

# GRANULOMATOUS INFLAMMATION

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This is a distinctive pattern of chronic inflammatory reaction characterized by focal accumulations of activated macrophages, which often develop an epithelioid (epithelial-like) appearance.

## Causes

Granulomatous inflammation is encountered in a number of immunologically mediated infectious and some noninfectious conditions, these include:-

1. Tuberculosis.
2. Sarcoidosis.
3. Cat-scratch disease.
4. Lymphogranuloma inguinale.
5. Leprosy.
6. Brucellosis.
7. Syphilis.
8. Some fungal infections.
9. Berylliosis.
10. Reactions of irritant.

Recognition of granulomas in a biopsy specimen is important because it shortens the list of the differential diagnosis. A granuloma is a focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelioid cells surrounded by a collar of mononuclear leukocytes, principally lymphocytes and occasionally plasma cells. The epithelioid cells have a pale pink granular cytoplasm with indistinct cell borders and a vesicular nucleus that is oval or elongate. Older granulomas develop an enclosing rim of fibroblasts and connective tissue. Frequently, epithelioid cells fuse to form giant cells in the periphery or sometimes in the center of granulomas. These **giant cells** may attain diameters of 40 to 50  $\mu\text{m}$ . (**Fig. 3-15**) They have a large mass of cytoplasm containing 20 or more small nuclei arranged either peripherally (Langhans-type giant cell) or haphazardly (foreign body-type giant cell).

## **There are two types of granulomas, which differ in their pathogenesis:**

**1. Foreign body granulomas**, which are provoked by foreign bodies. Typically, foreign body granulomas form when material such as talc (associated with intravenous drug abuse), sutures, or other fibers are large enough to preclude phagocytosis by a single macrophage and do not incite any specific inflammatory or immune response. Epithelioid cells and giant cells form and are apposed to the surface of the foreign body and/or actually include it. The foreign material can usually be identified in the center of the granuloma, particularly if viewed with polarized light, in which it appears refractile. (**Fig. 3-16**)

**2. Immune granulomas;** these are caused by insoluble, poorly degradable or particulate particles, typically microbes that are capable of inducing a cell-mediated immune response. In these responses, macrophages engulf the inciting agent, process it, and present some of it to appropriate T lymphocytes, causing them to become activated. The responding T cells produce cytokines, such as IL-2, which activates other T cells, perpetuating the response, and IFN- $\gamma$ , which is important in activating macrophages and transforming them into epithelioid cells and multinucleate giant cells.

The typical example of an immune granuloma is that caused by M. tuberculosis. In tuberculosis, the granulomatous reaction is referred to as a tubercle and is classically characterized by the presence of central caseous necrosis, whereas caseation is rare in other granulomatous diseases. (**Fig. 3-17**) It is always necessary to identify the specific etiologic agent by special stains for organisms (e.g., acid-fast stains for tubercle bacilli), by culture methods (e.g., in tuberculosis and fungal diseases), by molecular techniques (e.g., the polymerase chain reaction in tuberculosis), and by serologic studies (e.g., in syphilis). In sarcoidosis, the etiologic agent is unknown and the diagnosis is that of exclusion. (**Fig. 3-18**)

## **LYMPHATICS IN INFLAMMATION**

Lymph nodes filter the extravascular fluids brought to them by lymphatic vessels. They represent a secondary line of defense that operates whenever a local inflammatory reaction fails to contain and neutralize an external agent, such as a microbe.

Lymphatics are delicate channels that are difficult to visualize in ordinary tissue sections because they readily collapse. In inflammation lymph flow is increased and helps drain the edema fluid from the extravascular space. Not only fluid, but also leukocytes and cell debris may find their way into lymph. The drainage may transport the offending agent (chemical or microbial). The lymphatics may become secondarily inflamed (**lymphangitis**), as may the draining lymph nodes (**lymphadenitis**). Therefore, it is not uncommon in infections of the hand, for example, to observe red streaks along the entire arm up to the axilla following the course of the lymphatics (lymphangitis), accompanied by painful enlargement of the axillary lymph nodes (lymphadenitis). The nodal enlargement is usually caused by hyperplasia of the lymphoid follicles as well as by hyperplasia of the phagocytic cells lining the sinuses of the lymph nodes (reactive or inflammatory lymphadenitis). In severe infections, the lymph nodes may be overwhelmed and fail to halt the spread of infection. The organisms gain access to the vascular circulation, thus inducing a bacteremia. The phagocytic cells of the liver, spleen, and bone marrow constitute the next line of defense, but in massive infections,

bacteria seed distant tissues of the body. The heart valves, meninges, kidneys, and joints are favored sites of implantation for blood-borne organisms, and when this happens; endocarditis, meningitis, renal abscesses, and septic arthritis may develop.

### **SYSTEMIC EFFECTS OF INFLAMMATION**

The systemic changes associated with inflammation, especially infections, are collectively called the **acute phase response** (Systemic inflammatory response syndrome [**SIRS**]). These changes are reactions to cytokines produced in response to bacterial infections and other inflammatory stimuli.

#### **The acute phase response consists of several clinical and pathologic changes:**

1. Fever is a prominent manifestation; it is produced in response to pyrogens that act by stimulating PG synthesis in the vascular and perivascular cells of the hypothalamus.
2. Acute-phase proteins are plasma proteins, mostly synthesized in the liver, and whose plasma concentrations may increase several hundred times in inflammation. The best-known of these are
  - a. C-reactive protein (CRP).
  - b. Fibrinogen.
  - c. Serum amyloid A protein (SAA).

CRP and SAA, bind to microbial cell walls acting as opsonins and fixing complement. The rise in fibrinogen causes erythrocytes to form stacks (rouleaux) that sediment more rapidly than individual erythrocytes. This is the basis for the elevation of the ESR.

Prolonged production of SAA causes secondary amyloidosis in destructive chronic inflammations (e.g. rheumatoid arthritis).

Elevated serum levels of CRP are now used as a marker for increased risk of myocardial infarction in patients with atherosclerotic coronary artery disease. The inflammation involving atherosclerotic plaques in the coronary arteries may predispose to thrombosis and subsequent infarction, and CRP is produced during inflammation. On this basis, anti-inflammatory agents are being tested in patients to reduce the risk of myocardial infarction.

3. Leukocytosis is a common feature of the acute phase response, especially those induced by bacterial infection. The leukocyte count usually rises to 15,000 or 20,000 cells/ $\mu$ l, but sometimes it may reach very high levels of 40,000 to 100,000 cells/ $\mu$ l. These extreme elevations are referred to as leukemoid reactions because they are similar to the white cell counts obtained in leukemia. The leukocytosis occurs initially because of accelerated release of cells from the bone marrow reserve pool (induced by cytokines, including IL-1 and TNF) and is therefore associated with a rise in the number of more immature neutrophils in the blood (shift to the left).

Prolonged infection also induces proliferation of precursors in the bone marrow, caused by increased production of colony stimulating

factors (CSFs). Neutrophilia refers to an increase in the blood neutrophil count. Most bacterial infections induce neutrophilia. Viral infections such as infectious mononucleosis, mumps, and German measles produce a leukocytosis due to absolute lymphocytosis. In bronchial asthma, hay fever, and parasitic infestations, there is an absolute increase in the number of eosinophils, creating an eosinophilia. Certain infections (typhoid fever and infections caused by viruses, rickettsiae, and certain protozoa) are associated with a decreased number of circulating white cells (leukopenia). Leukopenia is also encountered in infections that overwhelm patients debilitated by disseminated cancer or uncontrolled tuberculosis.

4. Other manifestations of the acute phase response include increased pulse and blood pressure; decreased sweating; rigors, and anorexia.

5. Disseminated intravascular coagulation (DIC) & septic shock: in severe bacterial infections (sepsis), the large amounts of organisms and lipopolysaccharides (LPS) in the blood stimulate the production of enormous quantities of TNF and IL-1. High levels of TNF cause DIC. LPS and TNF induce tissue factor (TF) expression on endothelial cells, which initiates coagulation; the same agents inhibit natural anticoagulation mechanisms. Cytokines cause liver injury and impaired liver function, resulting in a failure to maintain normal blood glucose levels due to a lack of gluconeogenesis from stored glycogen. Overproduction of NO by cytokine-activated cardiac myocytes and vascular smooth muscle cells leads to heart failure and loss of perfusion pressure, respectively, resulting in cardiogenic shock. **The clinical triad of DIC, hypoglycemia, and cardiovascular failure is described as septic shock.**

Multiple organs show inflammation and intravascular thrombosis, which can produce organ failure. Lung damage (adult respiratory distress syndrome [ARDS]) results when neutrophil-mediated endothelial injury allows fluid to escape from the blood into the airspaces. The kidney and the bowel are also injured, largely due to reduced perfusion. Septic shock is often fatal.

## **CONSEQUENCES OF DEFECTIVE OR EXCESSIVE INFLAMMATION**

Defective inflammation typically results in:-

1. Increased susceptibility to infections.
2. Delayed healing or repair of wounds.
3. Tissue damage.

Delayed repair is due to the fact that the inflammatory response provides the necessary stimulus to get the repair process started.

**Excessive inflammation** is the basis of many categories of human disease that include allergies and autoimmune diseases.

Recent studies, however, are pointing to an important role of inflammation in a wide variety of human diseases that are not primarily disorders of the immune system. These include:-

1. Cancer.
2. Atherosclerosis.
3. Ischemic heart disease.
4. Some neurodegenerative diseases such as Alzheimer disease.

In addition, prolonged inflammation and the fibrosis that accompanies it are responsible for much of the pathology in many chronic infectious, metabolic and other diseases. **Since these disorders are some of the major curses of mankind**, it is not surprising that the normally protective inflammatory response is being called the "**silent killer**".

## **TISSUE REPAIR**

### **REGENERATION & HEALING BY FIBROSIS**

Critical to survival is the ability to repair the damage caused by injurious agents & inflammation. **Repair** refers to the restoration of tissue architecture and function after an injury. This occurs by regeneration &/or healing.

**Regeneration**: complete reinstatement of the damaged components of the affected tissue i.e. the tissue essentially returns to a normal state.

**Healing** is a reparative process characterized by laying down of connective (fibrous) tissue that results in scar formation. This mode occurs when:-

1. The injured tissues are incapable of complete regeneration, or
  2. The supporting structures of the tissue are severely damaged.
- Although the resulting fibrous scar is not normal, it provides enough structural stability that allows the injured tissue to function. Both regeneration and healing by fibrosis contribute in varying degrees to the ultimate repair.

#### **Repair involves:**

- a. The proliferation of various cells, and
- b. Close interactions between cells and the extracellular matrix (ECM).

Therefore, an understanding of the process of repair requires some knowledge of the control of cell proliferation and the functions of the ECM.

## **THE CONTROL OF CELL PROLIFERATION**

Several cell types proliferate during tissue repair.

These include:-

1. The remnants of the injured tissue (which attempt to restore normal structure).

2. Vascular endothelial cells (to create new vessels that provide the nutrients for the repair process).

3. Fibroblasts (the source of the fibrous tissue that fills defects).

The proliferation of the above cell types is driven by growth factors. The production of polypeptide growth factors, responses of cells to these factors, and the ability of these cells to divide and expand in numbers are all important determinants of the adequacy of the repair process.

The normal size of cell populations in any given tissue is determined by a balance of cell proliferation, cell death by apoptosis, and emergence of new differentiated cells from stem cells (**Fig. 4-1**).

### **THE CELL CYCLE**

The cell cycle represents the sequence of events that control DNA replication & mitosis in the proliferation of cells. It consists of a series of steps at which the cell checks for the accuracy of the process and instructs itself to proceed to the next step (**Fig. 4-2**).

The cycle consists of the presynthetic growth phase 1 ( $G_1$ ), the DNA synthesis phase (S), the premitotic growth phase 2 ( $G_2$ ), and the mitotic phase (M). Non-dividing cells are either in cell cycle arrest in  $G_1$  or they exit the cycle to enter a phase called  $G_0$ . Any stimulus that initiates cell proliferation, such as exposure to growth factors, needs to promote the  $G_0/G_1$  transition and the entry of cells into the  $G_1$ . Further progression is determined by the ability of the cell to pass through an intrinsic quality control mechanism for cell integrity, known as checkpoint control. Checkpoint controls prevent DNA replication or mitosis of damaged cells and either transiently stop the cell cycle to allow for DNA repair or eliminate irreversibly damaged cells by apoptosis. Progression through the cell cycle from  $G_1$  is regulated by proteins called cyclins, which form complexes with enzymes called cyclin-dependent kinases (CDKs). These complexes regulate the phosphorylation of proteins involved in cell cycle progression leading to DNA replication and mitosis, and thus are required for cell cycle progression.

A major action of growth factors is to overcome the checkpoint controls by liberating the suppression of CDK activity. Once cells enter the S phase, the DNA is replicated and the cell progresses through  $G_2$  and mitosis.