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Acute Inflammation

Acute inflammation is a rapid host response that serves to deliver leukocytes and plasma proteins, such as antibodies, to sites of infection or tissue injury. Acute inflammation has three major components: (1) *alterations in vascular caliber that lead to an increase in blood flow*, (2) *structural changes in the microvasculature that permit plasma proteins and leukocytes to leave the circulation*, and (3) *emigration of the leukocytes* from the microcirculation, *their accumulation* in the focus of injury, and *their activation* to eliminate the offending agent

STIMULI FOR ACUTE INFLAMMATION

Acute inflammatory reactions may be triggered by a variety of stimuli:

- *Infections* (bacterial, viral, fungal, parasitic) and microbial toxins are among the most common and medically important causes of inflammation. Mammals possess many mechanisms for sensing the presence of microbes. Among the most important receptors for microbial products are the family of Toll-like receptors (TLRs), named after the *Drosophila* protein Toll, and several cytoplasmic receptors, which can detect bacteria, viruses, and fungi. Engagement of these receptors triggers signaling pathways that stimulate the production of various mediators.
- *Tissue necrosis* from any cause, including *ischemia* (as in a myocardial infarct), *trauma*, and *physical and chemical injury* (e.g., thermal injury, as in burns or frostbite; irradiation; exposure to some environmental chemicals). Several molecules released from necrotic cells are known to elicit inflammation; these include uric acid, a purine metabolite; adenosine triphosphate, the normal energy store; a DNA-binding protein of unknown function called HMGB-1; and even DNA when it is released into the cytoplasm and not sequestered in nuclei, as it should be normally. *Hypoxia*, which often underlies cell injury, is also itself an inducer of the inflammatory response. This response is mediated largely by a protein called HIF-1α (hypoxia-induced factor-1α), which is produced by cells deprived of oxygen and activates the transcription of many genes involved in inflammation, including vascular endothelial growth factor (VEGF), which increases vascular permeability.
- *Foreign bodies* (splinters, dirt, sutures) typically elicit inflammation

because they cause traumatic tissue injury or carry microbes.

- *Immune reactions* (also called hypersensitivity reactions) are reactions in which the normally protective immune system damages the individual's own tissues. The injurious immune responses may be directed against self antigens, causing *autoimmune diseases*, or may be excessive reactions against environmental substances or microbes. Inflammation is a major cause of tissue injury in these diseases . Because the stimuli for the inflammatory responses (i.e., self tissues) cannot be eliminated, autoimmune reactions tend to be persistent and difficult to cure, are associated with chronic inflammation, and are important causes of morbidity and mortality. The inflammation is induced by cytokines produced by T lymphocytes and other cells of the immune system . The term *immune-mediated inflammatory disease* is often used to refer to this group of disorders.

All inflammatory reactions share the same basic features, although different stimuli may induce reactions with some distinctive characteristics. We first describe the typical sequence of events in acute inflammation, and then the chemical mediators responsible for inflammation and the morphologic appearance of these reactions.

REACTIONS OF BLOOD VESSELS IN ACUTE INFLAMMATION

In inflammation, blood vessels undergo a series of changes that are designed to maximize the movement of plasma proteins and circulating cells out of the circulation and into the site of infection or injury. The escape of fluid, proteins, and blood cells from the vascular system into the interstitial tissue or body cavities is known as *exudation*. An *exudate* is an extravascular fluid that has a high protein concentration, contains cellular debris, and has a high specific gravity. Its presence implies an increase in the normal permeability of small blood vessels in an area of injury and, therefore, an inflammatory reaction. In contrast, a *transudate* is a fluid with low protein content (most of which is albumin), little or no cellular material, and low specific gravity. It is essentially an ultrafiltrate of blood plasma that results from osmotic or hydrostatic imbalance across the vessel wall without an increase in vascular permeability . *Edema* denotes an excess of fluid in the interstitial tissue or serous cavities; it can be either an exudate or a transudate. *Pus*, a *purulent*

exudate, is an inflammatory exudate rich in leukocytes (mostly neutrophils), the debris of dead cells and, in many cases, microbes.

The vascular reactions of acute inflammation consist of changes in the flow of blood and the permeability of vessels. Proliferation of blood vessels (angiogenesis) is prominent during repair and in chronic inflammation.

Changes in Vascular Flow and Caliber

Changes in vascular flow and caliber begin early after injury and consist of the following.

- *Vasodilation* is one of the earliest manifestations of acute inflammation; sometimes it follows a transient constriction of arterioles, lasting a few seconds. Vasodilation first involves the arterioles and then leads to opening of new capillary beds in the area. The result is *increased blood flow*, which is the cause of heat and redness *(erythema)* at the site of inflammation. *Vasodilation is induced by the action of several mediators, notably histamine and nitric oxide (NO), on vascular smooth muscle*.
- Vasodilation is quickly followed by *increased permeability of the microvasculature*, with the outpouring of protein-rich fluid into the extravascular tissues; this process is described in detail below.
- The loss of fluid and increased vessel diameter lead to slower blood flow, concentration of red cells in small vessels, and increased viscosity of the blood. These changes result in dilation of small vessels that are packed with slowly moving red cells, a condition termed *stasis*, which is seen as *vascular congestion* (producing localized redness) upon examination of the involved tissue.
- As stasis develops, blood leukocytes, principally neutrophils, accumulate along the vascular endothelium. At the same time endothelial cells are activated by mediators produced at sites of infection and tissue damage, and express increased levels of adhesion molecules. Leukocytes then adhere to the endothelium, and soon afterward they migrate through the vascular wall into the interstitial tissue, in a sequence that is described later.

Increased Vascular Permeability (Vascular Leakage)

A hallmark of acute inflammation is increased vascular permeability leading to the escape of a protein-rich exudate into the extravascular tissue, causing *edema*. Several mechanisms are responsible for the increased vascular permeability:

- *Contraction of endothelial cells resulting in increased interendothelial spaces* is the most common mechanism of vascular leakage and is elicited by histamine, bradykinin, leukotrienes, the neuropeptide substance P, and many other chemical mediators. It is called the *immediate transient response* because it occurs rapidly after exposure to the mediator and is usually short-lived (15–30 minutes). In some forms of mild injury (e.g. after burns, x-irradiation or ultraviolet radiation, and exposure to certain bacterial toxins), vascular leakage begins after a delay of 2 to 12 hours, and lasts for several hours or even days; this *delayed prolonged leakage* may be caused by contraction of endothelial cells or mild endothelial damage. Late-appearing sunburn is a good example of this type of leakage.
- *Endothelial injury, resulting in endothelial cell necrosis and detachment.* Direct damage to the endothelium is encountered in severe injuries, for example, in burns, or by the actions of microbes that target endothelial cells. Neutrophils that adhere to the endothelium during inflammation may also injure the endothelial cells and thus amplify the reaction. In most instances leakage starts immediately after injury and is sustained for several hours until the damaged vessels are thrombosed or repaired.
- Increased transport of fluids and proteins, called *transcytosis*, through the endothelial cell. This process may involve channels consisting of interconnected, uncoated vesicles and vacuoles called the *vesiculovacuolar organelle*, many of which are located close to intercellular junctions. Certain factors, such as VEGF (Chapter 3), seem to promote vascular leakage in part by increasing the number and perhaps the size of these channels.

Although these mechanisms of increased vascular permeability are described separately, all probably contribute in varying degrees in responses to most stimuli. For example, at different stages of a thermal burn, leakage results

from chemically mediated endothelial contraction and direct and leukocyte-dependent endothelial injury. The vascular leakage induced by all these mechanisms can cause life-threatening loss of fluid in severely burned patients.

Responses of Lymphatic Vessels

Although much of the emphasis in our discussion of inflammation is on the reactions of blood vessels, lymphatic vessels also participate in the response. The system of lymphatics and lymph nodes filters and polices the extravascular fluids. Recall that lymphatics normally drain the small amount of extravascular fluid that has seeped out of capillaries. In inflammation, lymph flow is increased and helps drain edema fluid that accumulates due to increased vascular permeability. In addition to fluid, leukocytes and cell debris, as well as microbes, may find their way into lymph. Lymphatic vessels, like blood vessels, proliferate during inflammatory reactions to handle the increased load. The lymphatics may become secondarily inflamed *(lymphangitis)*, as may the draining lymph nodes *(lymphadenitis)*. Inflamed lymph nodes are often enlarged because of hyperplasia of the lymphoid follicles and increased numbers of lymphocytes and macrophages. This constellation of pathologic changes is termed *reactive*, or *inflammatory*, *lymphadenitis* . For clinicians the presence of red streaks near a skin wound is a telltale sign of an infection in the wound. This streaking follows the course of the lymphatic channels and is diagnostic of lymphangitis; it may be accompanied by painful enlargement of the draining lymph nodes, indicating lymphadenitis.

REACTIONS OF LEUKOCYTES IN INFLAMMATION

As mentioned earlier, a critical function of inflammation is to deliver leukocytes to the site of injury and to activate the leukocytes to eliminate the offending agents. The most important leukocytes in typical inflammatory reactions are the ones capable of phagocytosis, namely neutrophils and macrophages. These leukocytes ingest and kill bacteria and other microbes, and eliminate necrotic tissue and foreign substances. Leukocytes also produce growth factors that aid in repair. A price that is paid for the defensive potency of leukocytes is that, when strongly activated, they may induce tissue damage and prolong inflammation, because the leukocyte products that destroy microbes and necrotic tissues can also injure normal host tissues.

The processes involving leukocytes in inflammation consist of: their recruitment from the blood into extravascular tissues, recognition of microbes and necrotic tissues, and removal of the offending agent.

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