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

Acute inflammation may progress to chronic inflammation if the acute response cannot be resolved, either because of the persistence of the injurious agent or because of interference with the normal process of healing.

For example, a peptic ulcer of the duodenum initially shows acute inflammation followed by the beginning stages of resolution. However, recurrent bouts of duodenal epithelial injury interrupt this process, resulting in a lesion characterized by both acute and chronic inflammation

Chronic inflammation may arise in the following settings:

• Persistent infections by microbes that are difficult to eradicate. These include *Mycobacterium tuberculosis*, *Treponema pallidum* (the causative organism of syphilis), and certain viruses and fungi, all of which tend to establish persistent infections and elicit a T lymphocyte–mediated immune response called delayed-type hypersensitivity

• 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 as autoimmune
• Prolonged exposure to potentially toxic agents. Examples are non degradable exogenous materials such as inhaled particulate silica, which can induce a chronic inflammatory response in the lungs

• Mild forms of chronic inflammation may be important in the pathogenesis of many diseases that are not conventionally thought of as inflammatory disorders. Such diseases include neurodegenerative disorders such as Alzheimer disease, atherosclerosis, metabolic syndrome and the associated type 2 diabetes, and some forms of cancer

Chronic Inflammatory Cells and Mediators

A-Macrophages

Macrophages, the dominant cells of chronic inflammation, are tissue cells derived from circulating blood monocytes after their emigration from the bloodstream. Macrophages are normally diffusely scattered in most connective tissues and are also found in organs such as the liver **(where they are called Kupffer cells), spleen and lymph nodes (where they are called sinus histiocytes), central nervous system (microglial cells), and lungs (alveolar macrophages).** Together these cells constitute the so-called mononuclear phagocyte system, also known by the older name of reticuloendothelial system. In all tissues, macrophages act as

filters for particulate matter, microbes, and senescent cells, as well as the effector cells that eliminate microbes in cellular and humoral immune responses

Two major pathways of macrophage activation, classical and alternative, have been described

1- Classical macrophage activation is induced by microbial products such as endotoxin, by T cell–derived signals, importantly the cytokine IFN-γ, and by foreign substances including crystals and particulate matter.

Classically activated macrophages produce lysosomal enzymes, NO, and ROS, all of which enhance their ability to kill ingested organisms, and secrete cytokines that stimulate inflammation. These macrophages are important in host defense against ingested microbes and in many chronic inflammatory reactions.

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, including mast cells and eosinophils. Alternatively activated macrophages are not actively microbicidal; instead, their principal role is in tissue repair. They secrete growth factors that promote

angiogenesis, activate fibroblasts and stimulate collagen synthesis.

Inflammatory response.

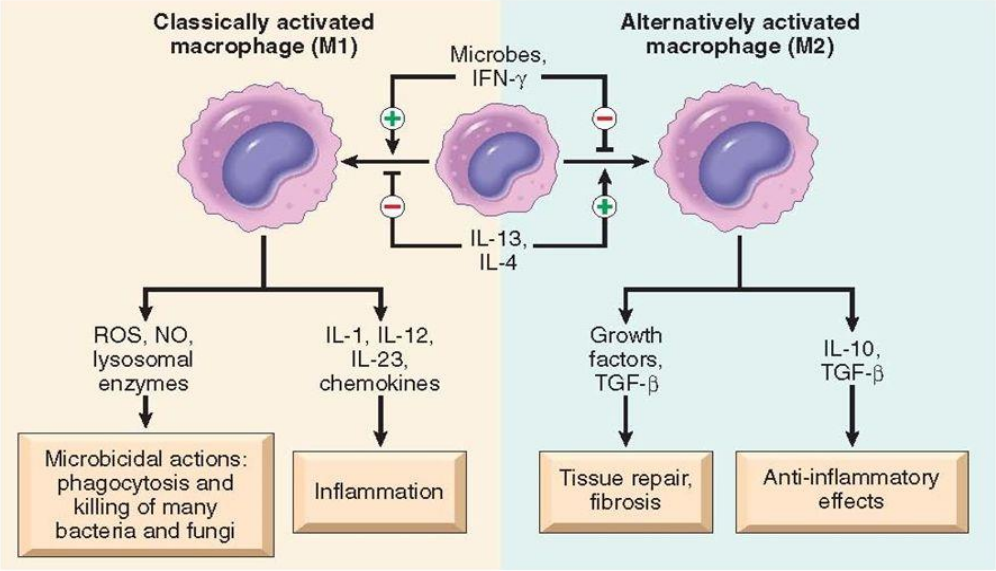
• Macrophages, like the other type of phagocyte, the neutrophils, ingest and eliminate microbes and dead tissues. Because macrophages respond to activating signals from T lymphocytes, they are the most important phagocytes in the cell-mediated arm of adaptive immune
responses .

• Macrophages initiate the process of tissue repair and are involved in scar formation and fibrosis.

• Macrophages secrete mediators of inflammation, such as cytokines (TNF, IL-1, chemokines, and others) and eicosanoids. These cells are therefore central to the initiation and propagation of all inflammatory reactions.

• Macrophages display antigens to T lymphocytes and respond to signals from T cells, thus setting up a feedback loop that is essential for defense against many microbes by cell mediated immune responses.

Classical and alternative macrophage activation



B- Lymphocytes

Lymphocytes are mobilized in the setting of any specific immune stimulus (i.e., infections) as well as non–immunemediated inflammation (e.g., due to ischemic necrosis or trauma), and are the major drivers of inflammation in many autoimmune and other chronic inflammatory diseases.

The activation of T and B lymphocytes is part of the adaptive immune response in infections and immunologic diseases .

Both classes of lymphocytes migrate into inflammatory sites using some of the same adhesion molecule pairs and chemokines that recruit other leukocytes. In the tissues, B lymphocytes may develop into plasma cells, which secrete antibodies, and CD4+ T lymphocytes are activated to secrete cytokines. By virtue of cytokine secretion, CD4+ T lymphocytes promote inflammation and influence the nature of the inflammatory reaction.

There are three subsets of CD4+ helper T cells that secrete different sets of cytokines and elicit different types of inflammation:

• TH1 cells produce the cytokine IFN-γ, which activates macrophages in the classical pathway.

• TH2 cells secrete IL-4, IL-5, and IL-13, which recruit and activate eosinophils and are responsible for the alternative pathway of macrophage activation.

• TH17 cells secrete IL-17 and other cytokines that induce the secretion of chemokines responsible for recruiting neutrophils and monocytes into the reaction.

3-Eosinophils

are characteristically found in inflammatory sites around parasitic infections and as part of immune

reactions mediated by IgE, typically associated with allergies. Their recruitment is driven by adhesion molecules similar to those used by neutrophils, and by specific chemokines (e.g., exotoxin) derived from leukocytes and epithelial cells. Eosinophil granules contain major basic protein, a highly charged cationic protein that is toxic to parasites but also causes epithelial cell necrosis.

4- Mast cells

are sentinel cells widely distributed in connective tissues throughout the body, and they can participate in both acute and chronic inflammatory responses. In atopic persons (those prone to allergic reactions), mast cells are “armed” with IgE antibody specific for certain

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:

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. Tuberculosis is the prototype of a granulomatous disease caused by infection and should always be excluded as the cause when granulomas are identified.

2- Granulomas may also develop in some immune mediated inflammatory diseases, notably Crohn disease, which is one type of inflammatory bowel disease and an important cause of granulomatous inflammation in the United States.

3-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.

Features of Chronic Inflammation

• Prolonged host response to persistent stimulus

• Caused by microbes that resist elimination, immune

responses against self and environmental antigens, and some toxic substances (e.g., silica); underlies many important diseases

• Characterized by persistent inflammation, tissue injury, attempted repair by scarring, and immune response

• Cellular infiltrate consisting of activated macrophages, lymphocytes, and plasma cells, often with prominent fibrosis

• Mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes).