Mediators of Inflammation

Inflammatory mediators (Here) include:–

1-Plasma-Derived Mediators of Inflammation.

(1) Coagulation cascade, (2) Kinin generation (3) Complement system

1-Hageman Factor:–

Hageman factor (clotting factor XII), generated within the plasma, is activated by exposure to negatively charged surfaces such as basement membranes, proteolytic enzymes, bacterial lipopolysaccharide and foreign materials. It triggers activation of additional plasma proteases, leading to:

a- Conversion of plasminogen to plasmin Here
b- Conversion of prekallikrein to kallikrein Here
c- Activation of the alternative complement pathway Here
d- Activation of the coagulation system Here

2- Kinins:–

Kinin are potent inflammatory agents formed in plasma and tissue by the action of serine protease kallikreins on specific plasma glycoproteins termed kininogens. Bradykinin and related peptides regulate multiple physiologic processes including blood pressure, contraction and relaxation of smooth muscle, plasma extravasation, cell migration, inflammatory cell activation and inflammatory-mediated pain responses. Kinins are rapidly inactivated by kininases, and therefore have rapid and short-lived functions. Perhaps the most significant function of kinins is their ability to amplify inflammatory responses by stimulating local tissue cells and inflammatory cells to generate additional mediators, including prostanoids, cytokines (especially tumor necrosis factor– [TNF–] and interleukins), nitric oxide and tachykinins.

3- Complement system (Here) :-

The complement system is a group of proteins found in plasma and on cell surfaces. Its primary function is defense against microbes. First identified as a heat-labile serum factor that kills bacteria and “complements” antibodies, the complement system consists of more than 30 proteins including plasma enzymes, regulatory proteins and cell lysis proteins. (1)
defense against pyogenic bacterial infection by opsonization, chemotaxis, activation of leukocytes and lysis of bacteria and cells; (2) bridging innate and adaptive immunity for defense against microbial agents by augmenting antibody responses and enhancing immunologic memory; and (3) disposal of immune products and products of inflammatory injury by clearance of immune complexes from tissues and removal of apoptotic cells. The proteins involved in activating the complement system are themselves activated by three convergent pathways termed classical, mannose-binding lectin (MBL) and alternative.

*Biological Activities of Complement Components:*

1-**Anaphylatoxins** (C3a, C4a, C5a): These proinflammatory molecules mediate smooth muscle contraction and increase vascular permeability

2-**Opsonins** (C3b, iC3b): Bacterial opsonization is the process by which a specific molecule (e.g., IgG or C3b) binds to the surface of the bacterium.

3-**Proinflammatory molecules** (MAC, C5a): These chemotactic factors also activate leukocytes and tissue cells to generate oxidants and cytokines and induce degranulation of mast cells and basophils.

4-**Lysis** (MAC): C5b binds C6 and C7, and subsequently C8 to the target cell; C9 polymerization is catalyzed to lyse the cell membrane.

![Plasma-Derived Mediators of Inflammation](image-url)
2-Cell-Derived Mediators of Inflammation.

Circulating platelets, basophils, PMNs, endothelial cells monocyte/macrophages, tissue mast cells and the injured tissue itself are all potential cellular sources of vasoactive mediators. In general, these mediators are (1) derived from metabolism of phospholipids and arachidonic acid (e.g., prostaglandins, thromboxanes, leukotrienes, lipoxins, platelet activating factor [PAF]), (2) preformed and stored in cytoplasmic granules (e.g., histamine, serotonin, lysosomal hydrolases) or (3) derived from altered production of normal regulators of vascular function (e.g., nitric oxide and neuropeptide Y).

1-Arachidonic Acid:-

Phospholipids and fatty acid derivatives released from plasma membranes are metabolized into mediators and homeostatic regulators by inflammatory cells and injured tissues. Once generated, arachidonic acid is further metabolized through two pathways: (1) cyclooxygenation, with subsequent production of prostaglandins and thromboxanes; and (2) lipoxygenation, to form leukotrienes and lipoxins.

Note:- Corticosteroids induce synthesis of an inhibitor of PLA2 and block release of arachidonic acid in inflammatory cells.

1-a-Prostanoids:

Arachidonic acid is further metabolized by cyclooxygenases 1 and 2 (COX-1, COX-2) to generate prostanoids. It is a key enzyme in the synthesis of prostaglandins, which in turn (1) protect the gastrointestinal mucosal lining, (2) regulate water/electrolyte balance, (3) stimulate platelet aggregation to maintain normal hemostasis and (4) maintain resistance to thrombosis on vascular endothelial cell surfaces.

Note:- Inhibition of COX is one mechanism by which nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, indomethacin and ibuprofen, exert their potent analgesic and anti-inflammatory effects.
1-b-Leukotrienes:-

Slow-reacting substance of anaphylaxis has potent chemotactic activity for neutrophils, monocytes and macrophages. (1) stimulate smooth muscle contraction, (2) enhance vascular permeability and (3) are responsible for many of the clinical symptoms associated with allergic-type reactions. They thus play a pivotal role in the development of asthma.

1-c-Lipoxins:-

They are proinflammatory generated during inflammation, atherosclerosis and thrombosis.

2-Platelet-Activating factor:

It is derived from membrane phospholipids is PAF, synthesized by virtually all activated inflammatory cells, endothelial cells and injured tissue cells. PAF has diverse functions. It stimulates platelets, neutrophils, monocyte/macrophages, endothelial cells and vascular smooth muscle cells. PAF induces platelet aggregation and degranulation at sites of tissue injury and enhances release of serotonin, thereby altering vascular permeability.

3-Cytokines:

Cytokines produced at sites of tissue injury regulate inflammatory responses, ranging from initial changes in vascular permeability to resolution and restoration of tissue integrity, these molecules are inflammatory hormones that have autocrine (affecting themselves), paracrine (affecting nearby cells) and endocrine (affecting cells in other tissues) functions. While most cells produce cytokines, they differ in their cytokine repertoire. Through production of cytokines, macrophages are pivotal in orchestrating tissue inflammatory responses.

4-Chemokines:-

Chemotactic cytokines, or chemokines, direct cell migration (chemotaxis). Accumulation of inflammatory cells at sites of tissue injury requires their migration from vascular spaces into
extravascular tissue. Chemokines are small molecules that interact with G-protein–coupled receptors on target cells.

The most important chemotactic factors for PMNs are:
  - C5a, derived from complement
  - Bacterial and mitochondrial products
  - Products of arachidonic acid metabolism
  - Chemokines

5-Reactive Oxygen Species (ROS):

Chemically reactive molecules derived from oxygen. ROS important in inflammation include superoxide (O2•, O2_), nitric oxide (NO•), hydrogen peroxide (H2O2) and hydroxyl radical (OH•)

6-Neurokinins:

These peptides are distributed throughout the central and peripheral nervous systems and represent a link between the endocrine, nervous and immune systems. It is now recognized that injury to nerve terminals during inflammation evokes an increase in neurokinins, which in turn influence production of inflammatory mediators, including histamine, NO• and kinins
**3-Extracellular Matrix Mediators.**

**Interactions of cells and extracellular matrix regulate tissue responses to inflammation.**

The extracellular environment consists of a macromolecular matrix specific to each tissue. During injury, resident inflammatory cells interact with this matrix, using this scaffolding for migration along a chemokine gradient. Collagen, elastic fibers, basement membrane proteins, glycoproteins and proteoglycans are among the structural macromolecules of the ECM. Matricellular proteins are secreted macromolecules that link cells to the ECM or that disrupt cell–ECM interactions.

**Matricellular proteins include:**

- SPARC (secreted protein acidic and rich in cysteine)
- Thrombospondins
- Tenascins C, X and R
- Syndecans
- Osteopontin

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