

## CHRONIC INFLAMMATION

Chronic inflammation is considered to be inflammation of prolonged duration (weeks or months) in which active inflammation, tissue destruction, and attempts at repair are proceeding simultaneously.

### CAUSES OF CHRONIC INFLAMMATION

Chronic inflammation arises in the following settings:

- 1- Persistent, low- grade infections by certain microorganisms, such as tubercle bacilli, *Treponema pallidum* (the causative organism of syphilis), and certain viruses, fungi, and parasites, these organisms are of low toxicity.
- 2- Prolonged exposure to potentially toxic agents, either exogenous or endogenous. Such as silica, talc, surgical suture material.
- 3- Immune-mediated inflammatory diseases
  - *hypersensitivity diseases*: Diseases that are caused by excessive and inappropriate activation of the immune system.
  - *autoimmune diseases*: immune reactions develop against the affected person's own tissues,

### MORPHOLOGIC FEATURES

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

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

## Chronic inflammatory cells

### Macrophages

Macrophages, the dominant cells of chronic inflammation, are tissue cells derived from circulating blood monocytes after their emigration into the tissue forming the tissue macrophage that are diffusely scattered in all connective tissues. They are called collectively as the mononuclear phagocyte system, (reticulo-endothelial cells).

**Macrophage are named** according to the site where they are present- :

Liver (Kupffer cells)

Spleen and lymph nodes (sinus histiocytes),

Lungs (alveolar macrophages).

Central nervous system (Microglial cell)

From the blood, monocytes migrate into various tissues and differentiate into macrophages. The half-life of blood monocytes is about 1 day. Macrophages are larger and have longer lifespan and greater capacity for phagocytosis than monocytes

**Activation of Macrophage:** Macrophages are activated by- :

- *Classical macrophage activation is induced by*

1- microbial products such as endotoxin,

2-T cell–derived signals, importantly the cytokine IFN- $\gamma$ ,

3- foreign substances.

- *Alternative macrophage activation* is induced by cytokines such as IL-4 and IL-13, produced by T lymphocytes and other cells, including mast cells and eosinophils.

## The products of activated macrophages serve to

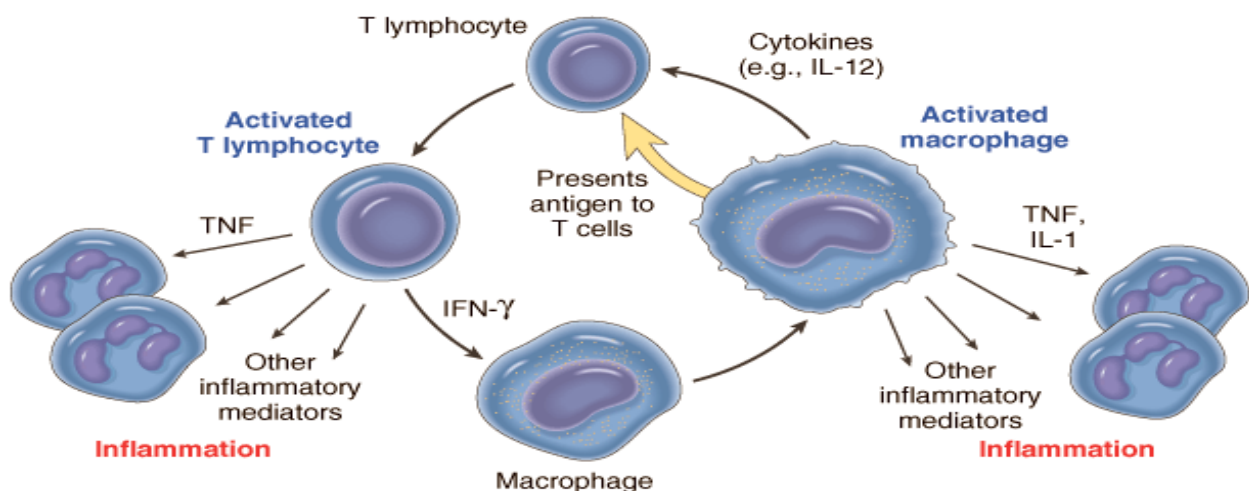
- 1 - ingest and eliminate microbes and dead tissue (**ROS, NO, lysosomal enzyme**)
- 2 - initiate the process of tissue repair and involved in scar formation (growth factor)
- 3- Secrete mediators of inflammation such as (Tumor necrotic factor TNF, Interleukin -1) IL -1 (and Cytokines) to promote leukocyte recruitment.
- 4- Macrophages display antigens to T lymphocyte and respond to signal from T cell

## Lymphocytes

Both T and B lymphocytes migrate into inflammatory sites using the same adhesion molecule pairs and chemokines that recruit other leukocytes.

Lymphocytes and macrophages interact in a bidirectional way, and these interactions play an important role in chronic inflammation. Macrophages produce cytokines (**IL-12**) that stimulate T-cell responses.

Activated T lymphocytes, in turn, produce cytokines, and one of these, **IFN- $\gamma$** , is a powerful activator of macrophages, promoting more antigen presentation and cytokine secretion. The result is a cycle of cellular reactions that fuel and sustain chronic inflammation.



## Macrophage-lymphocyte interactions in chronic inflammation

### **Plasma cells:**

These are activated B-lymphocyte that can produce immunoglobulin molecules. These immunoglobulin's (antibodies) are directed either against:

1 -Persistent antigens in the inflammatory site.

2 -Altered tissue components

In some strong chronic inflammatory reactions, the accumulations of lymphocytes, macrophages, plasma cells may assume the morphologic features of lymphoid organs (appear as lymph nodes and may even contain well- formed germinal centers).

### **Eosinophils:**

They are characteristically found in:

1-Inflammatory sites around parasitic infections

2-As a part of immune reactions mediated by IgE, typically associated with allergies.

Eosinophil granules contain major basic protein, a highly charged cationic protein that is toxic to parasites but also causes epithelial cell necrosis.

**Mast cells:** are widely distributed in connective tissues and participate in both acute and chronic inflammatory reactions. Mast cells express on their surface the receptor that binds the Fc portion of IgE antibody. Mast cells are also present in chronic inflammatory reactions, and may produce cytokines that contribute to fibrosis.

**GRANULOMATOUS INFLAMMATION:** is a distinctive pattern of chronic inflammation characterized by aggregates of activated macrophages which often develop an epithelial-like (epithelioid) appearance with scattered lymphocytes.

Granulomas can form under three settings:

1 .With persistent T-cell responses to certain microbes.

(such as *Mycobacterium tuberculosis*, *T. pallidum*, or *fungi*), in which T cell–derived cytokines are responsible for chronic macrophage activation.

2. Granulomas may also develop in some immune-mediated inflammatory diseases, like Crohn disease, which is one type of inflammatory bowel disease.

3 .They are also seen in a disease of unknown etiology called sarcoidosis.

4 .they develop in response to relatively inert foreign bodies (e.g., *suture or splinter*), forming so-called *foreign body granulomas*.

## **MORPHOLOGY:**

**Epithelioid cells:** activated macrophages in epithelial-like appearance. They have a pale pink granular cytoplasm with indistinct cell boundaries.

**Multinucleate giant cells:** these cells are derive from the fusion of multiple activated macrophages and about 40 to 50  $\mu\text{m}$  in diameter are found in granulomas and consist of a large mass of cytoplasm with many nuclei(20 or more) arranged either peripherally Langhans-type giant cell or haphazardly (foreign body-type giant cell).

## **Microscopically**

Typically, the granulomas are formed by the aggregates of epithelioid macrophages that surrounded by a collar of lymphocytes, frequently multinucleate giant cells are found in granuloma. Older granulomas may have a rim of fibroblasts and connective tissue.

**In granulomas associated with certain infectious organisms** (\tubercle bacillus), a combination of hypoxia and free radical injury leads to a central zone of necrosis.

**On gross examination**, this has a granular, cheesy appearance and is therefore called caseous necrosis. **On microscopic examination**, this necrotic material appears as eosinophilic amorphous, structureless, granular debris, with complete loss of cellular details.

**The granulomas associated with Crohn disease, Sarcoidosis, and foreign body reactions tend to not have necrotic centers and are said to be “noncaseating”.**

Healing of granulomas is accompanied by fibrosis that may be quite extensive.