Lecture 8 **General pathology** **Dr. Mustafa Ibrahim**

CHEMICAL MEDIATOR

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 perform 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 types particularly mast cells, basophils and platelets.

Function: 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:

Prostaglandins (PG):

1- Cause vasodilation and potentiates edema formation.

2- Involved in the pathogenesis of pain and fever in inflammation.

Leukotrienes:

1- A potent chemotactic agent for neutrophils.

2- 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 defence (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 represents 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

Leukopenia = 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.