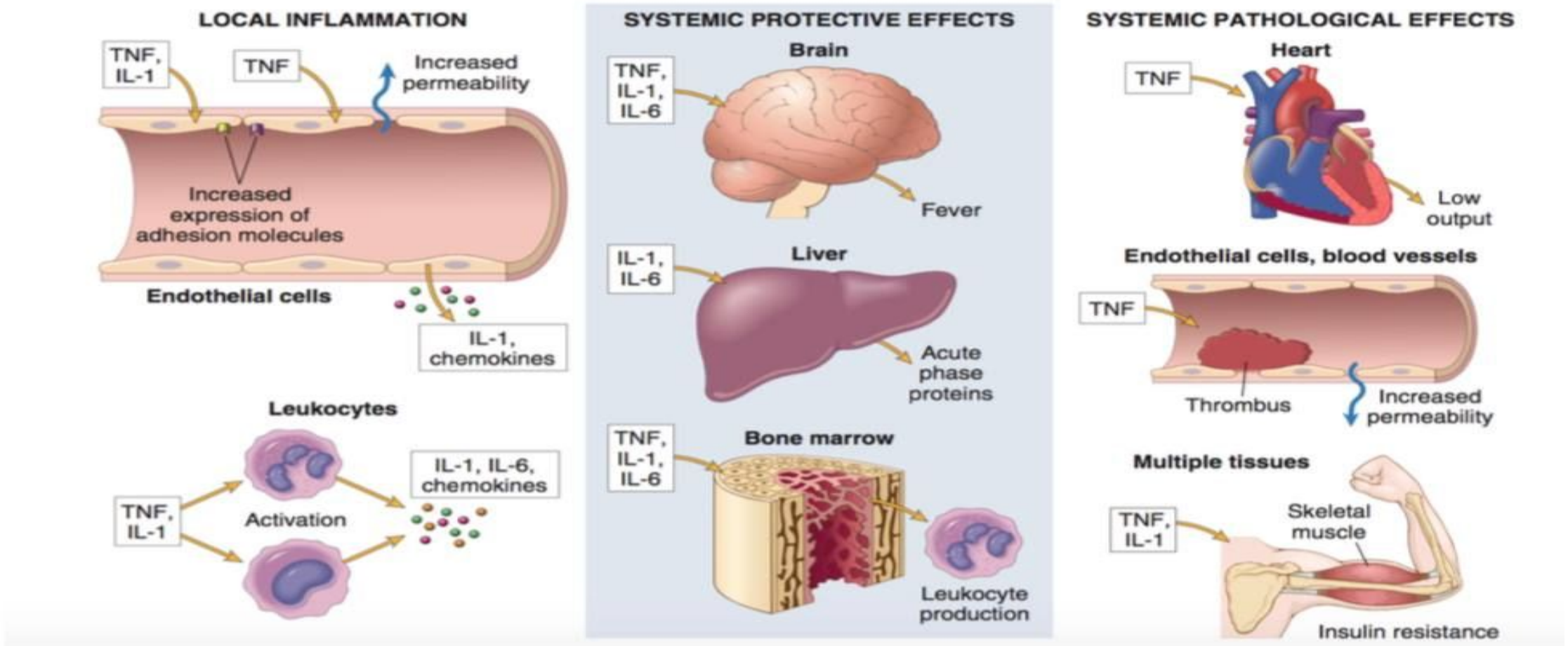
- **Platelet-Activating Factor (PAF) :**
- **Originally named for its ability to cause platelet aggregation and granulation, PAF is another phospholipid-derived mediator with a broad spectrum of inflammatory effects.**
- **Platelet-activating factor is generated from the membrane phospholipids of virtually all activated inflammatory cells and affects a variety of cell types.**
- **In addition to activating platelets, PAF stimulates neutrophils, monocytes/macrophages, endothelial cells, and vascular smooth muscle.**
- **Platelet activating factor-induced platelet aggregation and degranulation at the site of injury enhances serotonin release, thereby causing changes in vascular permeability.**
- **It also enhances leukocyte adhesion, chemotaxis, and leukocyte degranulation and stimulates the synthesis of other inflammatory mediators, especially the prostaglandins.**

- **Cytokines and Chemokines:**
- Cytokines are low- molecular-weight proteins that are important cellular messengers. They modulate the function of cells by paracrine and autocrine mechanisms to cause responses in neighboring cells and the cells that produced the cytokine, respectively.
- They are produced by many cell types, including activated macrophages and lymphocytes, endothelial cells, epithelial cells, and fibroblasts.
- Although well known for their role in adaptive immune responses, these proteins also play important roles in both acute and chronic inflammation.

- **Tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1):** are two of the major cytokines that mediate inflammation.
- **The major cellular source of TNF-α and IL-1 is activated macrophages Interleukin-1 is also produced by many other cell types, including neutrophils, endothelial cells, and epithelial cells (e.g., keratinocytes).**
- **The secretion of TNF-α and IL-1 can be stimulated by bacterial toxins, immune cells, injury, and a variety of inflammatory stimuli.**
- **TNF-α and IL-1 induce endothelial cells to express adhesion molecules and release other cytokines, chemokines, and reactive oxygen species.**
- **Tumor necrosis factor-α induces priming and aggregation of neutrophils, leading to augmented responses of these cells to other mediators.**
- **Interleukin-1 and TNF-α are also mediators of the acute-phase responses associated with infection or injury. Features of these systemic responses include fever, hypotension and increased heart rate, anorexia, release of neutrophils into the circulation, and increased levels of corticosteroid hormones.**

Central role of interleukin (IL)-1 and tumor necrosis factor (TNF)-α in inflammation.





Major roles of cytokines in acute inflammation.

- **Resolution:**
- the outcome of acute inflammation generally results in one of three processes : resolution, progression to chronic inflammation, or substantial scarring and fibrosis.
- Resolution involves the replacement of any irreversibly injured cells and return of tissues to their normal structure and function. It is seen with short-lived and minimal injuries and involves neutralization or degradation of inflammatory mediators, normalization of vascular permeability, and cessation of leukocyte infiltration.
- Progression to chronic inflammation may follow acute inflammation if the offending agent is not removed. Depending on the extent of injury, as well as the ability of the affected tissues to regenerate, chronic inflammation may be followed by restoration of normal structure and function.
- Scarring and fibrosis occurs when there is substantial tissue injury or when inflammation occurs in tissues that do not regenerate.

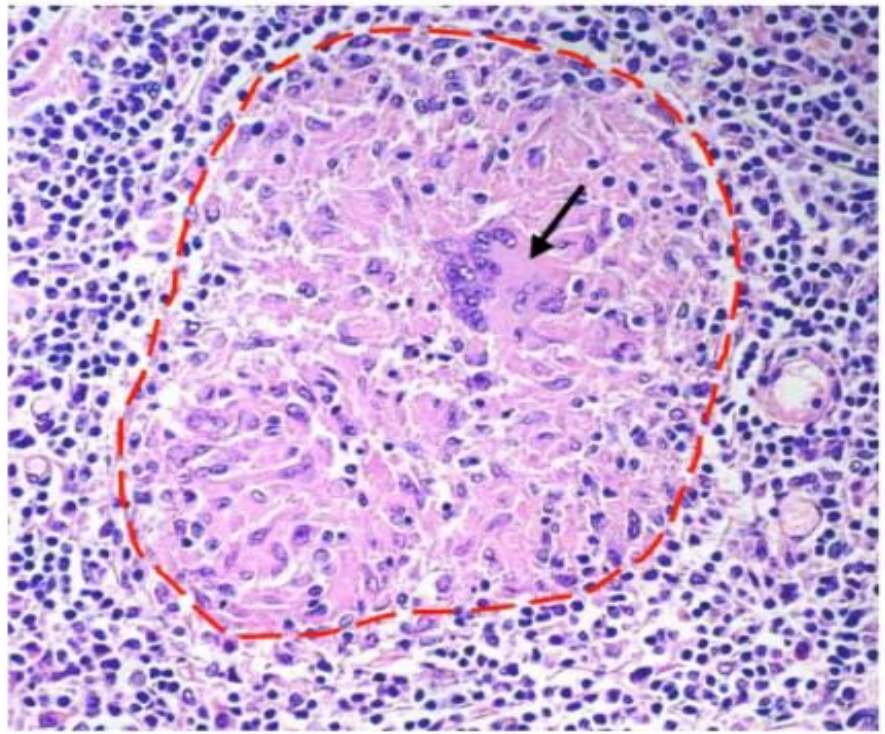
- **Chronic inflammation:**
- In contrast to acute inflammation, which is usually self- limited and of short duration, chronic inflammation is self-perpetuating and may last for weeks, months, or even years.
- It may develop as a result of a recurrent or progressive acute inflammatory process or from low- grade responses that fail to evoke an acute response.
- Instead of the vascular permeability changes, edema, and predominantly neutrophilic infiltration seen in acute inflammation, chronic inflammation is characterized by infiltration with mononuclear cells (macrophages, lymphocytes, and plasma cells) and attempted connective tissue repair involving angiogenesis and fibrosis.
- Chronic inflammation is the cause of tissue damage in some of the most common disabling diseases such as atherosclerosis, chronic lung disease, rheumatoid arthritis, and inflammatory bowel disease.
- There is also evidence that recurrent and persistent inflammation induces, promotes, and/or influences susceptibility to cancer by causing acid (DNA) damage, inducing tissue reparative proliferation, and/or creating an environment that is enriched with cytokines and growth factors that favor tumor development and growth.

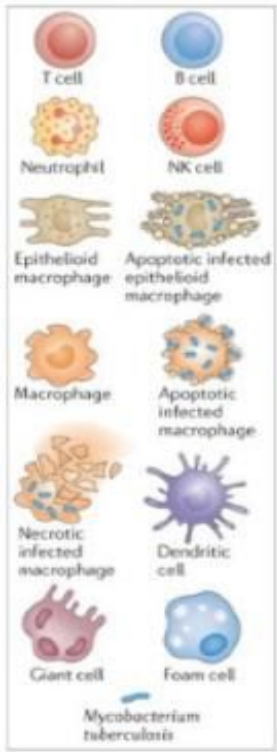
- **Causes of Chronic Inflammation:**
- Agents that evoke chronic inflammation typically are low-grade, persistent infections or irritants that are unable to penetrate deeply or spread rapidly.
- Among the causes of chronic inflammation are foreign agents such as talc, silica, asbestos, and surgical suture materials. Many viruses provoke chronic inflammatory responses, as do certain bacteria, such as the tubercle bacillus and the actinomyces, as well as fungi, and larger parasites of moderate to low virulence.
- Diseases that cause excessive and inappropriate activation of the immune system are increasingly being recognized as causes of chronic inflammation. Under certain conditions, immune reactions may develop against the person's own tissues, leading to autoimmune disease.

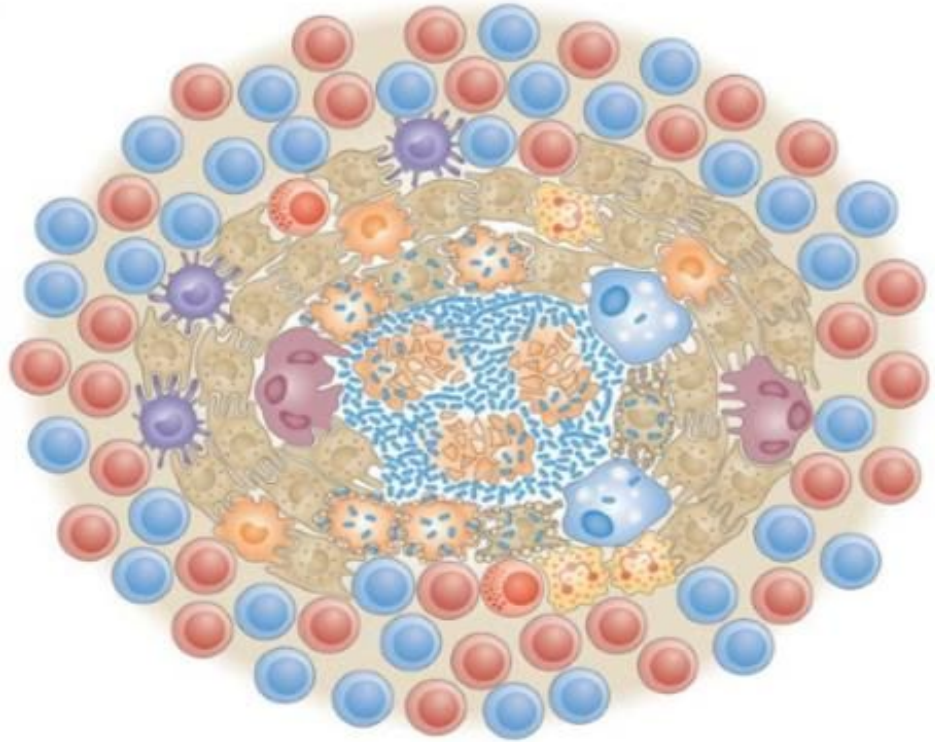
- **Granulomatous Inflammation:**
- **A granulomatous lesion is a distinctive form of chronic inflammation.**
- **A granuloma typically is a small, 1- to 2-mm lesion in which there is a massing of macrophages surrounded by lymphocytes.**
- **The macrophages are modified and, because they resemble epithelial cells, sometimes are called epithelioid cells. Like other macrophages, these epithelioid cells are derived originally from blood monocytes.**
- **Granulomatous inflammation is associated with foreign bodies such as splinters, sutures, silica, and asbestos and with microorganisms that cause tuberculosis, syphilis, sarcoidosis, deep fungal infections, and brucellosis. These types of agents have one thing in common: they are poorly degraded and usually are not easily controlled by other inflammatory mechanisms.**
- **The epithelioid cells in granulomatous inflammation may clump in a mass or coalesce, forming a multinucleated giant cell (often referred to as a foreign body giant cell) that attempts to surround the foreign agent .**

- **A dense membrane of connective tissue eventually encapsulates the lesion and isolates it.**

Mycobacterium Granulomas





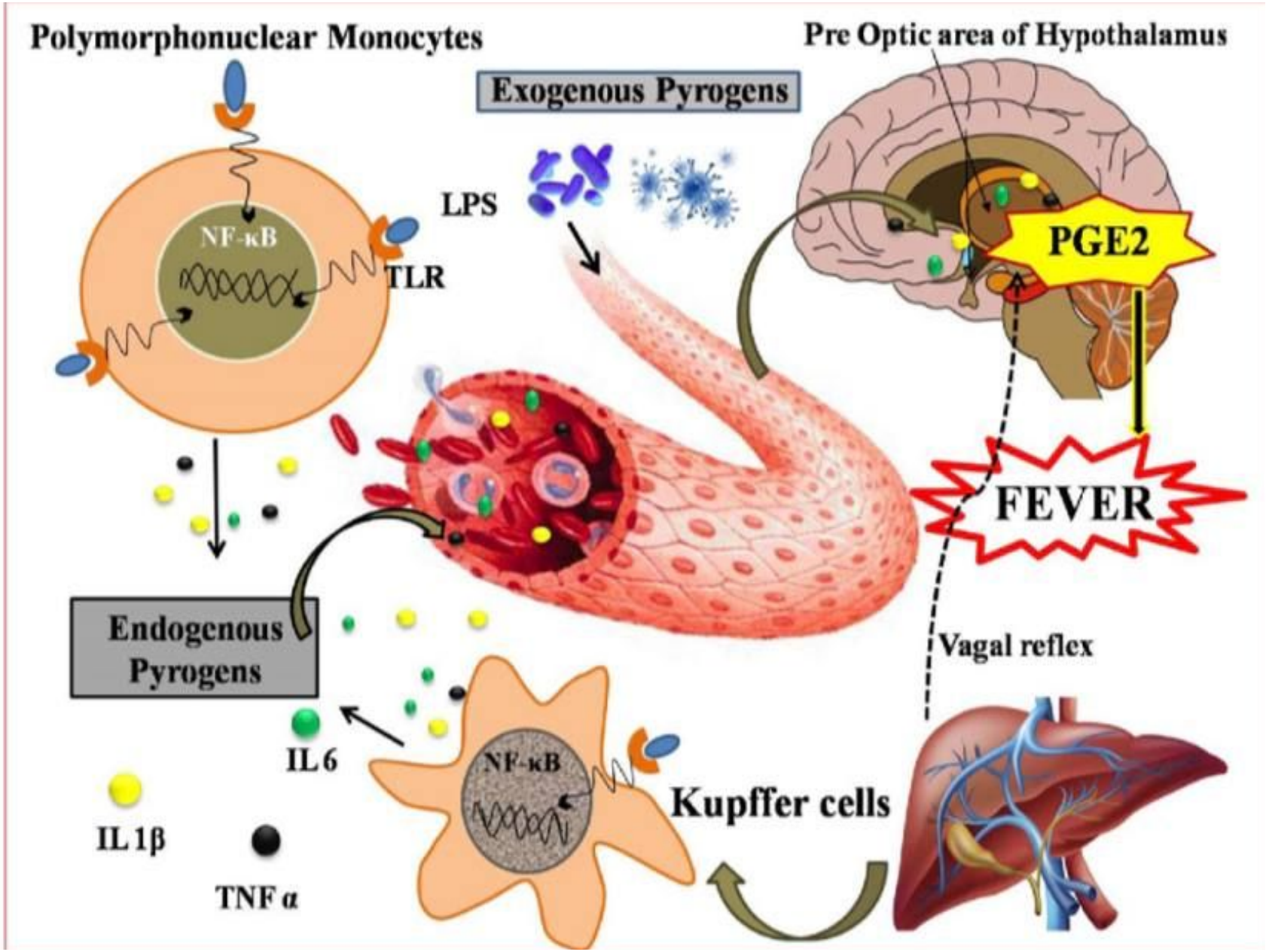


- **Acute-Phase Response**
- Along with the cellular responses that occur during the inflammatory response, a group of systemic effects called the *acute-phase response* occurs. The acute-phase response, which usually begins within hours or days of the onset of inflammation or infection includes:
- **Acute-Phase Proteins:**
- **During the acute-phase response, the liver dramatically increases the synthesis of acute-phase proteins such as fibrinogen, C-reactive protein (CRP), and serum amyloid A protein (SAA) that serve several different defense functions.**
- **The synthesis of these proteins is stimulated by cytokines, especially TNF-α, IL-1 (for SAA), and IL-6 (for fibrinogen and CRP).**

- **White Blood Cell Response :**
- ***Leukocytosis*, or the increase in white blood cells, is a frequent sign of an inflammatory response, especially those caused by bacterial infection.**
- **In acute inflammatory conditions, the white blood cell count commonly increases from a normal value of 4000 to 10,000 cells/µL to 15,000 to 20,000 cells/µL.**

- **Fever :**
- **Fever (pyrexia) is an elevation in body temperature caused by an upward displacement of the set point of the thermoregulatory center in the hypothalamus. It is one of the most prominent manifestations of the acute-phase response.**

Mechanism of Inducing fever

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