Pathophsiology

Inflammation and Repair

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Inflammation:- is a complex response of living tissue to infections and damaged tissues that brings cells and molecules of host defenses from the circulation to the sites where they are needed in order to eliminate the offending agents.

Inflammatory conditions are commonly named by adding the suffix -itis to the affected organ or system. e.g., appendix= appendicitis, pericardium= pericarditis, and nerve= neuritis…….etc.

Although, inflammation and repair protective process may be harmful and causing diseases : autoimmune, hypersensitivity and fibrosis.

The cells and molecules of host defense, including leukocytes and plasma proteins, normally circulate in the blood, **and the goal of the inflammatory reaction is** to bring them to the site of infection or tissue damage. In addition, resident cells of vascular walls and the cells and proteins of the extracellular matrix (ECM) are also involved in inflammation and repair.

The external manifestations of inflammation(cardinal signs)

- **Heat** (calor) due to vasodilatation
- **Redness** (rubor) due to vasodilatation
- **Swelling** (tumor) due to exudate
- **Pain** (dolor)due to seretion of PG,PK, nerve compression and irritation
- **Loss of function** (functio laesa) due to swelling and pain .

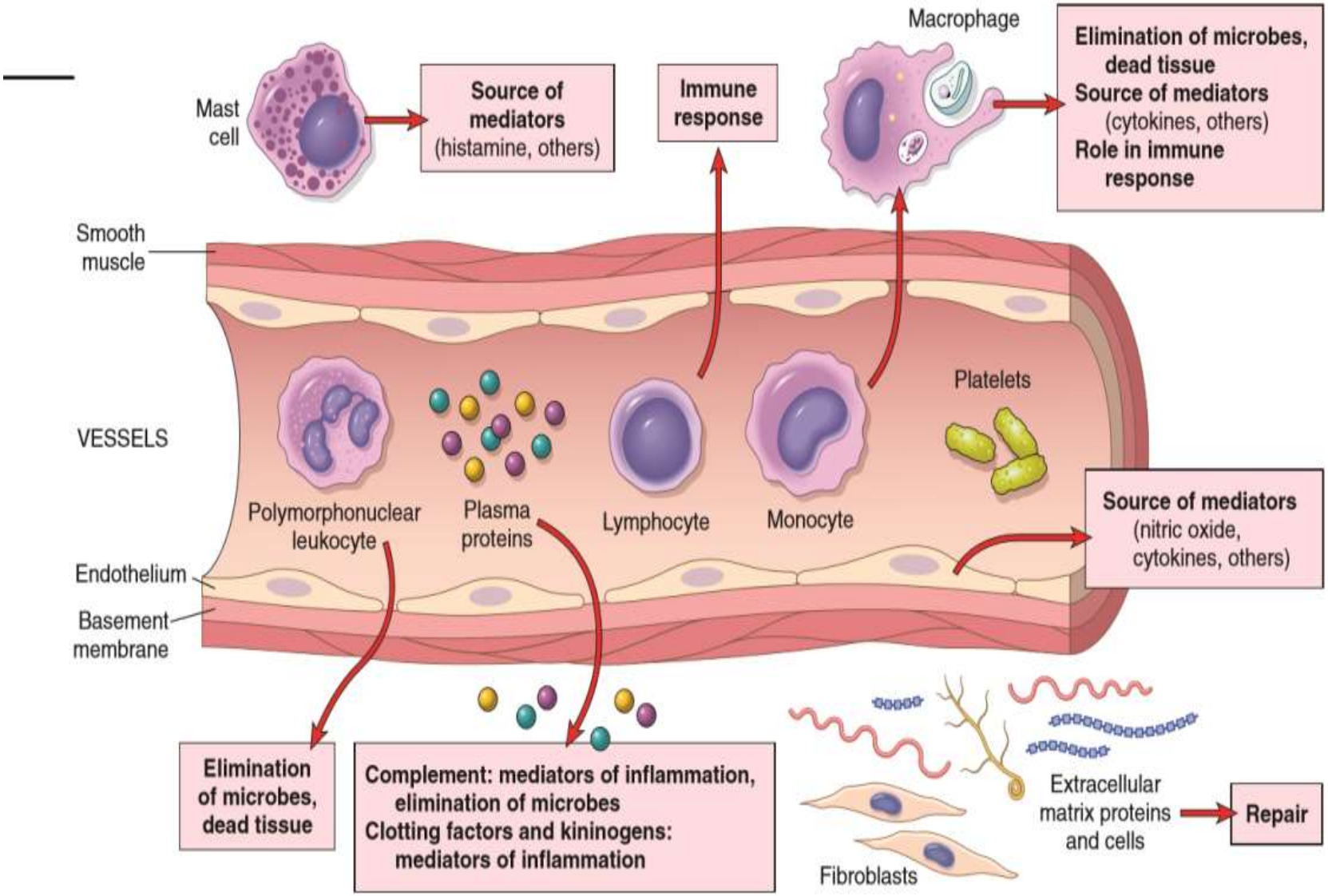

Figure 2–1 The components of acute and chronic inflammatory responses and their principal functions. The roles of these cells and molecules in inflammation are described in this chapter.

The steps of the inflammatory response

recognition of the injurious agent
recruitment of leukocytes
removal of the agent
regulation (control) of the response
resolution (repair)

Inflammation can be acute or chronic

Acute inflammation is rapid in onset and of short duration, lasting from a few minutes to as long as a few days, and is characterized by fluid and plasma protein exudation and a predominantly neutrophilc leukocyte accumulation.

Chronic inflammation may be more insidious, is of longer duration (days to years), and is typified by influx of lymphocytes and macrophages with associated vascular proliferation and fibrosis (scarring).

Stimuli for Acute Inflammation

- **Infections** (bacterial, viral, fungal, parasitic)
- **Trauma** (blunt and penetrating) and various physical and chemical agents (e.g., thermal injury, such as burns or frostbite; irradiation; toxicity from certain environmental chemicals)
- **Tissue necrosis** (from any cause), including ischemia (as in a myocardial infarct) and physical and chemical injury
- **Foreign bodies** (splinters, dirt, sutures, crystal deposits
- **Immune reactions** (also called hypersensitivity reactions) against environmental substances or against "self" tissues.

Acute inflammation has two major components

- **Vascular changes**: alterations in vessel caliber resulting in increased blood flow (vasodilatation) and changes in the vessel wall that permit plasma proteins to leave the circulation (increased vascular permeability). In addition, endothelial cells are activated, resulting in increased adhesion of leukocytes and migration of the leukocytes through the vessel wall.

- **Cellular events:** emigration of the leukocytes from the circulation and accumulation in the focus of injury (cellular recruitment), followed by activation of the leukocytes, enabling them to eliminate the offending agent. The principal leukocytes in acute inflammation are neutrophils (polymorphonuclear leukocytes).

Changes in Vascular Caliber and Flow

- After transient vasoconstriction (lasting only for seconds), arteriolar vasodilation occurs, resulting in locally increased blood flow and engorgement of the down-stream capillary beds. This vascular expansion is the cause of the redness (erythema) and warmth characteristic of acute inflammation.

- The microvasculature becomes more permeable, and protein-rich fluid moves into the extravascular tissues. This causes the red cells in the flowing blood to become more concentrated, thereby increasing blood viscosity and slowing the circulation. These changes are reflected microscopically by numerous dilated small vessels packed with red blood cells, called stasis.

- As stasis develops, leukocytes (principally neutrophils) begin to accumulate along the vascular endothelial surface—a process called margination. This is the first step in the journey of the leukocytes through the vascular wall into the interstitial tissue.

Increased Vascular Permeability

Increasing vascular permeability leads to the movement of protein-rich fluid and even blood cells into the extravascular tissues. This in turn increases the osmotic pressure of the interstitial fluid, leading to more outflow of water from the blood into the tissues. The resulting protein rich fluid accumulation is called an exudates.

Exudates must be distinguished from **transudates**, which are interstitial fluid accumulations caused by increased hydrostatic pressure, usually a consequence of reduced venous return. Transudates typically contain low concentrations of protein and few or no blood cells. Fluid accumulation in extravascular spaces, whether from an exudate or a transudate, produces tissue edema. Whereas exudates are typical of inflammation, transudates accumulate in various non inflammatory conditions.

Mechanisms of increased vascular permeability

- **Endothelial cell contraction**
- leading to intercellular gaps in venules
- is the most common cause of increased vascular permeability.
- Endothelial cell contraction occurs rapidly after binding of histamine, bradykinin, leukotrienes.
- It is usually short-lived (15 to 30 minutes).

❖ A slower and more prolonged retraction of endothelial cells, resulting from changes in the cytoskeleton, may be induced by cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1).

- This reaction may take 4 to 6 hours.

❑ Direct endothelial cell injury

❑ endothelial cell necrosis and detachment.

❑Endothelial cells are damaged after severe injury such as burns and some infections.

❑ Leakage begins immediately after the injury and persists for several hours or days until the damaged vessels are thrombosed or repaired.

❑ Venules, capillaries, and arterioles can all be affected.

❖ Direct injury to endothelial cells may also induce a delayed prolonged leakage that begins after a delay of 2 to 12 hours, lasts for several hours or even days, and involves venules and capillaries. Examples are mild to moderate thermal injury, certain bacterial toxins, and x- or ultraviolet irradiation.

❖ Endothelial cells may also be damaged as a consequence of leukocyte accumulation along the vessel wall. Activated leukocytes release many toxic mediators, that may cause endothelial injury or detachment.

- **Leakage from new blood vessels**.
- As in tissue repair involves new blood vessel formation (angiogenesis).
- These vessel sprouts remain leaky until proliferating endothelial cells mature sufficiently to form intercellular junctions.
- New endothelial cells also have increased expression of receptors for vasoactive mediators, and some of the factors that stimulate angiogenesis (e.g., VEGF) also directly induce increased vascular permeability.

Responses of Lymphatic Vessels

In inflammation, lymph flow is increased and helps drain edema fluid, leukocytes, and cell debris from the extravascular space. In severe inflammatory reactions, especially to microbes, the lymphatics may transport the offending agent, contributing to its dissemination.

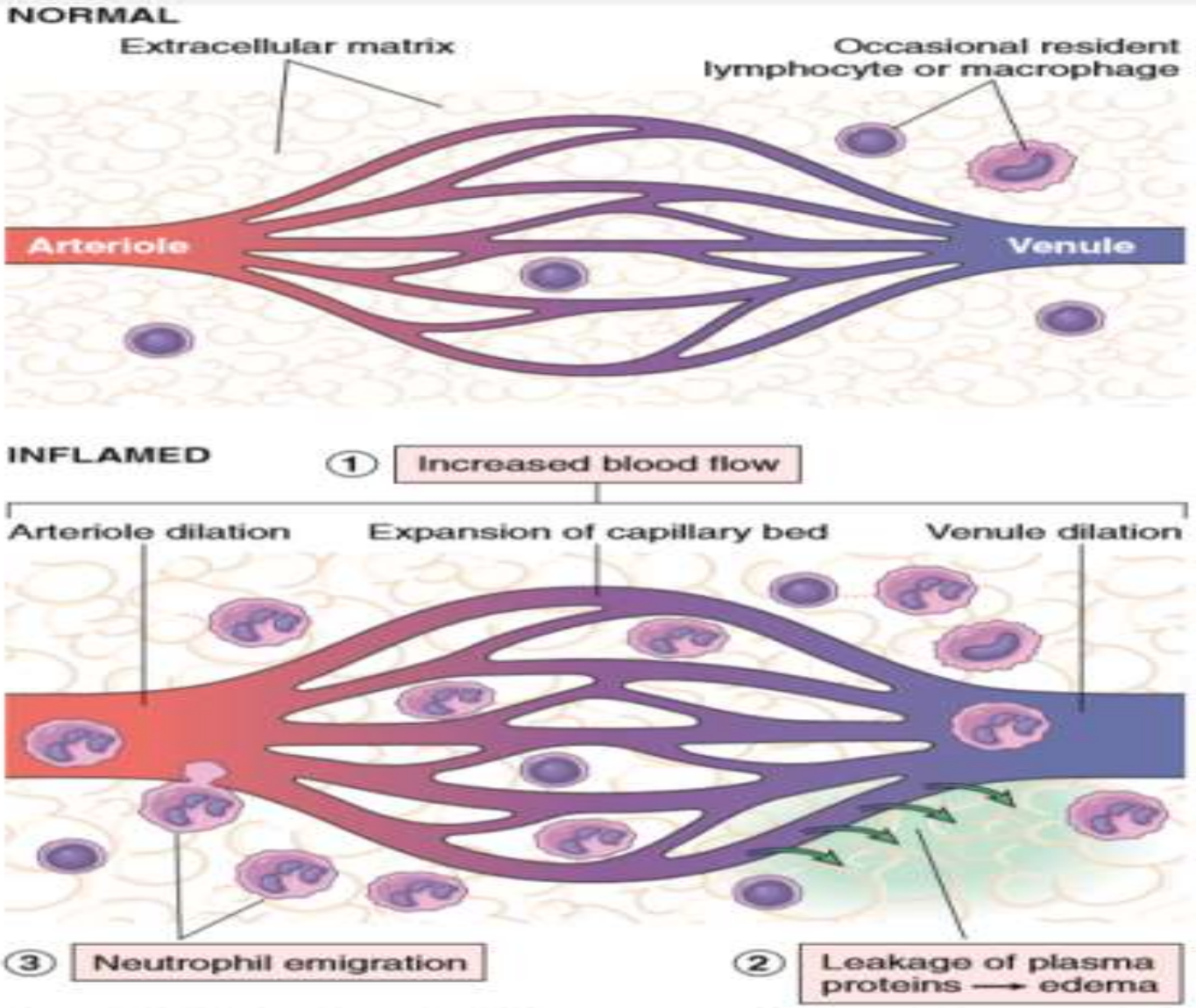

Figure 2–2 Vascular and cellular reactions of acute inflammation. The major local manifestations of acute inflammation, compared with normal, are *(1)* vascular dilation and increased blood flow (causing erythema and warmth), *(2)* extravasation of plasma fluid and proteins (edema), and *(3)* leukocyte (mainly neutrophil) emigration and accumulation.

Table 2–5 Actions of the Principal Mediators of Inflammation

Mediator	Source(s)	Actions
Cell-Derived		
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Serotonin	Platelets	Vasoconstriction
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage
Nitric oxide	Endothelium, macrophages	Vascular smooth muscle relaxation; killing of microbes
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	*Local*: endothelial activation (expression of adhesion molecules). *Systemic*: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Plasma Protein–Derived		
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (MAC), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain
Proteases activated during coagulation	Plasma (produced in liver)	Endothelial activation, leukocyte recruitment

IL-1, IL-6, interleukin-1 and -6; MAC, membrane attack complex; TNF, tumor necrosis factor.

Cellular Events: Leukocyte Recruitment and Activation

An important function of the inflammatory response is to deliver leukocytes to the site of injury and to activate them.

Leukocytes ingest offending agents, kill bacteria and other microbes, and eliminate necrotic tissue and foreign substances .

Therefore, host defense mechanisms include checks and balances that ensure that leukocytes are recruited and activated only when and where they are needed (i.e., in response to foreign invaders and dead tissues).

Steps of leukocyte Recruitment

(1) margination and rolling along the vessel wall; **(2)** firm adhesion to the endothelium; **(3)** transmigration between endothelial cells; and **(4)** migration in interstitial tissues toward a chemotactic stimulus.

Rolling, adhesion, and transmigration are mediated by the interactions of adhesion molecules on leukocytes and endothelial surfaces.

Chemical mediators— chemoattractants and certain cytokines— affect these processes by modulating the surface expression and binding affinity of the adhesion molecules and by stimulating directional movement of the leukocytes.

Margination and Rolling. As blood flows from capillaries into postcapillary venules, circulating cells are swept by laminar flow against the vessel wall. Because the smaller red cells tend to move faster than the larger white cells, leukocytes are pushed out of the central axial column and thus have a better opportunity to interact with lining endothelial cells, especially as stasis sets in. This process of leukocyte accumulation at the periphery of vessels is called **margination**. If the endothelial cells are activated by cytokines and other mediators produced locally, they express adhesion molecules to which the leukocytes attach loosely. These cells bind and detach and thus begin to tumble on the endothelial surface, a process called **rolling** .

Several families of cell adhesion molecules, including selectins, integrins, and the immunoglobulin superfamily, are involved in leukocyte recruitment and trafficking. 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 to endothelial cells.

The ***integrin*** superfamily consists of **30** structurally similar proteins that promote cell-to-cell and cell–to–extracellular matrix interactions.
Adhesion molecules of the immunoglobulin superfamily include intercellular adhesion and vascular adhesion molecules, all of which interact with integrins on leukocytes to mediate their recruitment.

Leukocyte Activation

Once leukocytes have been recruited to the site of infection or tissue necrosis, they must be activated to perform their functions.

Stimuli for activation include microbes, products of necrotic cells, and several mediators .

leukocytes use various receptors to sense the presence of microbes, dead cells, and foreign substances.

Engagement of these cellular receptors induces a number of responses in leukocytes that are part of their normal defensive functions and are grouped under the term leukocyte activation.

Morphologic Patterns Of Acute Inflammation:

The vascular and cellular reactions that characterize acute inflammation are reflected in the morphologic appearance of the reaction. The importance of recognizing these morphologic patterns is that they are often associated with different etiology and clinical situations.

- **Serous inflammation** is characterized by the outpouring of a watery, relatively protein-poor fluid that, depending on the site of injury, derives either from the plasma or from the secretions of mesothelial cells lining the peritoneal, pleural, and pericardial cavities. The skin blister resulting from a burn or viral infection is a good example of the accumulation of a serous effusion.
- **Fibrinous inflammation** occurs as a consequence of more severe injuries, resulting in greater vascular permeability that allows large molecules (such as fibrinogen) to pass the endothelial barrier. A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium, and pleura.

Suppurative (purulent) inflammation and abscess formation.

These are manifested by the collection of large amounts of purulent exudate **(pus)** consisting of neutrophils, necrotic cells, and edema fluid.

Certain organisms (e.g., staphylococci) are more likely to induce such localized suppuration and are therefore referred to as pyogenic (pus-forming).

Abscesses are focal collections of pus that may be caused by seeding of pyogenic organisms into a tissue or by secondary infections of necrotic foci. Abscesses typically have a central, largely necrotic region rimmed by a layer of preserved neutrophils with a surrounding zone of dilated vessels and fibroblast proliferation indicative of attempted repair.

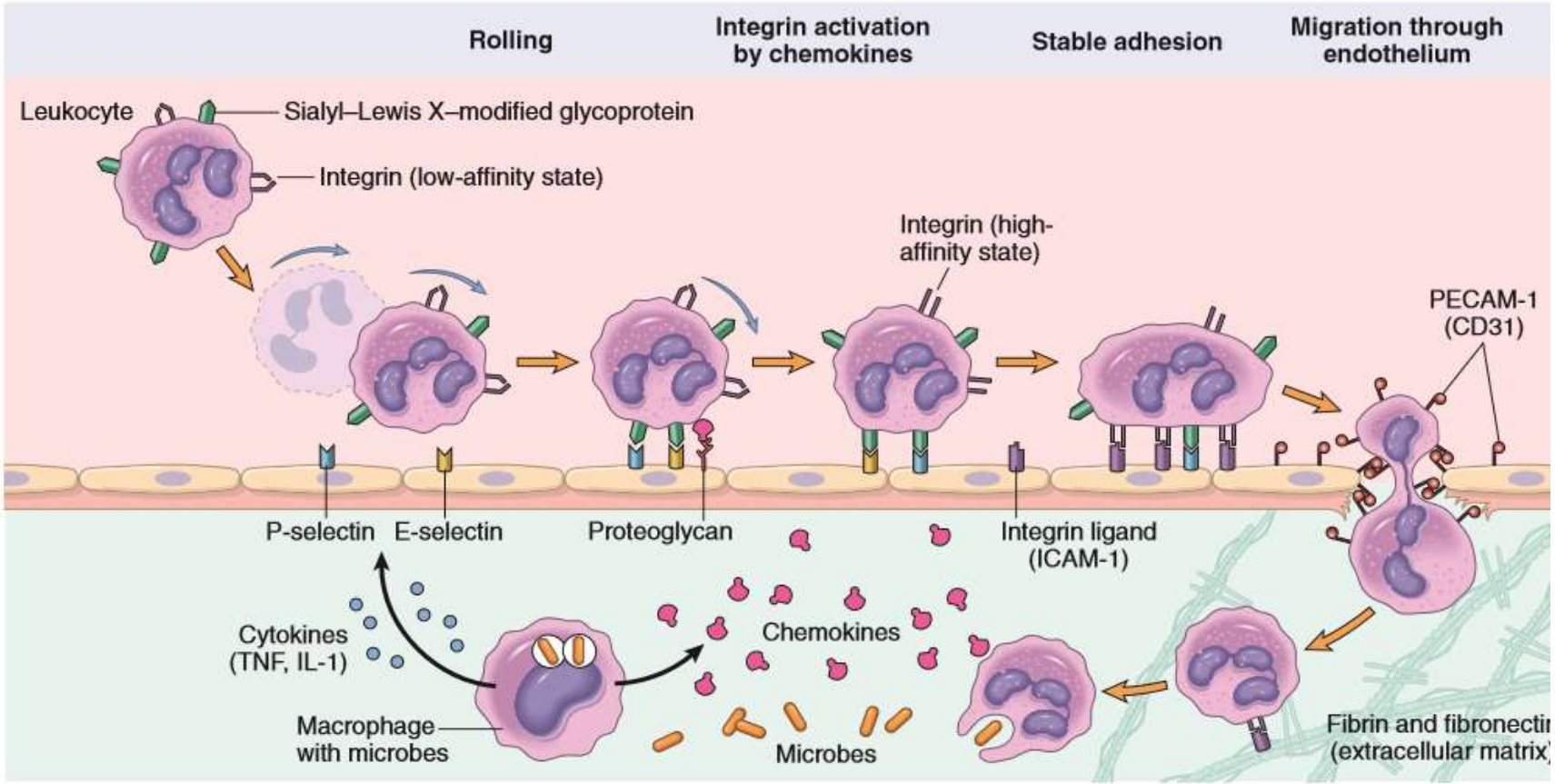

Figure 2–5 Mechanisms of leukocyte migration through blood vessels. The leukocytes (neutrophils shown here) first roll, then become activa and adhere to endothelium, then transmigrate across the endothelium, pierce the basement membrane, and migrate toward chemoattractants emar ing from the source of injury. Different molecules play predominant roles in different steps of this process: selectins in rolling; chemokines (usu displayed bound to proteoglycans) in activating the neutrophils to increase avidity of integrins; integrins in firm adhesion; and CD31 (PECAM-1 transmigration. ICAM-1, intercellular adhesion molecule-1; IL-1, interleukin-1; PECAM-1, platelet endothelial cell adhesion molecule-1; TNF, tur necrosis factor.

Outcomes of Acute Inflammation

- **Resolution:** Regeneration and repair. When the injury is limited or short-lived, when there has been no or minimal tissue damage, and when the injured tissue is capable of regenerating, the usual outcome is restoration to structural and functional normalcy .

- **Chronic inflammation** may follow acute inflammation if the offending agent is not removed**,** or it may be present from the onset of injury (e.g., in viral infections or immune responses to self-antigens). Depending on the extent of the initial and continuing tissue injury, as well as the capacity of the affected tissues to regrow, chronic inflammation may be followed by restoration of normal structure and function or may lead to scarring.

- **Scarring** is a type of repair after substantial tissue destruction (as in abscess formation) or when inflammation occurs in tissues that do not regenerate, in which the injured tissue is filled in by connective tissue.

In organs in which extensive connective tissue deposition occurs in attempts to heal the damage or as a consequence of chronic inflammation, the outcome is fibrosis, a process that can significantly compromise function.

Chronic inflammation

Chronic inflammation is inflammation of prolonged duration (weeks to years) in which continuing inflammation, tissue injury, and healing, often by fibrosis, proceed simultaneously. In contrast with acute inflammation, which is distinguished by vascular changes, edema, and a predominantly neutrophilic infiltrate.

chronic inflammation is characterized by a different set of reactions

- Infiltration with mononuclear cells, including macrophages, lymphocytes, and plasma cells
- Tissue destruction, largely induced by the products of the inflammatory cells
- Repair, involving new vessel proliferation (angiogenesis) and fibrosis.

Chronic inflammation may arise in the following settings

- Persistent infections by microbes that are difficult to eradicate. These include Mycobacterium tuberculosis and certain viruses and fungi
- Prolonged exposure to potentially toxic agents. Examples are non degradable exogenous materials such as inhaled particulate silica, and endogenous agents such as cholesterol crystals.

- Mild forms of chronic inflammation may be important in the pathogenesis of many diseases Such diseases include neurodegenerative disorders such as Alzheimer disease, atherosclerosis, metabolic syndrome and the associated type 2 diabetes, and some forms of cancer

❑Immune-mediated inflammatory diseases (hypersensitivity diseases). Diseases that are caused by excessive and inappropriate activation of the immune system are increasingly recognized as being important health problems . Under certain conditions, immune reactions develop against the affected person's own tissues, leading to autoimmune diseases. In such diseases, autoantigens evoke a self-perpetuating immune reaction that results in tissue damage and persistent inflammation. Autoimmunity plays an important role in several common and debilitating chronic inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis. Immune responses against common environmental substances are the cause of allergic diseases, such as bronchial asthma. Immune-mediated diseases may show morphologic patterns of mixed acute and chronic inflammation because they are characterized by repeated bouts of inflammation

Granulomatous Inflammation

Granulomatous inflammation is a distinctive pattern of chronic inflammation characterized by aggregates of activated macrophages with scattered lymphocytes.

Granulomas are characteristic of certain specific pathologic states; consequently, recognition of the granulomatous pattern is important because of the limited number of conditions (some life-threatening) that cause it. Granulomas can form under three settings:

- With persistent T-cell responses to certain microbes (such as Mycobacterium tuberculosis, syphilis , or fungi)
- Granulomas may also develop in some immune- mediated inflammatory diseases, notably Crohn disease.

- They are also seen in a disease of unknown etiology called sarcoidosis, and they develop in response to relatively inert foreign bodies (e.g., suture or splinter), forming so-called foreign body granulomas.

The formation of a granuloma effectively “walls off” the offending agent and is therefore a useful defense mechanism. However, granuloma formation does not always lead to eradication of the causal agent, which is frequently resistant to killing or degradation, and granulomatous inflammation with subsequent fibrosis may even be the major cause of organ dysfunction in some diseases, such as tuberculosis

Some of the activated macrophages in granulomas have pink, granular cytoplasm with indistinct cell boundaries; these are called **epithelioid cells** because of their resemblance to epithelia. Typically, the aggregates of epithelioid macrophages are surrounded by a collar of lymphocytes. Older granulomas may have a rim of fibroblasts and connective tissue. Frequently, but not invariably, **multinucleate giant cells** 40 to 50 µm in diameter are found in granulomas. Such cells consist of a large mass of cytoplasm and many nuclei, and they derive from the fusion of multiple activated macrophages.

Overview Of Tissue Repair

Critical to the survival of an organism is the ability to repair the damage caused by toxic insults and inflammation.

The inflammatory response to microbes and injured tissues not only serves to eliminate these dangers but also sets into motion the process of repair. Repair, sometimes called healing, refers to the restoration of tissue architecture and function after an injury. It occurs by two types of reactions: regeneration of the injured tissue and scar formation by the deposition of connective tissue.

Regeneration. Some tissues are able to replace the damaged cells and essentially return to a normal state; this process is called regeneration. Regeneration occurs by proliferation of residual (uninjured) cells that retain the capacity to divide, and by replacement from tissue stem cells. It is the typical response to injury in the rapidly dividing epithelia of the skin and intestines, and some parenchymal organs, notably the liver.

Scar formation. If the injured tissues are incapable of regeneration, or if the supporting structures of the tissue are severely damaged, repair occurs by the laying down of connective (fibrous) tissue, a process that results in scar formation. Although the fibrous scar cannot perform the function of lost parenchymal cells, it provides enough structural stability that the injured tissue is usually able to function. The term fibrosis is most often used to describe the extensive deposition of collagen that occurs in the lungs, liver, kidney, and other organs as a consequence of chronic inflammation, or in the myocardium after extensive ischemic necrosis (infarction). If fibrosis develops in a tissue space occupied by an inflammatory exudate, it is called **organization** (as in organizing pneumonia affecting the lung). After many common types of injury, both regeneration and scar formation contribute in varying degrees to the ultimate repair.

Cell Proliferation and Growth

Tissue growth and repair involve cell proliferation, differentiation, and apoptosis.

Cell proliferation:- is the process whereby tissues acquire new or replacement cells through mitotic cell division.

Cell differentiation:- is the orderly process in which proliferating cells are transformed into different and more specialized cell types. It determines the microscopic characteristics of the cell, its functions, and its life span. Cells that are fully differentiated often have reduced rates of proliferation.

Apoptosis:- is a form of programmed cell death that eliminates senescent and some types of injured cells (e.g. , those with DNA damage or hydrogen peroxide–induced injury).

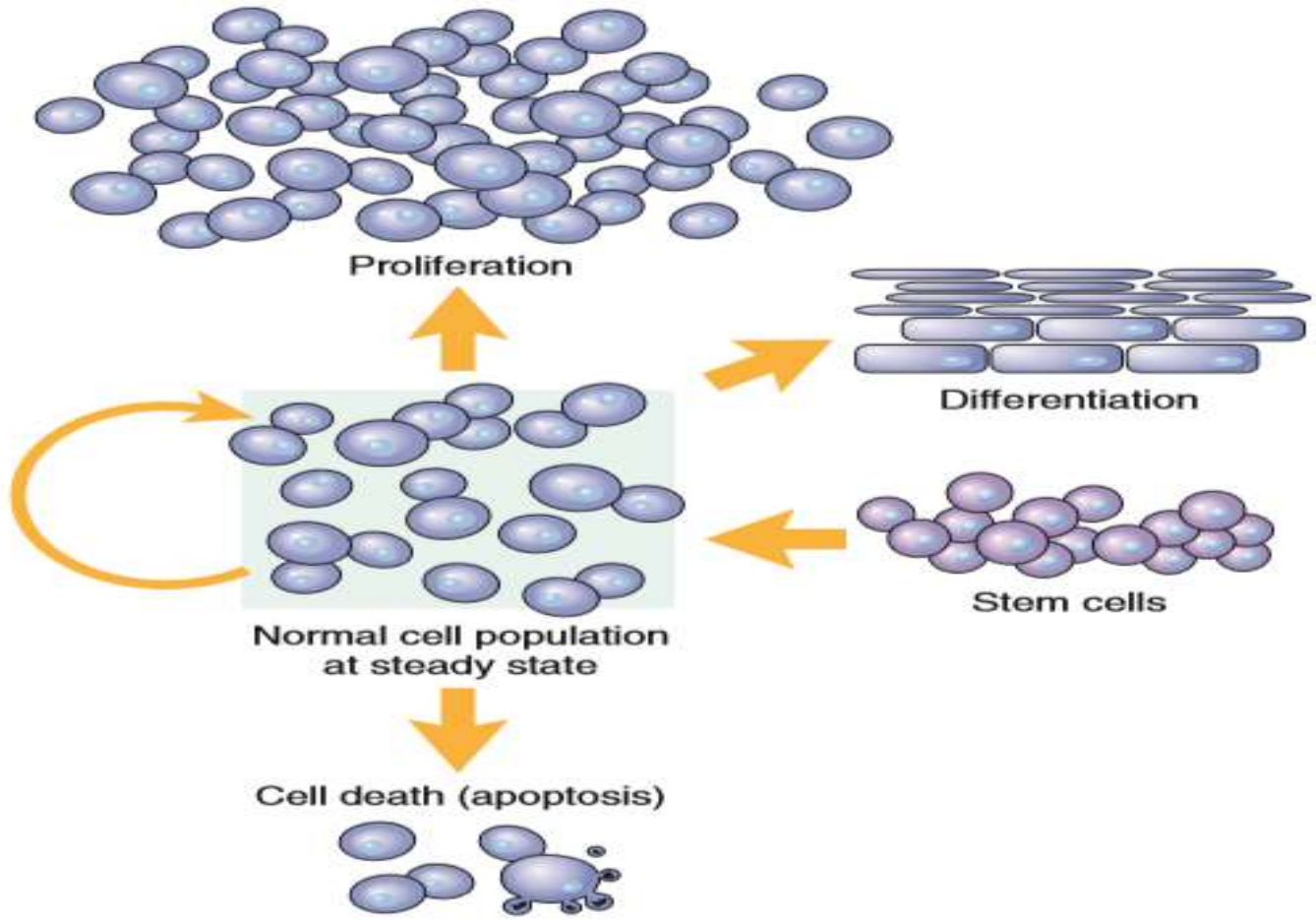

Figure 2–25 Mechanisms regulating cell populations. Cell numbers can be altered by increased or decreased rates of stem cell input, cell death by apoptosis, or changes in the rates of proliferation or differentiation.
(Modified from McCarthy NJ, et al: Apoptosis in the development of the immune system: growth factors, clonal selection and bcl-2. Cancer Metastasis Rev 11:157, 1992.)

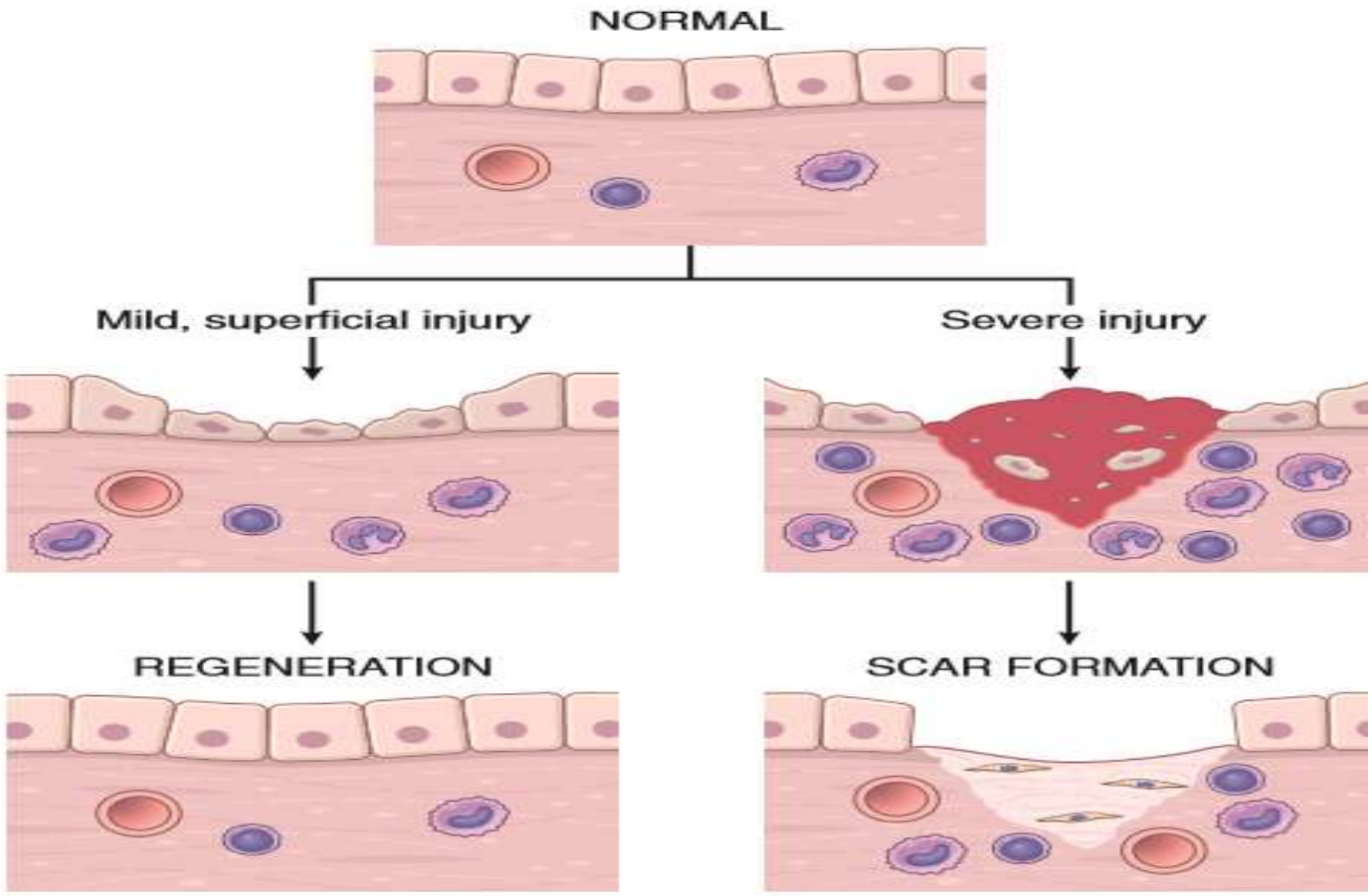

Figure 2–24 Mechanisms of tissue repair: regeneration and scar forma
tion. After mild injury, which damages the epithelium but not the underly
ing tissue, resolution occurs by regeneration, but after more severe injur
with damage to the connective tissue, repair is by scar formation.

References

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