GENERAL PATHOLOGY

Lecture 7,8 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, Treponemapallidum (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-Infi1**.**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- **γ**,

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-injust and eliminate microbs and dead tissue (**ROS**, **NO**, **lysosomal enzyme**)

2-initiate the process of tissue repair and involved in scar formation (growth factor)

3-Secreate mediators of inflammation such as (Tumor necrotic factor TNF,

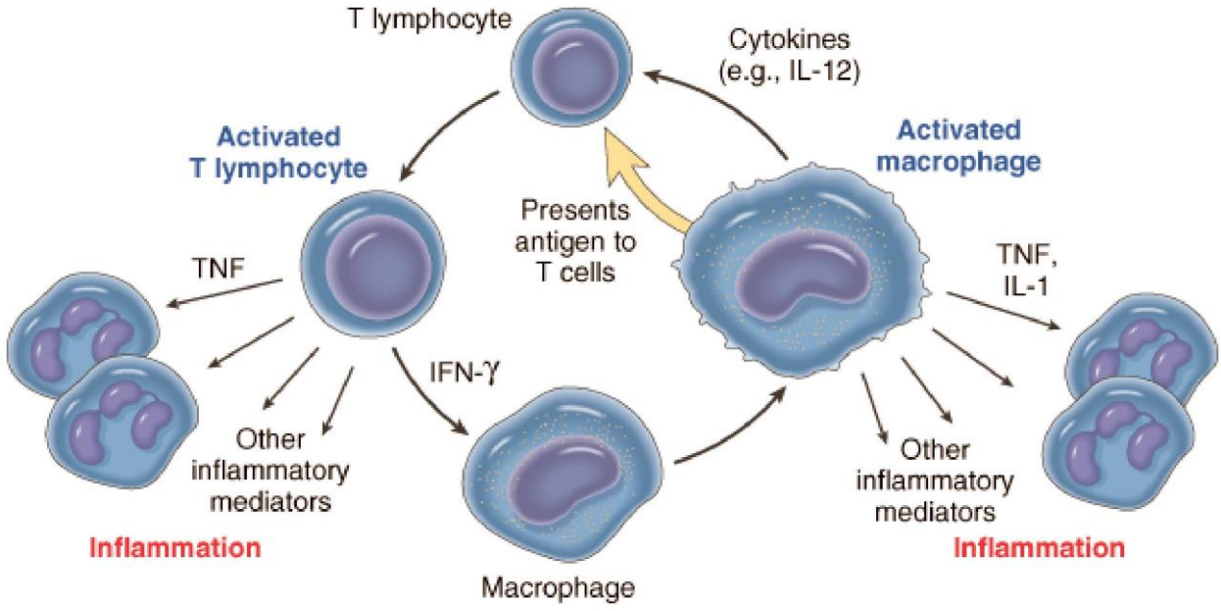
Interleukin -1)IL -1 (and Cytokines) to promote leukocyte recruitment.
4-Macrophages display antigens to T lymphocyte and respond to signal from T cell

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-γ**, 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. 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 μm in diameter are found in granulomas and consist of a large mass of cytoplasm with many nuclei(20 or more) arranged either peripheraly 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.

CHEMICAL MEDIATOR OF ACUTE INFLAMMATION

These are chemical materials that are responsible for vascular and cellular events in acute inflammation and the accompanying morphologic alterations. Although inflammation is precipitated by injury, these chemical mediators are responsible of its signs and symptoms.

TYPES OF CHEMICAL MEDIATOR:

1- Cell Derived Mediators:-

Mediators may be produced locally by cells at the site of inflammation. ex. Histamine, prostaglandins and cytokines.

2- Plasma Protein-Derived Mediators:-

These are proteins circulating in the plasma (typically synthesized by the liver) as inactive precursors that are activated at the site of inflammation. ex. complement proteins, kinins.

MODE OF ACTION:-

- Most mediators induce their effects by binding to specific receptors on the target cells.
- Mediators may act on only one or a very few targets, or they may have widespread actions.
- Some mediators have direct enzymatic and/or toxic activities (ex. lysosomal proteases and Reactive Oxygen Species).

REGULATION OF ACTION:

- The actions of most mediators are tightly regulated.
- Once activated and released from the cell, mediators will performed their action and then will quickly either decay , inactivated by enzymes ,eliminated or inhibited

CELL-DERIVED MEDIATORS:-

Tissue macrophages, mast cells, and endothelial cells at the site of inflammation, as well as leukocytes that are recruited to the site from the blood, are all capable of producing different mediators of inflammation.

1-Vasoactive Amines:

The two vasoactive amines **histamine** and **serotonin** are stored as preformed molecules in mast cells and other cells and are among the first mediators to be released in acute inflammatory reactions.

Histamine:-It is produced by many cell type particularly mast cells, basophils and platelets.

Fuunction: histamine causes vasodilation and increased vascular permeability.

2. Arachidonic Acid Metabolites (AA):

Prostaglandins ,Leukotrienes, Lipoxins

Products derived from the metabolism of AA and can mediate every step of inflammation. It is produced by many cell types Leukocytes, mast cells, endothelial cells, platelets

Functions of AA metabolites:

Prostoglandins (PG):

cause vasodilation and potentiates edema formation.

involved in the pathogenesis of pain and fever in inflammation.

Leukotrienes:

is a potent chemotactic agent for neutrophils.

increased vascular permeability.

Lipoxins:

anti-inflammatory mediators, which inhibit neutrophil chemotaxis and adhesion to endothelium and thus serve as endogenous antagonists of leukotrienes.

3-Platelet-Activating Factor: PAF

Originally named for its ability to aggregate platelets and cause their degranulation.

Function of Platelet-Activation Factor:

- stimulating platelets.
- bronchoconstriction
-Vasodilation -100 to 1,000 times more potent than is histamine
- Increased vascular permeability.
- Induce most of the reactions of inflammation, including enhanced leukocyte adhesion, chemotaxis, leukocyte degranulation, and the intracellular killing.

4-Cytokines

Cytokines are polypeptide products of many cell types that function as mediators of inflammation and immune responses.

Interleukins (IL) as a group of cytokines are capable of mediating communications
between leukocytes. Interleukins are of different types and functions; they are named by numbering (IL-1, IL-2…)

The major cytokines in acute inflammation are Tumor Necrosis Factor (TNF) and IL-1, as well as a **group of chemo-attractant cytokines called chemokines**. Other cytokines that are more important in chronic inflammation include interferon-γ (IFN-γ) and IL-12.

Tumor Necrosis Factor and Interleukin-1

TNF and IL-1 are produced by activated macrophages, as well as mast cells, endothelial cells, and some other cell types.

Functions:

- The principal role of these cytokines in inflammation is in endothelial activation by stimulating the expression of adhesion molecules on endothelial cells, resulting in increased leukocyte binding and recruitment,
- TNF also increases the aggregation and activation of neutrophils.
- IL-1 activates tissue fibroblasts, resulting in increased proliferation.

Chemokines

The chemokines are a family of small structurally related proteins that act primarily as chemo-attractants for different subsets of leukocytes.

Functions of Chemokines:

- The main function of chemokines is leukocyte recruitment or attraction during
inflammation
- Chemokines also activate leukocytes, by increasing the affinity of leukocytes
adhesion site for their ligands on endothelial cells.

5- Reactive Oxygen Species (ROS):-

ROS are oxygen-derived free radicals. They are synthesized within lysosomes and released from neutrophils and activated macrophages.

Functions:

They are essential to destroy phagocytosed microbes and necrotic cells.

- ROS in low concentration can increase chemokine, cytokine, and adhesion molecule expression,.
- At higher levels, they are responsible for tissue injury by several mechanisms, including:-

(1) endothelial damage.

(2) direct injury to other cell types (ex. tumor cells, erythrocytes, parenchymal cells).

6- Nitric Oxide (NO):

NO is a short-lived, soluble, free-radical gas produced by endothelial cells, and macrophages.

Functions:

NO has many roles in inflammation:

(1) It is used by Macrophages as a cytotoxic metabolite for killing microbes and tumor cells.

(2) In the endothelial cells (vasodilation)

(3) At the end of the acute inflammation NO suppresses the inflammatory responses

7- Lysosomal Enzymes of Leukocytes:

The lysosomal granules of neutrophils and monocytes contain many molecules that can mediate acute inflammation.

They may be released after cell death, by leakage during the formation of the phagocytic vacuole, or during unsuccessful attempts to phagocytose large, indigestible surfaces.

The most important lysosomal enzymes:-

- Acid proteases are generally active only within phagolysosomes.
- Neutral proteases, including elastase, collagenase and cause destructive tissue injury by degrading elastin, collagen, basement membrane and other matrix proteins.

8- Neuropeptides

These are small proteins, such as substance P, that transmit pain signals, regulate vessel tone, and modulate vascular permeability.

PLASMA PROTEIN-DERIVED MEDIATORS

Circulating proteins (in the blood) involved in several aspects of the inflammatory reaction and composed of three interrelated systems:-

1. Complement.

2. Coagulation systems.

3. kinin.

1- Complement

- The complement system consists of plasma proteins that play an important role in host defense (immunity) and inflammation.

- They are present in the blood as an in-active enzymes, or enzyme precursors.

- Upon activation, the different types of complement proteins will have different actions:-

* Increase vascular permeability and leukocyte chemotaxis.

* Opsonization: Complement will act as coating particles. They will cover the microbes so it will help phagocytosis and destruction. They induce formation of pore like membrane attack complex (MAC) that produce holes in the membranes of invading microbes.

2- Coagulation factors

They are group of proteins present in the blood as an in active form. The factor which starts the intrinsic cascade of coagulation is factor XII (Hageman factor) . Factor XII is a protein synthesized by the liver and circulates in the blood. It is activated when it come in contact with activated platelets at the site of inflammation. Activated factor XII will induce clotting and generation of group of circulating mediators of inflammation.

3- kinin

Kinin system activation leads ultimately to the formation of bradykinin from its circulating precursor.

Like histamine**, bradykinin causes**

increased vascular permeability,

vasodilation,

bronchial smooth muscle

contraction, pain.

The actions of bradykinin are short-lived because it is rapidly degraded by kininases present in plasma and tissues.

Kallikrein, is an intermediate in the kinin cascade with chemotactic activity, and potent activator of Hageman factor and thus it represent a link between the kinin and clotting systems.

Systemic Manifestations of Inflammation

Generally, the inflammatory response remains confined to a localized area. However, in some cases local injury can result in prominent systemic manifestations as inflammatory mediators are released into the circulation.

The most prominent systemic manifestations of inflammation are:

1-**Acute phase response**:

Changes in the concentrations of plasma proteins, increased erythrocyte sedimentation rate (ESR), fever, lethargy.

2- **Alterations in white blood cell count:**

leukocytosis=increase leukocyte number

leucopenia= decrease leukocyte number

3- Lymphadenitis:

Localized acute and chronic inflammation may lead to a reaction in the lymph nodes that drain the affected area. This will result in painful palpable nodes.

4- Sepsis and septic shock:

Also called the systemic inflammatory response, represent the severe systemic manifestations of inflammation occur due to the presence of **toxins** in the blood resulting in induction of histamine in the circulation ending with generalized vasodilation leading to septic shock