Chapter 3

Inflammation, the Inflammatory Response, and Fever

Inflammation is a complex nonspecific response to tissue injury intended to minimize the effects of injury or infection, remove the damaged tissue, generate new tissue, and facilitate healing. As part of the innate immune system, inflammation dilutes, destroys, and gets rid of damaged or necrotic tissues and foreign agents, such as microbes. Although first described over 2000 years ago, the inflammatory response has been the subject of intense research during the past several decades. As a result, it is now recognized as playing a key role in both the contributing factors and consequences of numerous diseases and altered health states including, but not limited to, atherosclerosis, obesity and diabetes, many types of cancers, stroke, bronchial asthma, rheumatoid arthritis, and certain dementias, including Alzheimer disease.

The discussion in this chapter is divided into four sections: (1) the general features of inflammation, (2) acute inflammation, (3) chronic inflammation, and (4) systemic manifestations of inflammation, including fever. The innate and adaptive immune responses that are closely intertwined with the inflammatory response are discussed in Chapter 15.

General Features of Inflammation

Inflammation is the reaction of vascularized tissues to cell injury or death. It is characterized by the production and release of inflammatory mediators and the movement of fluid and leukocytes from the vasculature into the extravascular tissues.[1–4] Inflammatory conditions are commonly named by adding the suffix *-itis* to the affected organ or system. For example, *appendicitis* refers to inflammation of the appendix, *pericarditis* to inflammation of the pericardium, and *neuritis* to inflammation of the nerve.

Inflammation can be acute or chronic.[1,2] *Acute inflammation* is triggered by noxious stimuli, such as infection or tissue injury, is rapid in onset (typically minutes), and is of relatively short duration, lasting from a few minutes to several days. It is characterized by the exudation of fluid and plasma proteins and emigration of leukocytes. *Chronic inflammation* is of a longer duration, lasting for days to years, and is often associated with the proliferation of blood vessels (angiogenesis), tissue necrosis, and fibrosis (scarring). Acute and chronic inflammation may coexist, with episodes of acute inflammation being superimposed on chronic inflammation.

Cells of Inflammation

Many cells and tissue components are involved in the inflammatory process, including the endothelial cells that line blood vessels and form capillaries, circulating platelets and leukocytes, cells in the connective tissue (mast cells, fibroblasts, tissue macrophages), and components of the extracellular matrix (Fig. 3-1).[1–3] The principal leukocytes in acute inflammation are neutrophils, whereas macrophages, lymphocytes, eosinophils, and mast cells predominate in chronic infection.

Endothelial Cells

Endothelial cells, which make up the single-cell-thick linings of blood vessels, help to separate the intravascular and extravascular spaces.[1,2,5] They normally have a nonthrombogenic surface and produce agents that maintain vessel patency, as well as vasodilators and vasoconstrictors that regulate blood flow. Endothelial cells are also key players in the inflammatory response. As such, they provide a selective permeability barrier to exogenous (microbial) and endogenous inflammatory stimuli; regulate leukocyte extravasation by expression of adhesion molecules and receptor activation; contribute to the regulation and modulation of immune responses through synthesis and release of inflammatory mediators; and regulate immune cell proliferation through secretion of hematopoietic colony-stimulating factors (CSFs). Endothelial cells also participate in the repair process that accompanies inflammation through the production of growth factors that stimulate angiogenesis and extracellular matrix synthesis.

Platelets

Platelets or thrombocytes are small, membrane-bound disks circulating in the blood that play an active role in normal hemostasis (see Chapter 12). Activated platelets also release a number of potent inflammatory mediators, thereby increasing vascular permeability and altering the chemotactic, adhesive, and proteolytic properties of the endothelial cells.[6,7] When a platelet undergoes activation, over 300 proteins are released. While the functions of only a relatively small proportion of these proteins have been fully elucidated, it appears that many help mediate inflammation.[6] The association between the platelet and inflammatory diseases is highlighted by the number of inflammatory disease processes (e.g., atherosclerosis, migraine headaches, systemic lupus erythematosus) shown to be associated with platelet activation.[6]

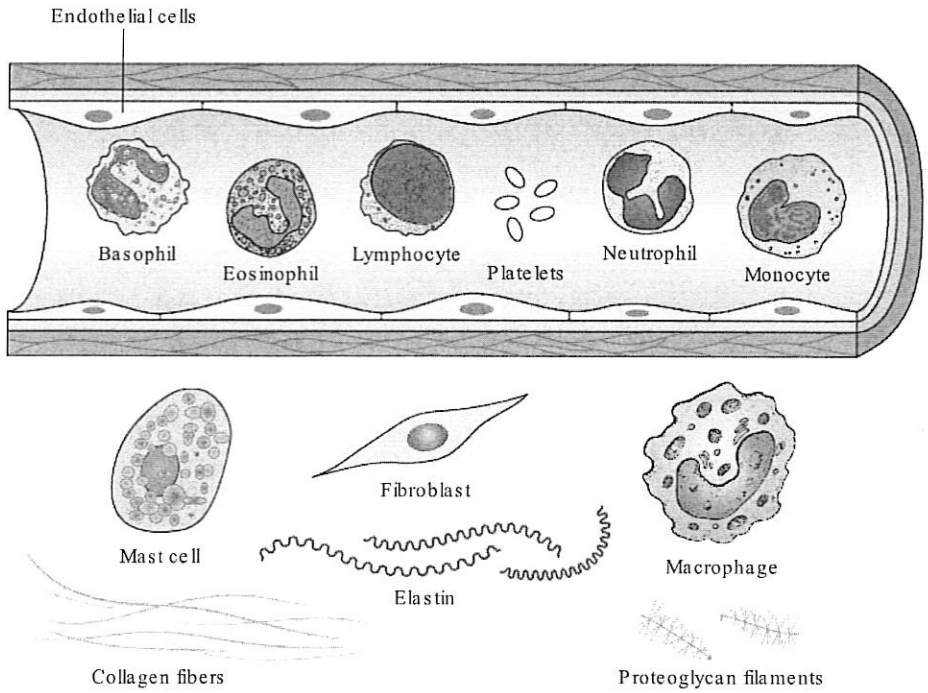

FIGURE 3-1. Cells involved in the inflammatory process.

Leukocytes

Leukocytes or white blood cells are the major cellular components of the inflammatory response. They include the granulocytes (neutrophils, eosinophils, and basophils), which contain specific cytoplasmic granules and a multilobed nucleus, and the agranulocytes (monocytes/macrophages and lymphocytes), which lack cytoplasmic granules and have a single nucleus.

Neutrophils. Neutrophils are the most numerous leukocytes in the circulating blood, accounting for 60% to 70% of all white blood cells. These leukocytes have nuclei that are divided into three to five lobes; therefore, they often are referred to as *polymorphonuclear neutrophils (PMNs)*. Because of their ability to form pseudopods used in ameboid movement, neutrophils are highly mobile, and are the first cells to appear at the site of acute inflammation, usually arriving within 90 minutes of injury (Fig. 3-2A). Neutrophils are scavenger cells capable of engulfing bacteria and other cellular debris through phagocytosis. Their cytoplasmic granules, which resist staining and remain a neutral color, contain enzymes and other antibacterial substances that are used in destroying and degrading engulfed microbes and dead tissue.[3,8,9] Neutrophils also have oxygen-dependent metabolic pathways that generate toxic reactive oxygen (e.g., hydrogen peroxide) and nitrogen (e.g., nitric oxide) species that aid in the destruction of engulfed pathogens. Neutrophils have a short life span. They die by apoptosis and disappear within 24 to 48 hours after entering the site of inflammation.

Eosinophils. Eosinophils account for 2% to 3% of circulating leukocytes and are recruited to tissues in a similar way as the neutrophils. Their appearance at the site of inflammation occurs 2 to 3 hours after the neutrophils. This is, in part, because of their slower mobility and comparatively slower reaction to chemotactic stimuli.

The granules of eosinophils, which stain pink with the acid dye eosin, contain a protein that is highly toxic to large parasitic worms that cannot be phagocytized. Eosinophils also play an important role in allergic reactions by controlling the release of specific chemical mediators. They interact with basophils and are prominent in allergic reactions such as hay fever and bronchial asthma. Eosinophils have a longer life span than neutrophils and therefore are present in chronic inflammation.

Basophils and Mast Cells. Basophils are granulocytes with granules that stain blue with a basic dye. Although they account for less than 1% of the circulating leukocytes, they are important participants in inflammatory reactions and are most prominent in allergic reactions mediated by immunoglobulin E (IgE). Binding of IgE triggers release of histamine and vasoactive agents from the basophil granules.

Mast cells derive from the same hematopoietic stem cells as basophils but do not develop until they leave the circulation and lodge in tissue sites. They are particularly prevalent along mucosal surfaces of the lung, gastrointestinal tract, and dermis of the skin.[2,10] This distribution places them in a sentinel position between environmental antigens and the host for a variety of acute and chronic inflammatory conditions.[2] Activation of mast cells

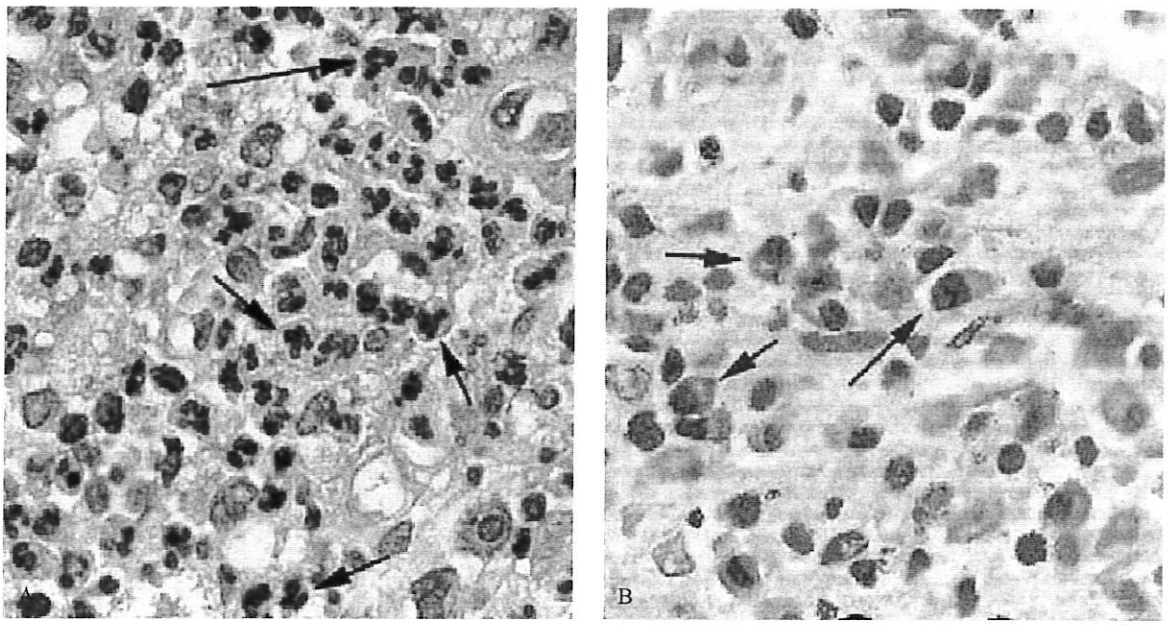

FIGURE 3-2. Inflammatory cells of acute and chronic inflammation. **(A)** Acute inflammation with densely packed polymorphonuclear neutrophils with multilobed nucleus (arrows). **(B)** Chronic inflammation with lymphocytes, plasma cells (arrows), and a few macrophages. (From Murphy HS. Inflammation. In: Rubin R, Strayer DS, eds. Rubin's Pathology: Clinicopathologic Foundations of Medicine. 5th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008:39.)

results in release of the preformed contents of their granules (e.g., histamine, proteases, cytokines such as tumor necrosis factor-α [TNF-α] and interleukin-16 [IL-16], growth factors such as vascular endothelial growth factor [VEGF]) and synthesis of lipid mediators derived from cell membrane precursors (arachidonic acid metabolites, such as prostaglandins, and platelet-activating factor). Finally, the release of mast cell contents stimulates cytokine and chemokine synthesis by other inflammatory cells such as monocytes and macrophages.

Monocyte/Macrophages. *Monocytes* constitute 3% to 8% of the white blood cell count. They have a single kidney-shaped nucleus and are the largest of the circulating leukocytes. The half-life of circulating monocytes is about a day, after which they begin to migrate to the site of injury and mature into larger macrophages, which have a longer half-life and greater phagocytic ability than do blood monocytes. Circulating monocytes have been linked to a number of inflammatory disorders, particularly atherosclerosis, in which they are transformed into macrophages that accumulate in atherosclerotic plaques and turn into lipid-laden foam cells (see Chapter 18).

Monocyte/macrophages produce potent vasoactive mediators including prostaglandins and leukotrienes, platelet-activating factor (PAF), inflammatory cytokines, and growth factors that promote regeneration of tissues.[8,9] As their name implies, macrophages are capable of phagocytosis and are active in bacterial killing. They engulf larger and greater quantities of foreign material than the neutrophils, and their circulating life span is three to four times longer than that of any granulocyte. These longer-lived phagocytes help to destroy the causative agent, aid in the signaling processes of immunity, serve to resolve the inflammatory process, and contribute to initiation of the healing processes. Macrophages are especially important in maintaining chronic inflammation.

Lymphocytes and Plasma Cells. Lymphocytes are the smallest of the leukocytes and have a thin rim of cytoplasm surrounded by a deeply staining nucleus (Fig. 3-2B). They participate in immune-mediated inflammation caused by infectious agents as well as non–immune-mediated inflammation associated with cell injury and death. Both T and B lymphocytes (T and B cells) migrate into inflammatory sites using some of the same adhesion molecules and chemokines that recruit neutrophils and other leukocytes (discussed in Chapter 15). Lymphocytes and macrophages communicate in a bidirectional way, and these interactions play an important role in chronic inflammation. Macrophages display antigen to T cells, express membrane molecules called costimulators (meaning that their response requires the action of two signaling molecules), and produce cytokines that stimulate T-cell responses.[2] Activated T cells, in turn, produce cytokines that activate macrophages, increasing antigen presentation and further cytokine production. (Cytokines and other inflammatory mediators are discussed later in this chapter.) The result is a perpetuating cycle of cellular responses that fuel and sustain chronic inflammation.

Plasma cells develop from B lymphocytes that have become activated after encountering an antigen and receiving T cell help. In the inflammatory site, they produce antibodies directed against persistent antigens and altered tissue components. In some intense, chronic inflammatory reactions, plasma cells and other lymphocytes may accumulate to form geminal centers that resemble lymph nodes.[2] This pattern of lymphocyte accumulation, with formation of germinal centers, is often seen in the inflamed synovium of persons with long-standing rheumatoid arthritis.

Cell Adhesion Molecules

Several families of cell adhesion molecules, including selectins, integrins, and the immunoglobulin superfamily, are involved in leukocyte recruitment and trafficking (see Chapter 1).[8,11,12] The *selectins* are a family of three closely related proteins (E-selectin, L-selectin, P-selectin) that differ in their cellular distribution but all function in adhesion of leukocytes or platelets to endothelial cells. The *integrins* consist of different types of structurally similar transmembrane receptor proteins that function as heterodimers to promote cell-to-cell and cell–to–extracellular matrix interactions. The name *integrin* derives from the hypothesis that they *integrate* the signals of extracellular ligands with cytoskeleton-dependent motility, shape change, and phagocytic responses of immune cells. *Cell adhesion molecules* of the immunoglobulin superfamily include intercellular adhesion and vascular adhesion molecules, which interact with integrins on leukocytes to mediate their recruitment.

The importance of the leukocyte adhesion molecules is demonstrated in persons with an inherited disorder called *leukocyte adhesion deficiency (LAD) type I*, in which deficiency of a member of the integrin superfamily leads to severe leukocytosis and recurrent infections. A similar deficiency is seen in individuals with impaired expression of a member of the selectin superfamily and has been labeled *LAD type 2*.[8] There is also evidence that excessive expression of cell adhesion molecules or their receptors contributes to the pathogenesis of some chronic inflammatory diseases such as rheumatoid arthritis.

SUMMARY CONCEPTS

- Inflammation is the body's response to injury and is characterized by the elaboration of chemical mediators and movement of fluid and leukocytes from the vascular compartment into the extravascular tissue space.
- There are two types of inflammation: acute inflammation, which is of short duration and characterized by the exudation of fluid and

plasma proteins, and chronic inflammation, which is associated with angiogenesis, tissue necrosis, and fibrosis (scarring).

- Many cells and tissue components contribute to the inflammatory response, including the endothelial cells that form capillaries and line blood vessels, circulating platelets and white blood cells, cells in connective tissue, and components of the extracellular matrix.

Acute Inflammation

Acute inflammation is the early or almost immediate reaction of local tissues and their blood vessels to injury. It typically occurs before the adaptive immune response becomes established (see Chapter 15) and is aimed primarily at removing the injurious agent and limiting the extent of tissue damage. Acute inflammation can be triggered by a variety of stimuli, including infections, immune reactions, blunt and penetrating trauma, physical or chemical agents (e.g., burns, frostbite, irradiation, caustic chemicals), and tissue necrosis from any cause.

The classic description of inflammation has been handed down through the ages. In the first century AD, the Roman physician Aulus Celsus described the local reaction of injury in terms that are now known as the *cardinal signs* of inflammation.[1] These signs are *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). In the second century AD, the Greek physician Galen added a fifth cardinal sign, *functio laesa* (loss of function). In addition to the cardinal signs that appear at the site of injury, systemic manifestations (e.g., fever) may occur as chemical mediators (e.g., cytokines) produced at the site of inflammation lead to increased levels in the plasma. The constellation of systemic manifestations and increases in serum proteins that may occur during acute inflammation is known as the *acute-phase response.*

Stages of Acute Inflammation

Acute inflammation has two stages: vascular and cellular. The vascular stage is characterized by increased blood flow (vasodilation) and structural changes (increased vascular permeability) that allow plasma proteins to leave the circulation. The cellular stage involves the emigration of leukocytes (mainly neutrophils) from the microcirculation and their accumulation at the site of injury or infection.

Vascular Stage

The vascular changes that occur with inflammation involve the arterioles, capillaries, and venules of the microcirculation. These changes begin almost immediately after injury and are characterized by vasodilation and changes in blood flow followed by increased vascular permeability and leakage of protein-rich fluid into the extravascular tissue space.[1,2]

Vasodilation, which is one of the earliest manifestations of inflammation, follows a transient constriction of the arterioles, lasting a few seconds. Dilation begins in the arterioles and opens capillary beds in the area. As a result, the area becomes congested, causing the redness (erythema) and warmth associated with acute inflammation. Vasodilation is induced by the action of several mediators, most notably histamine and nitric oxide.

Vasodilation is quickly followed by increased permeability of the microvasculature, with the outpouring of a protein-rich fluid (exudate) into the extravascular spaces. The loss of fluid results in an increased concentration of blood constituents (red blood cells, leukocytes, platelets, and clotting factors), stagnation of flow, and clotting of blood at the site of injury. This aids in limiting the spread of infectious microorganisms. The loss of plasma proteins reduces the intracapillary osmotic pressure and increases the osmotic pressure of the interstitial fluid, increasing fluid movement from the vascular compartment into the tissue space and producing the swelling, pain, and impaired function that are the cardinal signs of acute inflammation. The exudation of fluid into the tissue spaces also serves to dilute the offending agent.

The increased permeability characteristic of acute inflammation results from formation of endothelial gaps in the venules of the microcirculation. Binding of the chemical mediators to endothelial receptors causes contraction of endothelial cells and separation of intercellular junctions. This is the most common mechanism of vascular leakage and is elicited by histamine, bradykinin, leukotrienes, and many other classes of chemical mediators.

Depending on the severity of injury, the vascular changes that occur with inflammation follow one of three patterns of responses.[2] The first pattern is an *immediate transient response,* which occurs with minor injury. It develops rapidly after injury and is usually reversible and of short duration (15 to 30 minutes). The second pattern is an *immediate sustained response,* which occurs with more serious types of injury and continues for several days. It affects all levels of the microcirculation (arterioles, capillaries, and venules) and is usually due to direct damage of the endothelium by injurious stimuli, such as burns or the products of bacterial infections.[2] Neutrophils that adhere to the endothelium may also injure endothelial cells. The third pattern is a *delayed response,* in which the increased permeability begins after a delay of 2 to 12 hours, lasts for several hours or even days, and involves venules as well as capillaries.[2] A delayed response often accompanies injuries due to radiation, such as sunburn.

Cellular Stage

The cellular stage of acute inflammation is marked by changes in the endothelial cells lining the vasculature and movement of phagocytic leukocytes into the area of

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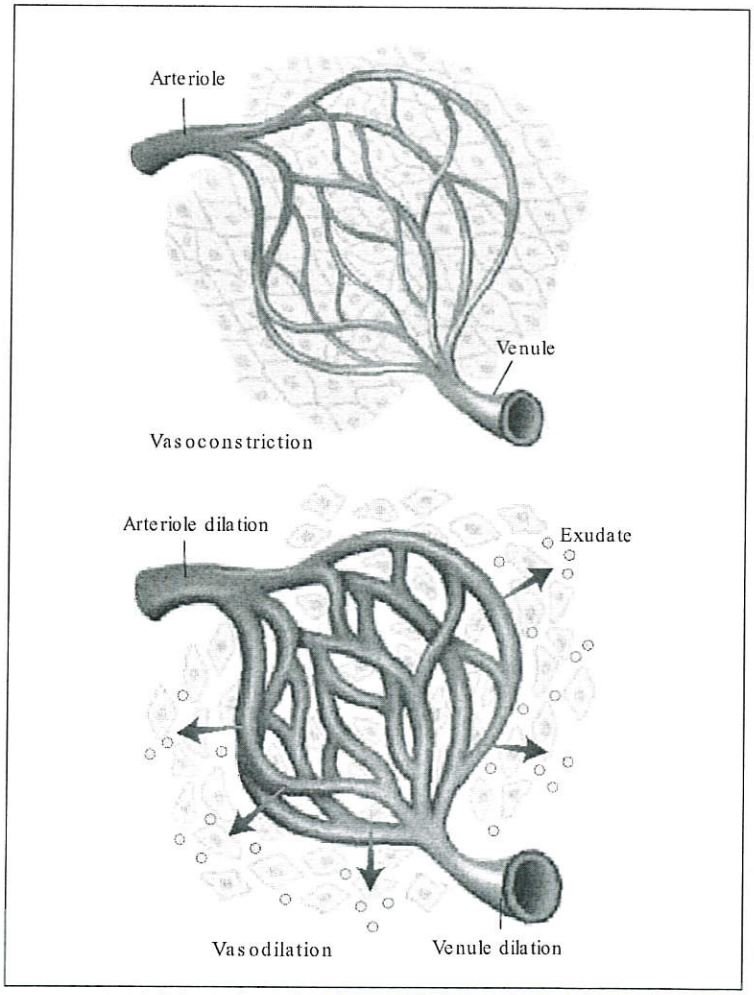
UNDERSTANDING → Acute Inflammation

Acute inflammation is the immediate and early response to an injurious agent. The response, which serves to control and eliminate altered cells, microorganisms, and antigens, occurs in two phases: (1) the vascular phase, which leads to an increase in blood flow and changes in the small blood vessels of the microcirculation; and (2) the cellular phase, which leads to the migration of leukocytes from the circulation and their activation to eliminate the injurious agent. The primary function of the inflammatory response is to limit the injurious effect of the pathologic agent and remove the injured tissue components, thereby allowing tissue repair to take place.

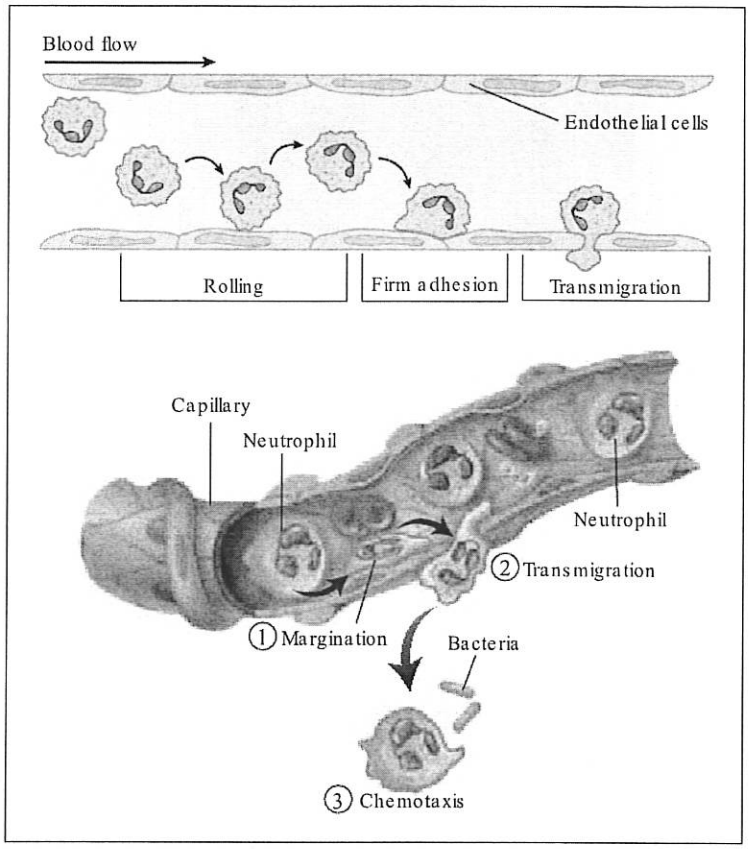
1

Vascular Phase. The vascular phase of acute inflammation is characterized by changes in the small blood vessels at the site of injury. It begins with 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 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 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.



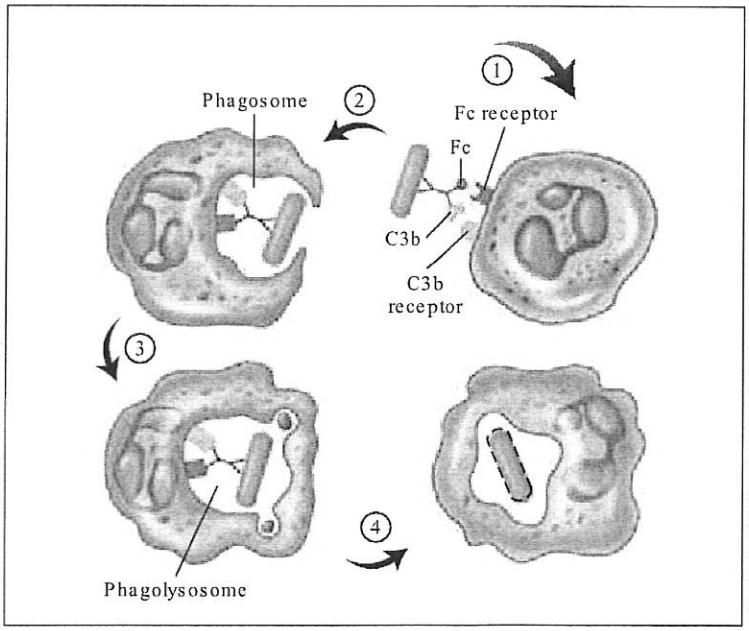
2

Cellular Phase: Leukocyte Margination, Adhesion, and Transmigration. 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.



3

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. 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 and actin assembly 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.



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injury or infection. Although attention has been focused on the recruitment of leukocytes from the blood, a rapid response also requires the release of chemical mediators from certain resident cells in the tissues (mast cells and macrophages). The sequence of events in the cellular response to inflammation includes leukocyte (1) margination and adhesion, (2) transmigration, (3) chemotaxis, and (4) activation and phagocytosis.[1–3]

During the early stages of the inflammatory response, signaling between blood leukocytes and the endothelial cells defines the inflammatory event and ensures arrest of the leukocytes along the endothelium.[9] As a consequence, blood flow—and leukocyte circulation—slows. This process of leukocyte accumulation is called *margination*. The subsequent release of cell communication molecules called *cytokines* causes the endothelial cells lining the vessels to express cell adhesion molecules that bind to carbohydrates on the leukocytes. This interaction, which is called *tethering*, slows their flow and causes the leukocytes to roll along the endothelial cell surface, finally coming to rest and adhering strongly to intercellular adhesion molecules on the endothelium.[1,2] The adhesion is followed by endothelial cell separation, allowing the leukocytes to extend pseudopodia and *transmigrate* through the vessel wall and then, under the influence of chemotactic factors, migrate into the tissue spaces.

Chemotaxis is a dynamic and energy-directed process of cell migration.[1] Once leukocytes exit the capillary, they move through the tissue guided by a gradient of secreted chemoattractants, such as chemokines, bacterial and cellular debris, and fragments generated from activation of the complement system (see Chapter 15). Chemokines, an important subgroup of chemotactic cytokines, are small proteins that direct the trafficking of leukocytes during the early stages of inflammation or injury.[13] Several immune (e.g., macrophages) and nonimmune cells secrete these chemoattractants to ensure the directed movement of leukocytes to the site of infection.

During the next and final stage of the cellular response, neutrophils, monocytes, and tissue macrophages are activated to engulf and degrade the bacteria and cellular debris in a process called *phagocytosis*.[1,2,14] Phagocytosis involves three distinct steps: recognition and adherence, engulfment, and intracellular killing. It is initiated by recognition and binding of particles by specific receptors on the surface of phagocytic cells. This binding is essential for trapping the agent, triggering engulfment, and intracellular killing of microbes. Microbes can be bound directly to the membrane of phagocytic cells by several types of pattern recognition receptors (e.g., toll-like and mannose receptors) or indirectly by receptors that recognize microbes coated with carbohydrate-binding lectins, antibody, and/or complement (see innate immunity, Chapter 15). The enhanced binding of an antigen to a coated microbe or particle is called *opsonization*. Engulfment follows the recognition of an agent as foreign. During the process of engulfment, extensions of cytoplasm move around and eventually enclose the particle in a membrane-surrounded phagocytic vesicle or *phagosome*. Once in the cell cytoplasm, the phagosome fuses with a cytoplasmic lysosome containing antibacterial molecules and enzymes that can kill and digest the microbe (see Chapter 1).

Intracellular killing of pathogens is accomplished through several mechanisms, including toxic reactive oxygen- and nitrogen-containing species, lysozymes, proteases, and defensins. The metabolic burst pathways that generate toxic reactive oxygen- and nitrogen-containing species (e.g., hydrogen peroxide, nitric oxide) require oxygen and metabolic enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide synthetase. Individuals who are born with genetic defects in some of these enzymes have immunodeficiency conditions that make them susceptible to repeated bacterial infection.

Inflammatory Mediators

Having described the events of acute inflammation, we can now turn to a discussion of the chemical mediators responsible for the events. Inflammatory mediators may be derived from the plasma or produced locally by cells at the site of inflammation (Fig. 3-3). The *plasma-derived mediators*, which are synthesized in the liver, include the acute-phase proteins, coagulation (clotting) factors (discussed in Chapter 12), and complement proteins (discussed in Chapter 15). 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.

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.

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 and factors in the coagulation system (see Chapter 12). One 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

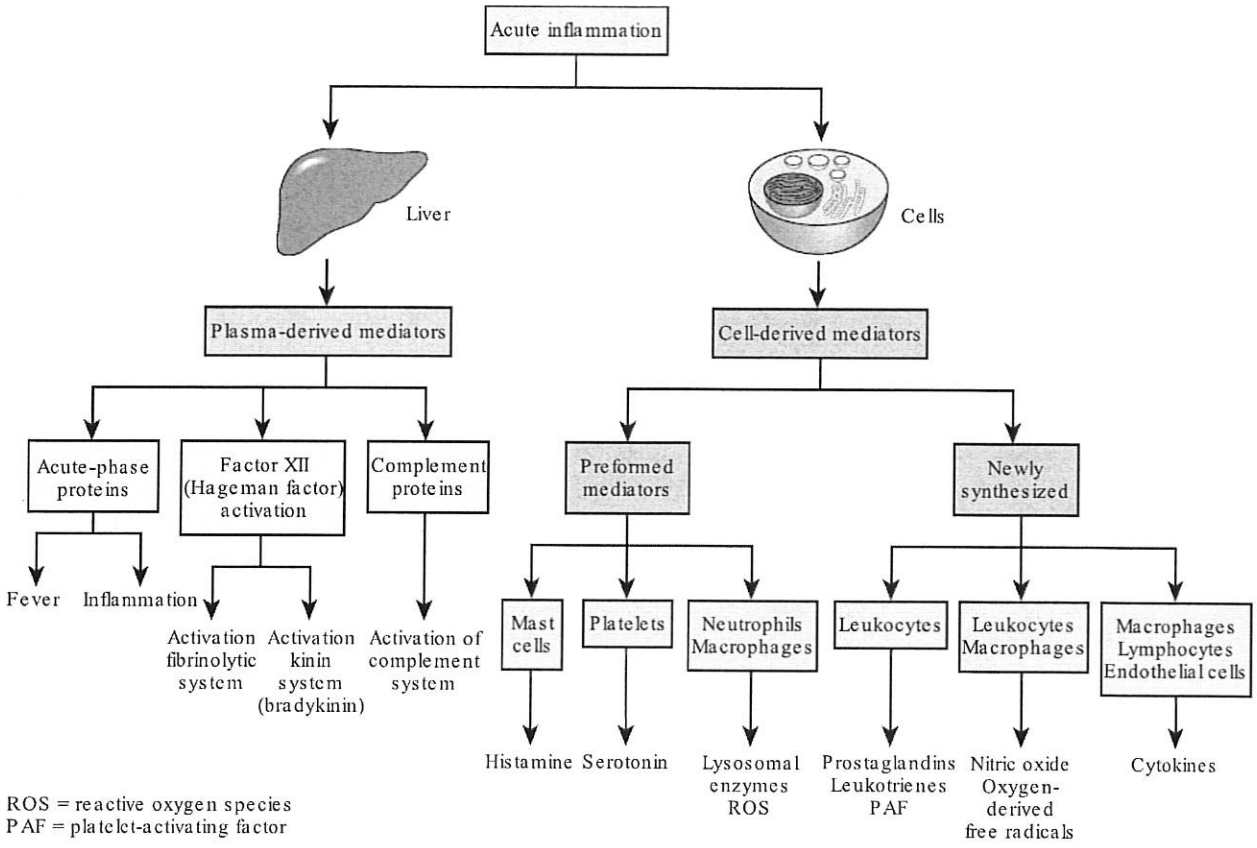

FIGURE 3-3. Plasma- and cell-derived mediators of acute inflammation.

increasing vascular permeability; (2) promoting leukocyte activation, adhesion, and chemotaxis; and (3) augmenting phagocytosis (see Chapter 15).

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, as are platelets, which are cellular fragments (see Fig. 3-3).

Histamine and Serotonin. Histamine and serotonin are classified as *vasoactive amines*, meaning they are derived from amino acids (histamine from histidine and serotonin from tryptamine) and act by producing changes in blood vessel tone. 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.

Preformed histamine is widely distributed in tissues, the highest concentrations being found in mast cells adjacent to blood vessels.[1,2] It is also found in circulating platelets and basophils and is released in response to a variety of stimuli, including trauma and immune reactions involving binding of IgE to basophils and mast cells. Histamine produces dilation of arterioles and increases the permeability of venules. It acts at the level of the microcirculation by binding to histamine$_1$ (H_1) receptors on endothelial cells and is considered the principal mediator of the immediate transient phase of increased vascular permeability in the acute inflammatory response. Antihistamine drugs (H_1 receptor antagonists), which bind to the H_1 receptors, act to competitively antagonize many of the effects of the immediate inflammatory response. Serotonin (5-hydroxytryptamine) is also a preformed vasoactive mediator, with 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).[15] 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 (Fig. 3-4). The corticosteroid drugs block the inflammatory effects of both pathways by inhibiting phosphodiesterase activity and thus preventing the release of arachidonic acid.[16]