Pathophysiology

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inflammation

Inflammation is a response of vascularized tissues to infections and tissue damage that brings cells and molecules of host defense from the circulation to the sites where they are needed, to eliminate the offending agents and limit the spread of injurious agents as well as to remove the consequent necrosed cells and tissues.

Inflammation divided to two types, acute inflammation & chronic inflammation

Acute Inflammation

Acute inflammation is the early (almost immediate) reaction of local tissues and their blood vessels to injury. It typically occurs before adaptive immunity becomes established and is aimed primarily at removing the injurious agent and limiting the extent of tissue damage.

Causes of acute inflammation

1- Microbial Infections (bacterial, viral ,fungal ,parasitic ,microbial toxins)

2- Hypersensitivity (immune) reactions (acute phase).

3- Tissue necrosis (physical ,chemical, ischemia ,trauma , tumor etc)

4- foreign bodies (splinter, dirt , sutures ,cholesterol in atherosclerosis , urate crystals in gout.

The typical inflammatory reaction develops through a series of sequential steps:

1-The offending agent, which is located in extravascular tissues, is recognized by host cells and molecules.

2- Leukocytes and plasma proteins are recruited from the circulation to the site where the offending agent is located

3- The leukocytes and proteins are activated and work together to destroy and eliminate the offending substance.

4- The reaction is controlled and terminated.

5-The damaged tissue is repaired.

Signs of Acute Inflammation:

1- redness(rubor)

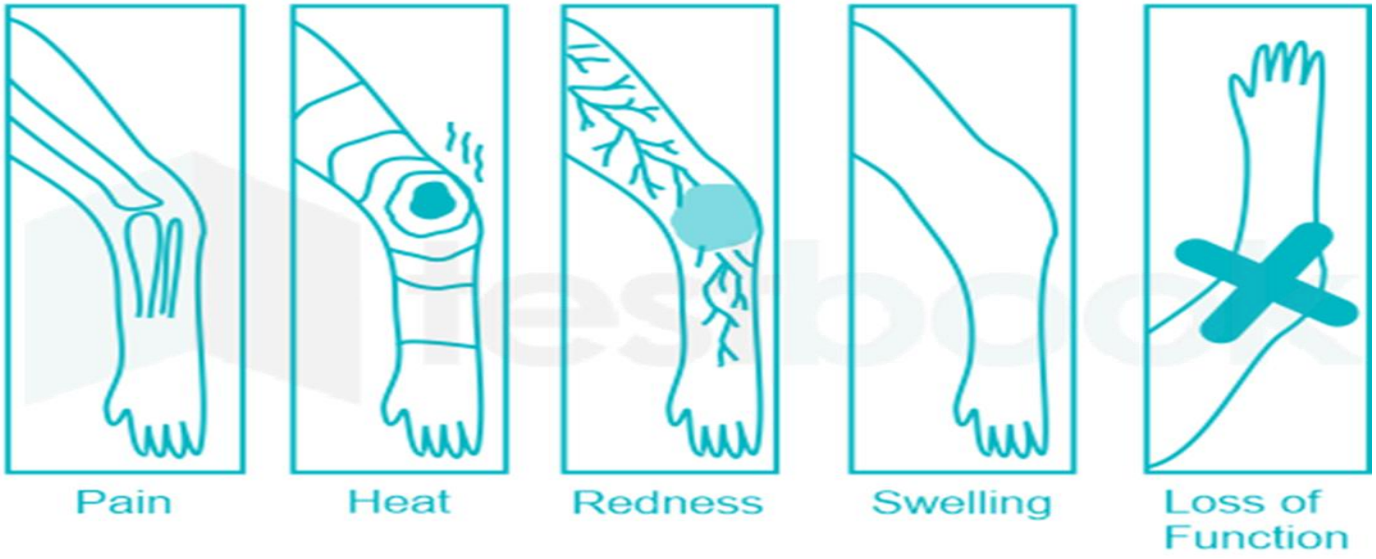
2- swelling (tumor)

3- heat (calor)

4- pain(dolor)

And last thing the fifth sign

5 - loss of function

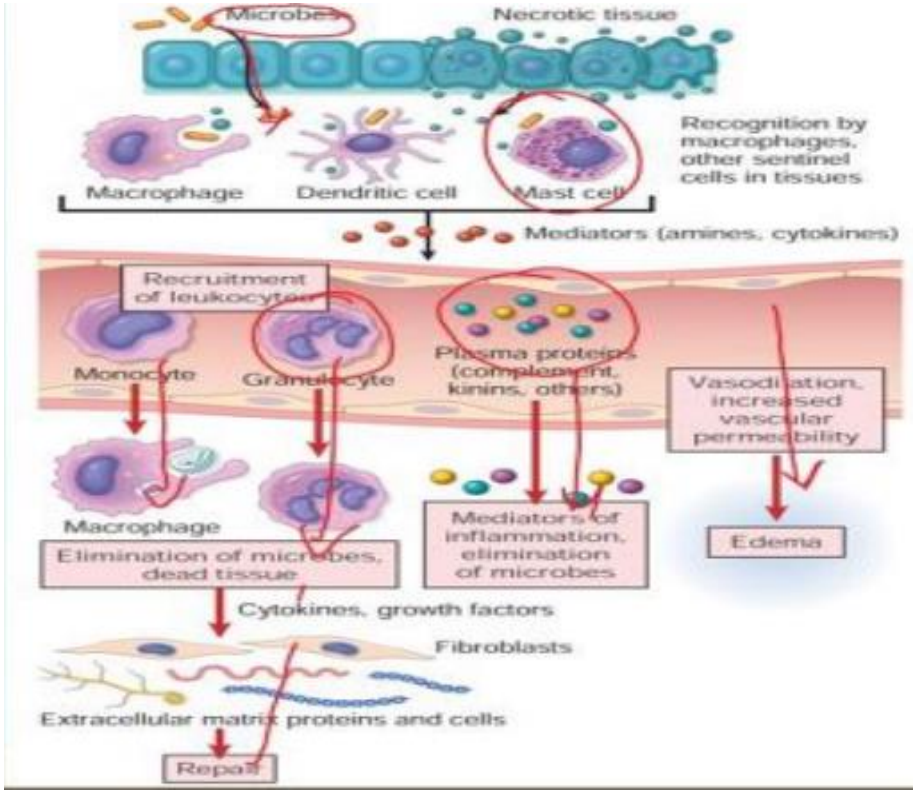


Characteristic of acute inflammation

1-Short duration (minutes, hours, few days)

2-Represent the early body reaction.

3-Usually followed by repair.



Sequence of events in an inflammatory reaction

Acute inflammation involves two major components:

- **the vascular stage** (which leads to an increase in blood flow and changes in the small blood vessels of the microcirculation)
- **cellular stages**(which leads to the migration of leukocytes from the circulation and their activation to eliminate the injurious agent

vascular events: It begins with:

1-Momentary vasoconstriction followed rapidly by vasodilation. Vasodilation involves the arterioles and venules with a resultant increase in capillary blood flow, causing heat and redness, which are two of the cardinal signs of inflammation. This is accompanied by

2-An increase in vascular permeability with outpouring of protein-rich fluid (exudate) into the extravascular spaces. The loss of proteins reduces the capillary osmotic pressure and increases the interstitial osmotic pressure. This, coupled with an increase in capillary pressure, causes

3-A marked outflow of fluid and its accumulation in the tissue spaces, producing the swelling, pain, and impaired function that represent the other cardinal signs of acute inflammation. As fluid moves out of the vessels, stagnation of flow and clotting of blood occur. This aids in localizing the spread of infectious microorganisms.

Cellular Phase: Leukocyte Margination, Adhesion, and Transmigration

The cellular phase of acute inflammation involves:

1- 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 & margination, transmigration, and chemotaxis.

2- The recruitment of leukocytes to the precapillary venules, where they exit the circulation, is facilitated by the slowing of blood flow and

3-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.

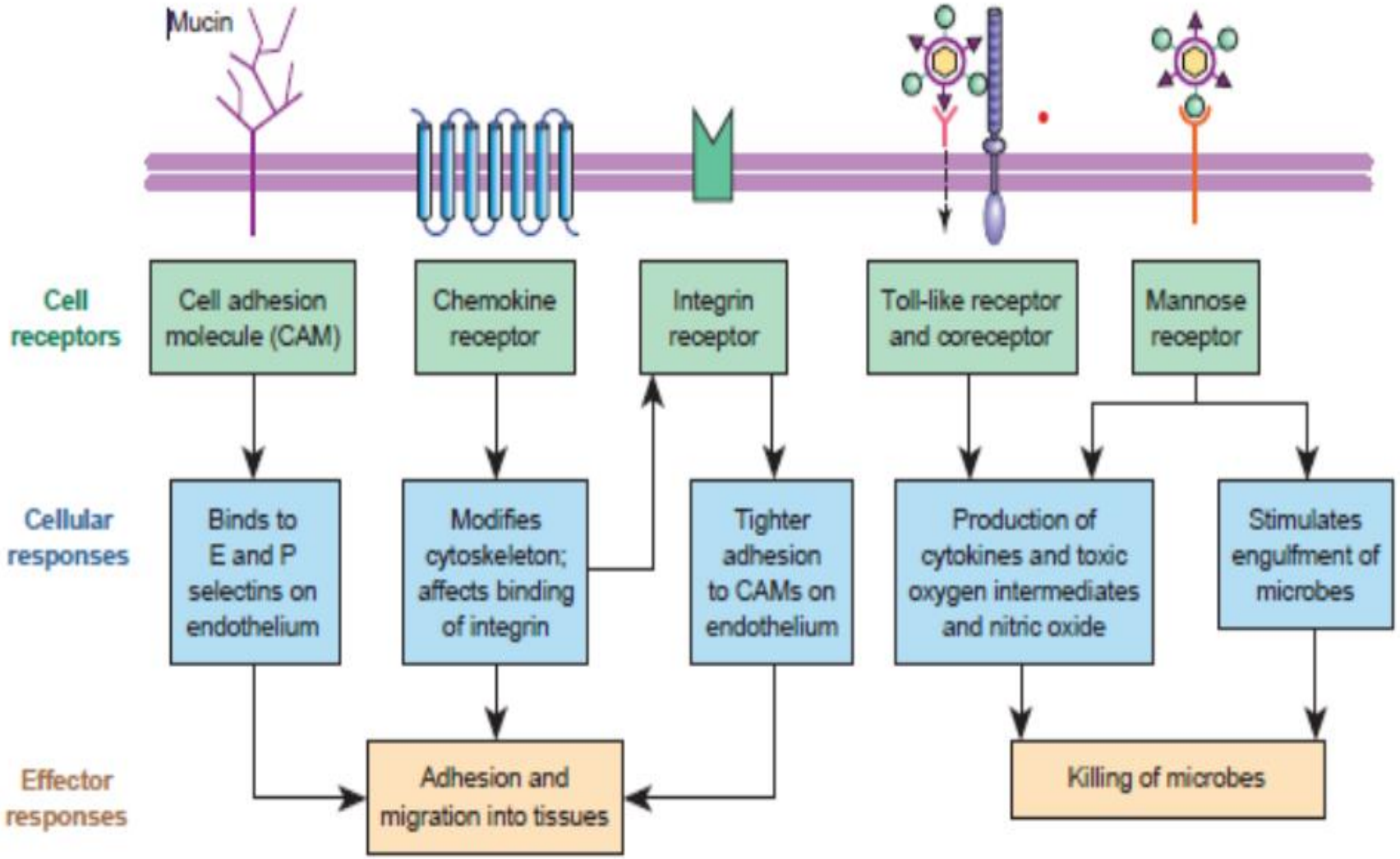
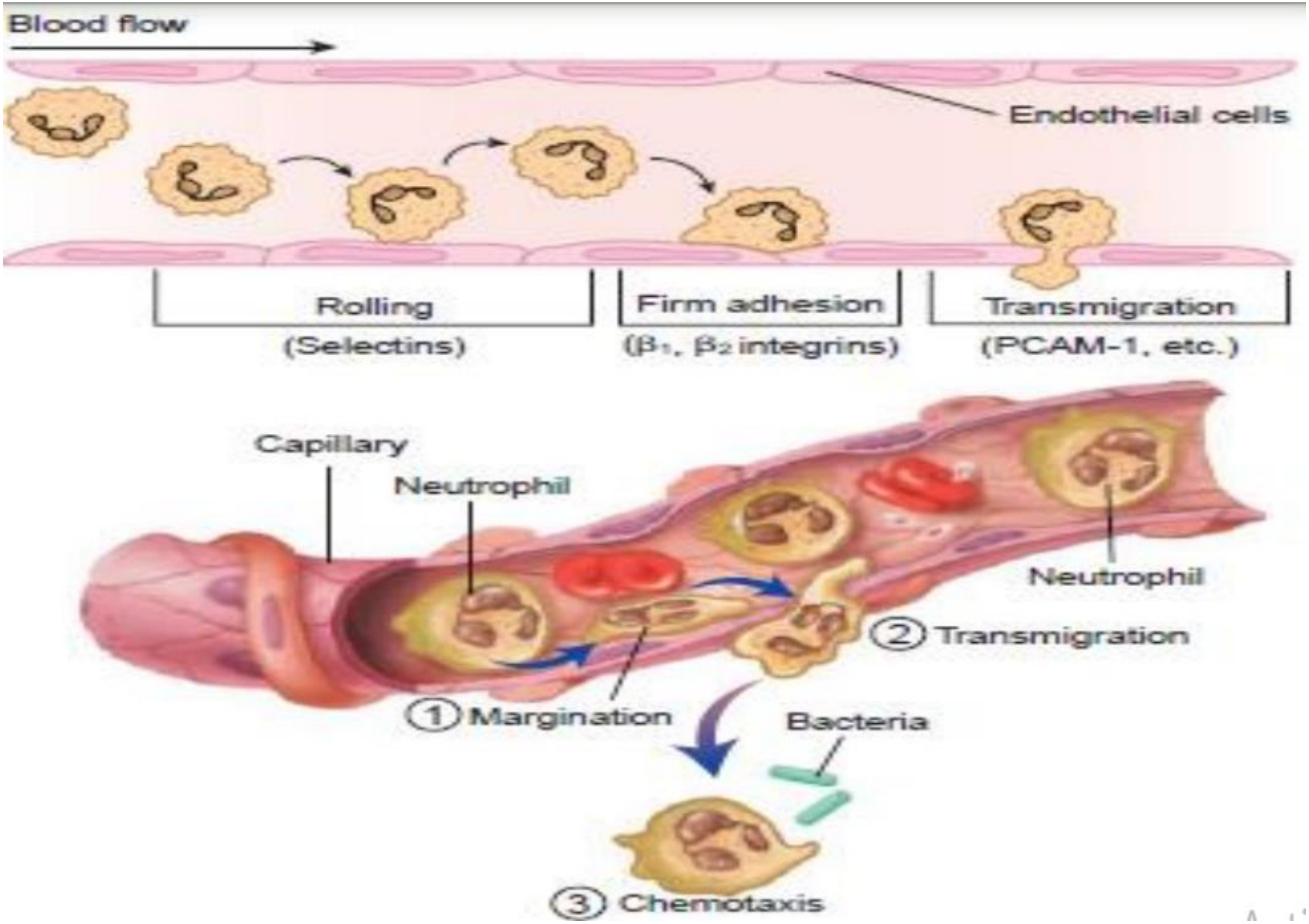


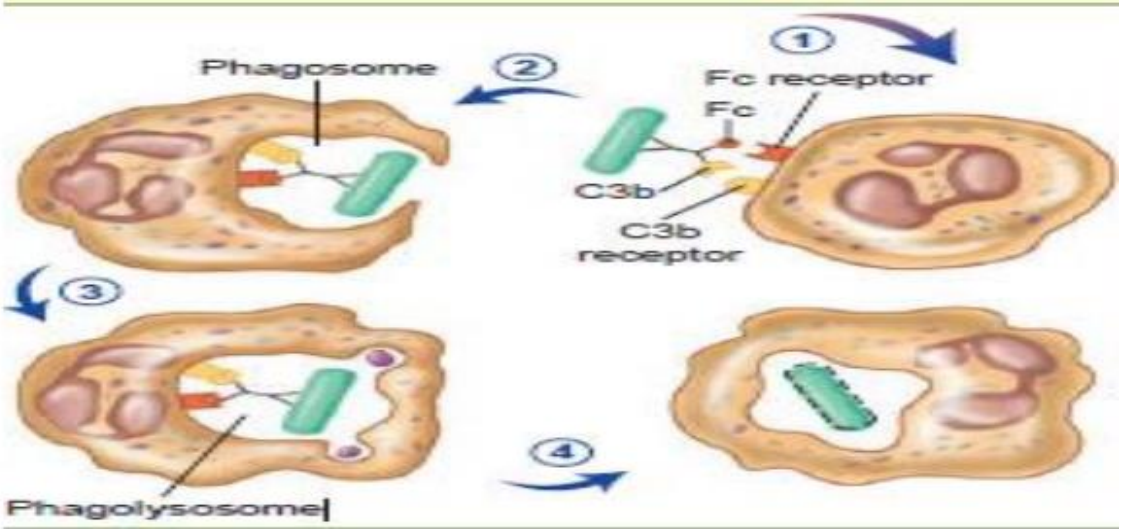
FIGURE 14.2 • Leukocyte activation. Different classes of leukocyte cell surface receptors recognize different stimuli. The receptors initiate responses that mediate the functions of the leukocytes.


Blood flow
Endothelial cells
Rolling
(Selectins)
Firm adhesion
(β1, β2 integrins)
Transmigration
(PCAM-1, etc.)
Capillary
Neutrophil
Neutrophil
② Transmigration
① Margination
Bacteria
③ Chemotaxis

Leukocyte Activation and Phagocytosis:

The products generated by tissue injury trigger a number of leukocyte responses, including phagocytosis and cell killing.

Opsonization of microbes (1) by complement factor C3b and antibody facilitates recognition by neutrophil C3b and the antibody Fc receptor. Receptor activation (2) triggers intracellular signaling in the neutrophil, leading to formation of pseudopods that enclose the microbe within a phagosome. The phagosome (3) then fuses with an intracellular lysosome to form a phagolysosome into which lysosomal enzymes and oxygen radicals (4) are released to kill and degrade the microbe.



Inflammatory Mediators:

Although inflammation is precipitated by infection and injury, its signs and symptoms are produced by chemical mediators. Mediators can originate either from the plasma or from cells. The plasma-derived mediators, which are synthesized in the liver, include the coagulation factors and the 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 are newly synthesized (e.g., cytokines) in response to a stimulus, although the major sources of these mediators are platelets, neutrophils, monocytes/macrophages, and mast cells, endothelial cells, smooth muscle, fibroblasts, and most epithelial cells can be induced to produce some of these mediators. The production of active mediators is triggered by microbes or host proteins, such as those of the complement, kinin, or coagulation systems, that are themselves activated by microbes or damaged tissues. Mediators can act on one or a few target cells(have diverse targets), or have differing effects on different types of cells. Once activated and released from the cell, most mediators are short-lived, they may be transformed into inactive metabolites, inactivated by enzymes, or otherwise scavenged or degraded.

Inflammatory mediators can be classified by function:

(1) Those with vasoactive and smooth muscle–constricting properties such as histamine, arachidonic acid metabolites (prostaglandins and leukotrienes), and PAF (Platelet activating factor).

(2) Plasma proteases that activate members of the complement system, coagulation factors of the clotting cascade, and vasoactive peptides of the kinin system

(3) Chemotactic factors such as complement fragments and chemokines

(4) Reactive molecules and cytokines liberated from leukocytes, which when released into the extracellular environment can affect the surrounding tissue and cells

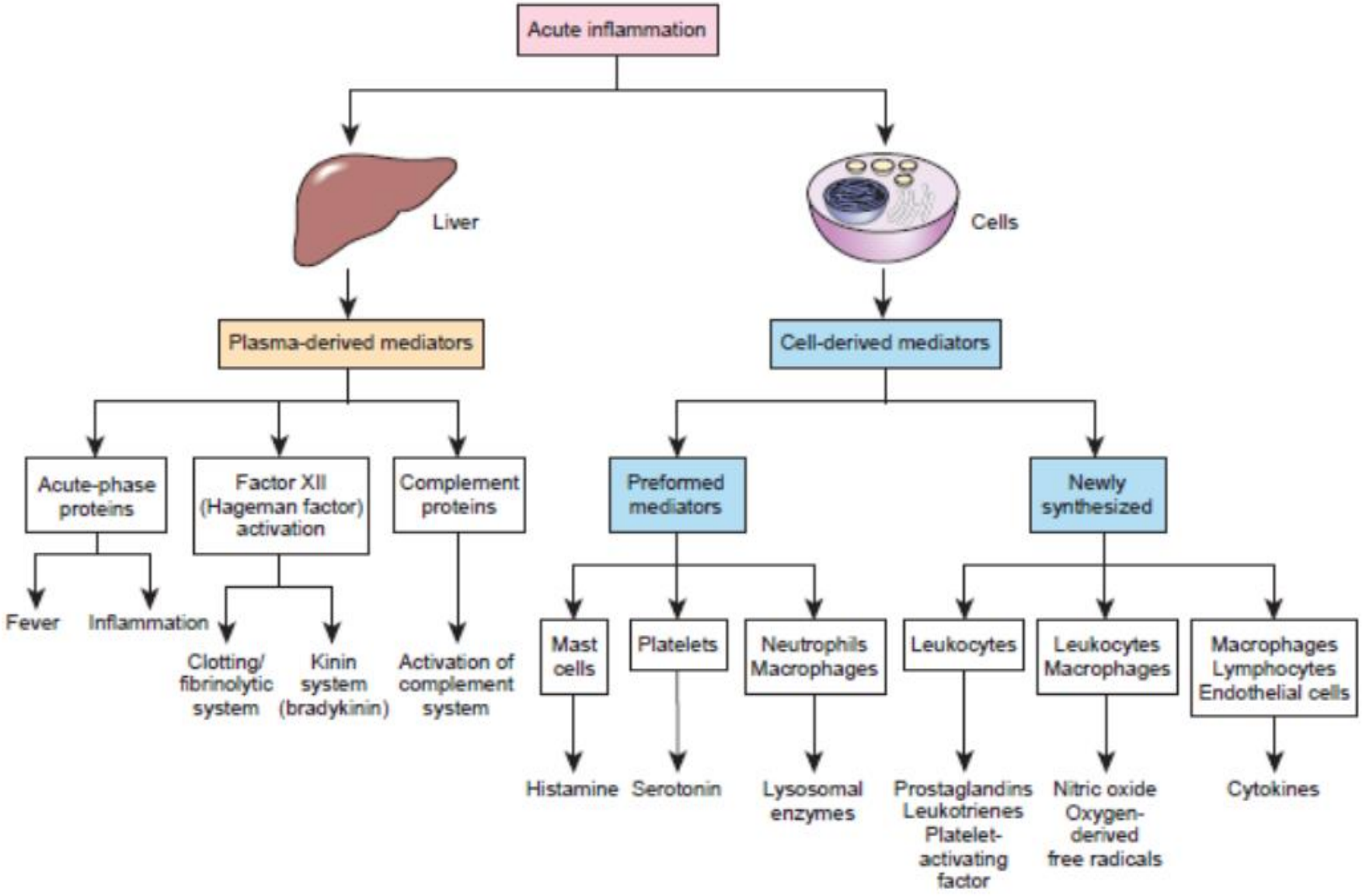


FIGURE 14.3 • Plasma- and cell-derived mediators of acute inflammation.

Chronic Inflammation

Is a response of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts at repair coexist, in varying combinations. 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 the result of a recurrent or progressive acute inflammatory process or from low-grade, smoldering responses that fail to evoke an acute response. Characteristic of chronic inflammation is an infiltration by mononuclear cells (macrophages) and lymphocytes instead of the Influx of neutrophils commonly seen in acute inflammation. Chronic inflammation also involves the proliferation of fibroblasts instead of exudates. As a result, the risk of scarring and deformity usually is greater than in acute inflammation. Agents that evoke chronic inflammation typically are low-grade, persistent infections or irritants that are unable to penetrate deeply or spread rapidly.

Causes of chronic inflammation

1-Foreign bodies such as talc, silica, asbestos, and surgical suture materials.
2-Many viruses provoke chronic inflammatory responses, as do certain bacteria, fungi, and larger parasites of moderate to low virulence. Examples are the tubercle bacillus and the treponeme of syphilis.
3-The presence of injured tissue such as that surrounding a healing fracture also may incite chronic inflammation.
4-Immunologic mechanisms are thought to play an important role in chronic inflammation.

Two patterns of chronic inflammation are:

- Nonspecific chronic inflammation and

- Granulomatous inflammation.

Nonspecific Chronic Inflammation

Nonspecific chronic inflammation involves a diffuse accumulation of macrophages and lymphocytes at the site of injury. Ongoing chemotaxis causes macrophages to infiltrate the inflamed site, where they accumulate owing to prolonged survival and immobilization. These mechanisms lead to fibroblast proliferation, with subsequent scar formation that in many cases replaces the normal connective tissue or the functional parenchymal tissues of the involved structures. For example, scar tissue resulting from chronic inflammation of the bowel causes narrowing of the bowel lumen.

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. These modified macrophages resemble epithelial cells and sometimes are called **epithelioid cells**. Like other macrophages, the 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 digested 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 that attempts to surround the foreign agent

A dense membrane of connective tissue eventually encapsulates the lesion and isolates it. These cells are often referred to as foreign body giant cells.

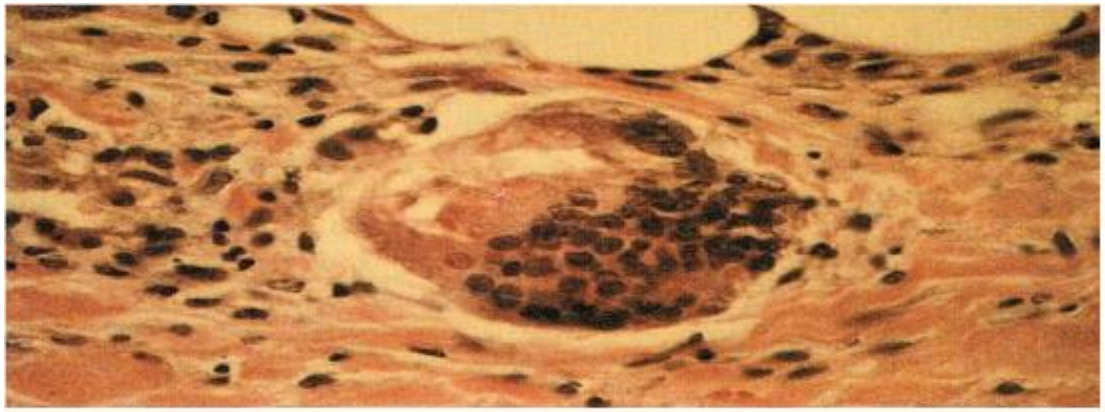


FIGURE 14.7 • Foreign body giant cell. The numerous nuclei are randomly arranged in the cytoplasm.

Tissue Repair

is a response to tissue injury and represents an attempt to maintain normal body structure and function. It can take the form of regeneration in which the injured cells are replaced with cells of the same type, sometimes leaving no residual trace of previous injury, or it can take the form of replacement by connective tissue, which leaves a permanent scar. Both regeneration and repair by connective tissue replacement are determined by similar mechanisms involving cell migration, proliferation, and differentiation, as well as interaction with the ECM

Tissue Regeneration:

Body organs and tissues are composed of two types of structures: parenchymal and stromal. The parenchymal tissues contain the functioning cells of an organ or body part (e.g., hepatocytes, renal tubular cells). The stromal tissues consist of the supporting connective tissues, blood vessels, ECM, and nerve fibers. Tissue regeneration involves replacement of the injured tissue with cells of the same type, leaving little or no evidence of the previous injury. The capacity for regeneration varies with the tissue and cell type.

Body cells are divided into three types according to their ability to undergo regeneration: **labile, stable**, or **permanent cells**. Labile cells are those that continue to divide and replicate throughout life, replacing cells that are continually being destroyed. They include the **surface epithelial cells of the skin, oral cavity, and cervix, the columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes, the transitional epithelium of the urinary tract and bone marrow cells**.

Stable cells are those that normally stop dividing when growth ceases. However, these cells are capable of undergoing regeneration when confronted with an appropriate stimulus and are thus capable of reconstituting the tissue of origin. This category include **the parenchymal cells of the liver and kidney, smooth muscle cells, and vascular endothelial cells**.

Permanent or fixed cells cannot undergo mitotic division. The fixed cells include **nerve cells, skeletal muscle cells, and cardiac muscle cells**. These cells do not normally regenerate; once destroyed, they are replaced with fibrous scar tissue that lacks the functional characteristics of the destroyed tissue.

Fibrous Tissue Repair

Severe or persistent injury with damage to both the parenchymal cells and ECM leads to a situation in which the repair cannot be accomplished with regeneration alone. Under these conditions, repair occurs by replacement with connective tissue, a process that involves generation of granulation tissue and formation of scar tissue.

Granulation tissue is a glistening red, moist connective tissue that contains newly formed capillaries, proliferating fibroblasts, and residual inflammatory cells. The development of granulation tissue involves the growth of new capillaries (angiogenesis), fibrogenesis, and involution to the formation of scar tissue.