GENERAL PATHOLOGY

Chronic inflammation

Definition: Chronic inflammation is a response of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts at repair coexist in varying combinations.

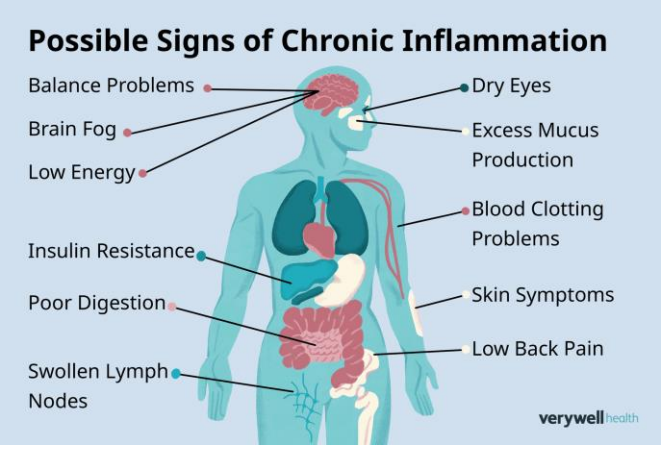
It may follow acute inflammation, as described earlier, or chronic inflammation may begin insidiously, as a low-grade, smoldering response without any manifestations of a preceding acute reaction. Different stimuli may cause variations in the morphological appearances but, overall, in the chronic inflammatory infiltrate lymphocytes, macrophages and plasma cells predominate, in contrast to acute inflammation where the major cell type is the neutrophil. Chronic inflammation may be subdivided as follows:

1.Non-specific chronic inflammation: arises following non-resolution of acute inflammation, e.g. chronic peptic ulcer, chronic abscess.

2.Specific (primary) chronic inflammation: arises de novo in response to certain types of injurious agents, e.g. rheumatoid arthritis, idiopathic pulmonary fibrosis

3.Granulomatous inflammation: is a subset of specific chronic inflammation characterized by the presence

of granulomas, e.g., sarcoidosis, tuberculosis.



Causes of Chronic Inflammation

1. ***Persistent infections*** **by microorganisms that are difficult to eradicate, such as mycobacteria and certain viruses, fungi, and parasites. These organisms often evoke an immune reaction called delayed-type hypersensitivity.**
2. ***Hypersensitivity diseases*****. Chronic inflammation plays an important role in a group of diseases that are caused by excessive and inappropriate activation of the immune system. Under certain conditions, immune reactions develop against the individual's own tissues, leading to autoimmune diseases. In these diseases, autoantigens trigger a self-perpetuating immune reaction that results in chronic tissue damage and inflammation;** ***examples*** **of such diseases include rheumatoid arthritis and multiple sclerosis. In other cases, Immune responses against common environmental substances are the cause of allergic diseases, such as bronchial asthma.**

3. ***Prolonged exposure to potentially toxic agents*****, either exogenous or endogenous. An example of an exogenous agent is particulate silica, results in an inflammatory lung disease called silicosis. Example of endogenous agent is Atherosclerosis is a chronic inflammatory process of the arterial wall induced, at least in part, by excessive production and tissue deposition of endogenous cholesterol and other lipids.**

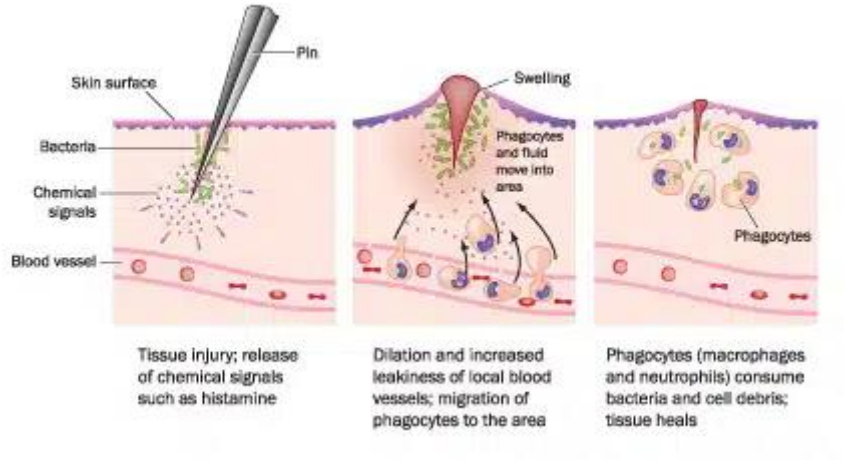
Morphologic Features

In contrast to acute inflammation, which is manifested by vascular changes, edema, and predominantly neutrophilic infiltration, chronic inflammation is characterized by the following:

• Infiltration with mononuclear cells, which include macrophages, lymphocytes, and plasma cells.

• Tissue destruction, induced by the persistent offending agent or by the inflammatory cells.

• Attempts at healing by connective tissue replacement of damaged tissue, accomplished by angiogenesis (proliferation of small blood vessels) and, in particular, fibrosis.



Cells and Mediators of Chronic Inflammation

The combination of leukocyte infiltration, tissue damage, and fibrosis that characterize chronic inflammation is the result of the local activation of several cell types and the production of mediators.

Role of Macrophages

The dominant cells in most chronic inflammatory reactions are macrophages, which contribute to the reaction by secreting cytokines and growth factors that act on various cells, destroying foreign invaders and tissues, and activating other cells, notably T lymphocytes.

Function: **Macrophages are professional phagocytes that eliminate microbes and damaged tissues. They also serve important roles in the repair of injured tissues.**

Origin: **Macrophages are tissue cells derived from hematopoietic stem cells in the bone marrow in postnatal life and from progenitors in the embryonic yolk sac and fetal liver during early development.**

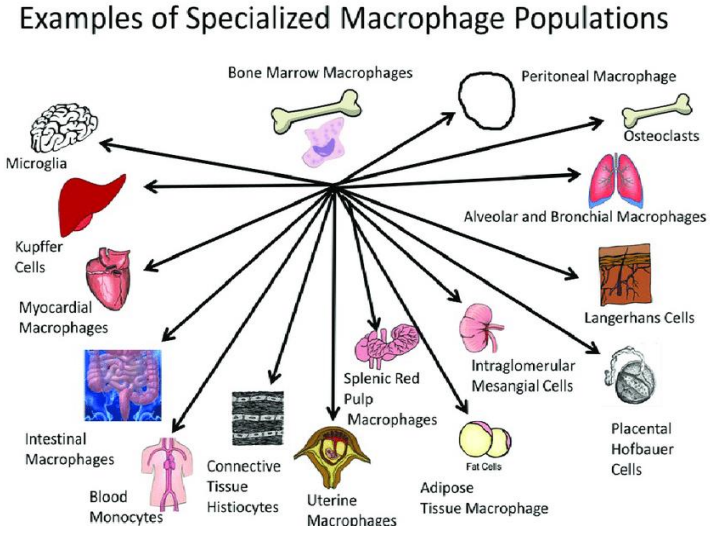
Names in specific locations in organs:

Liver→ called Kupffer cells

spleen and lymph nodes → called sinus histiocytes

central nervous system→ called microglial cells

lungs→ called alveolar macrophages



Together, these cells comprise the mononuclear phagocyte system, also known by the older (an inaccurate) name reticuloendothelial system.

Circulating cells of this lineage are known as monocytes migrate into various tissues, and differentiate into macrophages. The half-life of blood monocytes is about 1 day, whereas the lifespan of tissue macrophages may be several months or years.

Major pathways of macrophage activation,

1. ***Classical macrophage activation* may be induced by**
   a. **microbial products such as endotoxin.**

b. **by T cell–derived signals, importantly the cytokine IFN-γ, in immune responses.**

c. **by foreign substances, including crystals and particulate matter.**

2. ***Alternative macrophage activation*** **is induced by cytokines other than IFN-γ, such as IL-4 and IL-13, produced by T lymphocytes and other cells. These macrophages are not actively microbicidal; instead, their principal functions are to terminate.**

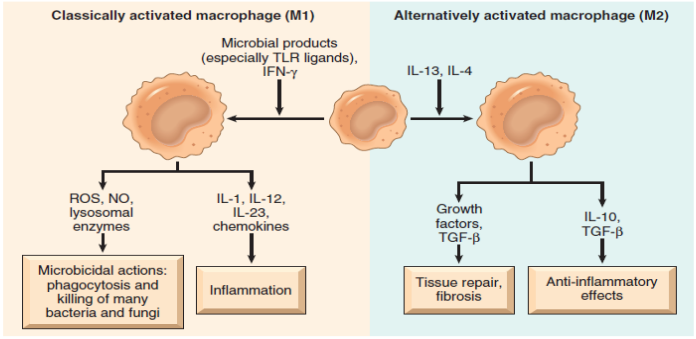


Figure 3.20 Classical and alternative macrophage activation. Different stimuli activate monocytes/macrophages to develop into functionally distinct populations. Classically activated macrophages are induced by microbial products and cytokines, particularly interferon-γ (IFN-γ). They phagocytose and destroy microbes and dead tissues and can potentiate inflammatory reactions. Alternatively activated macrophages are induced by other cytokines and are important in tissue repair and resolution of inflammation. *IL*, Interleukin; *NO*, nitric oxide; *ROS*, reactive oxygen species; *TGF-β*, transforming growth factor-β; *TLR*, Toll-like receptor.

3. **inflammation and promote tissue repair.**

<u>The products of activated macrophages serve to</u>

1. **Macrophages, like the other type of phagocytes, the neutrophils, ingest and eliminate microbes and dead tissues.**
2. **Macrophages initiate the process of tissue repair and are involved in scar formation and fibrosis.**
3. **Macrophages secrete mediators of inflammation, such as cytokines (TNF, IL-1, chemokines, and others Thus, macrophages contribute to the initiation and propagation of inflammatory reactions.**
4. **Macrophages display antigens to T lymphocytes and respond to signals from T cells, that is essential for defense against many microbes by cell-mediated immune responses.**

Role of Lymphocytes

Microbes and other environmental antigens activate T and B lymphocytes, which amplify and propagate chronic inflammation.

1. **the inflammation tends to be persistent and severe, in part because lymphocyte activation leads to the generation of long-lived memory cells.**
2. **Some of the persistent chronic inflammatory reactions, such as granulomatous inflammation.**
3. **Lymphocytes may be the dominant population in the chronic inflammation seen in various autoimmune diseases.**
4. **By virtue of their ability to secrete cytokines, CD4+ T lymphocytes promote inflammation and influence the nature of the inflammatory reaction. There are three subsets of CD4+ T cells:**
   a. **Th1 cells produce the cytokine IFN-γ**
   b. **Th2 cells secrete IL-4, IL-5, and IL-13, which recruit and activate eosinophils.**
   c. **Th17 cells secrete IL-17 and other cytokines, which induce the secretion of chemokines responsible for recruiting neutrophils (and monocytes) into the reaction.**

- **Both Th1 and Th17 cells are involved in defense against many types of bacteria and viruses and in autoimmune diseases in which tissue injury is caused by chronic inflammation.**
- **Th2 cells are important in defense against helminthic parasites and in allergic inflammation.**

Plasma cells:

Activated B lymphocytes **and antibody-producing** ***plasma cells*** **are also often present at sites of chronic**

inflammation. The antibodies produced

1.may be specific for persistent foreign antigens.

2. self-antigens in the inflammatory site or against altered tissue components.

some chronic inflammatory reactions, the accumulated lymphocytes, antigen-presenting cells, and plasma cells cluster together to form organized lymphoid follicles resembling those seen in lymph nodes.

Other Cells in Chronic Inflammation

1. ***Eosinophils*** **are abundant in immune reactions mediated by IgE and in parasitic infections. derived from leukocytes and epithelial cells. Eosinophils have granules that contain major basic protein, a highly cationic protein that is toxic to helminths but also may injure host epithelial cells. This is why eosinophils are of benefit in controlling helminth infections, yet they also contribute to tissue damage in immune reactions such as allergies.**
2. ***Mast cells*** **are widely distributed in connective tissues and participate in both acute and chronic inflammatory reactions. In immediate hypersensitivity reactions, IgE antibodies bound to the cells' Fc receptors specifically recognize antigen, and the cells degranulate and release mediators such as histamine and prostaglandins, this type of response occurs during allergic reactions to foods, insect venom, or drugs.**

Granulomatous Inflammation

Granulomatous inflammation is a form of chronic inflammation characterized by collections of activated macrophages, often with T lymphocytes, and sometimes associated with necrosis.

The defining feature of granulomatous inflammation is the presence of activated epithelioid macrophages and multinucleate giant cells derived from macrophages. Epithelioid macrophages are so named because they bear some resemblance histologically to epithelial (squamous) cells.

There are two types of granulomas, which differ in their pathogenesis.

• *Foreign body granulomas* are incited by inert foreign bodies, which induce inflammation in the absence of T cell–mediated immune responses. Typically,

foreign body granulomas form around materials such as talc (associated with intravenous drug abuse), sutures, or other fibers that are large enough to preclude phagocytosis by a macrophage and are not immunogenic, so they do not incite any specific immune response.

• *Immune granulomas* are caused by a variety of agents that are capable of inducing a persistent T cell–mediated immune response. This type of immune response usually produces granulomas when the inciting agent is difficult to eradicate, such as a persistent microbe. In some parasitic infections.

MORPHOLOGY

1. **The aggregates of epithelioid macrophages are surrounded by a collar of lymphocytes.**
2. **Older granulomas may have a rim of fibroblasts and connective tissue.**
3. **multinucleated giant cells 40 to 50 µm in diameter are found in granulomas; these are called *Langhans giant cells*. They consist of a large mass of cytoplasm and many nuclei, and they derive from the fusion of multiple activated macrophages.**
4. **In granulomas associated with certain infectious organisms (most classically Mycobacterium tuberculosis) a combination of hypoxia and free radical–mediated injury leads to a central zone of necrosis.**
5. **Grossly, this has a granular, cheesy appearance and is therefore called caseous necrosis**
6. ***Microscopically*, this necrotic material appears as amorphous, structureless, eosinophilic, granular debris, with complete loss of cellular details (as opposed to coagulative necrosis, in which cell outlines are preserved).**
7. **The granulomas in Crohn disease, sarcoidosis, and foreign body reactions tend to not have necrotic centers and are said to be noncaseating.**
8. **Healing of granulomas is accompanied by fibrosis that may be extensive in involved organs**