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Study on current perspective of Inflammation

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Abstract: Inflammation involves a complex interaction of many different inflammatory cells that release a spectrum of chemical mediators ultimately affecting various target tissues. Included among these mediators are arachidonic acid derivatives (leukotrienes and prostaglandins), vasoactive peptides (kinins), phospholipid mediators (platelet activating factor), and cytokines (interleukins and other bioresponse modifiers). Although the clinical manifestations of the allergic response vary depending on the tissue and antigen involved, it is now understood that the allergic reaction consists of an early-phase response primarily involving mast cell degranulation accompanied by the release of histamine and other mediators including cytokines and a late-phase response that is characterized by the migration of inflammatory cells from the circulation.

Keywords: Inflammation, Chemotaxis, Mediators, Histamine, Leukotrienes

Introduction:

The survival of all organisms requires that they eliminate foreign invaders, such as infectious pathogens, & damaged tissues. These functions are mediated by a complex host response called inflammation.[1] An inflammatory response can be linked to nearly every serious illness diagnosed in modern medicine. The body's inflammatory response is a primary component of most chronic diseases. Acute, chronic internal

inflammation can be linked to wide range of health conditions and overall poor health. To maintain optimal health, our body constantly searches to achieve a fine balance between opposing forces. When this balance is constantly disrupted, chronic disease and poor health can result.[2] Although inflammation helps clear infections and other noxious stimuli and initiates repair, the inflammatory reaction and the subsequent repair process can cause considerable harm. The cells and molecules of host defence normally circulate in the blood, and the goal of the inflammatory reaction is to bring them to the site of infection or tissue damage. Several type of cells and molecules play important role in inflammation. These include leukocytes and plasma proteins, cells of vascular walls, and cells and extracellular matrix (ECM) of the surrounding connective tissue.[1]

Inflammation is defined as the local response of living mammalian tissues to injury due to any agent. It is a body defence reaction in order to eliminate or limit the spread of injurious agent, followed by removal of the necroses cells and tissues.

Agents causing inflammation may be as under:

1. Infective agents like bacteria, viruses, and their toxins, fungi, parasites.
2. Immunological agents like cell mediated and antigen antibody reactions.
3. Physical agents like heat, cold, radiation, mechanical trauma.
4. Chemical agents like organic and inorganic poisons.
5. Inerts materials such as foreign bodies.[3, 4]

Inflammation is characterized in acute phase by increased blood flow and vascular permeability along with the accumulation of fluid, leukocytes and inflammatory mediators such as cytokines. In the sub acute/chronic phase it is characterized by the development of specific humoral and cellular immune responses to pathogens present at the site of tissue injury.[5, 6]

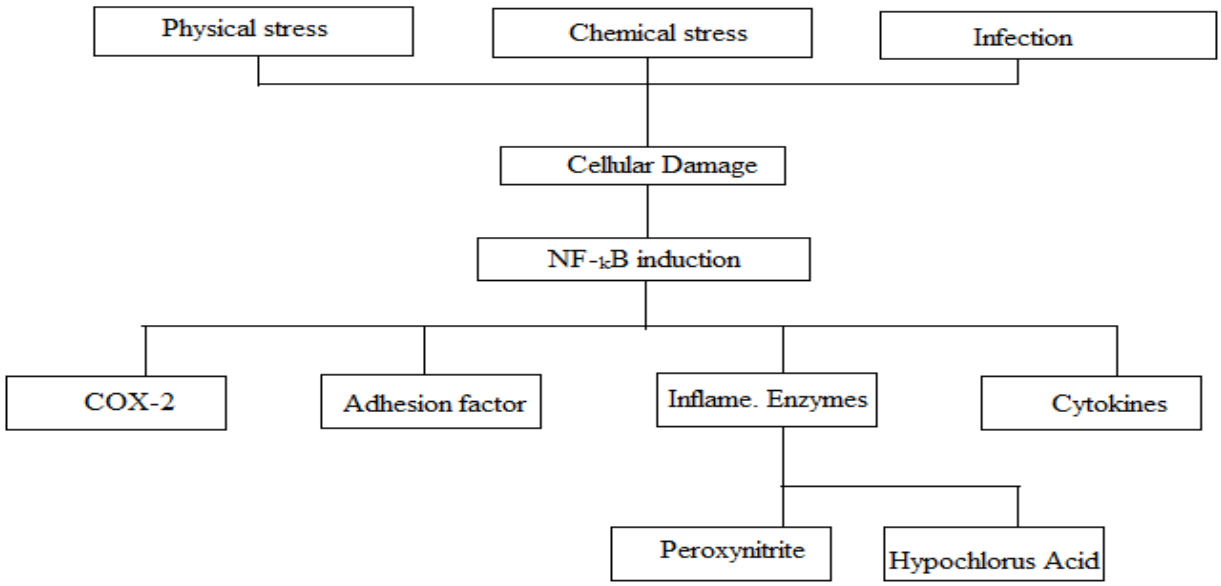

Fig no. 1 Overview of inflammation

Types of inflammation: - Depending upon the defence capacity of the host and duration of response, inflammation can be classified as acute and chronic.

Acute inflammation is of short duration (lasting less than 2 weeks) and represents the early body reaction, resolves quickly and is usually followed by healing. The main features of acute inflammation are:

1. Accumulation of fluid and plasma at the effected site;
2. Intravascular activation of platelets; and
3. Polymorphonuclear neutrophils as inflammatory cells.

Chronic inflammation is of longer duration and occurs either after the causative agent of acute inflammation persists for long time or the stimulus is such that it induces chronic inflammation from beginning.[3] It 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.[1]

Acute inflammation: - It can be divided into following two events:

1. Vascular events
2. Cellular events.

Vascular changes: alteration in vessel calibre resulting in increased blood flow (vasodilatation) and structural changes that permit plasma proteins to leave the circulation (increased vascular permeability).[1, 3]

- Irrespective of the type of injury, immediate vascular response is of transient vasoconstriction of arterioles. With mild form of injury, the blood flow may be re-established in 3-5 seconds while with more severe injury the vasoconstriction may last for about 5 minutes.
- Next follows persistent progressive vasodilation which involves mainly the arterioles, but to a lesser extent, affects other components of the microcirculation like venules and capillaries. This change is obvious within half an hour of injury. Vasodilation results in increased blood volume in microvascular bed of the area, which is responsible for redness and warmth at the site of inflammation.
- Progressive vasodilation may elevate the local hydrostatic pressure resulting in transudation of fluid into the extracellular space. This is responsible for swelling at the local site of acute inflammation.
- Slowing or stasis of microcirculation follows which causes increased concentration of red cells, and thus, raised blood viscosity.
- Stasis or slowing is followed by leucocytic margination or peripheral orientation of leucocytes (mainly neutrophils) along the vascular endothelium. The leucocytes stick to the vascular endothelium briefly, and then move and migrate through the gaps between the endothelial cells into the extravascular space. This process is known as emigration.

The features of hemodynamic changes in inflammation are best demonstrated by Lewis Experiment. He induced the changes in skin of inner aspect of forearm by firmly stroking with a blunt point. The reaction elicited is known as triple response or red line response. It consists of following:

- Red line appears within a few seconds following stroking and is due to local vasodilation of capillaries and venules.
- Flare is the bright reddish appearance or flush surrounding the red line and results from the vasodilation of the adjacent arterioles.
- Wheal is the swelling or edema of the surrounding skin due to transudation of fluid into the extravascular space.

These features elicited the classical signs of inflammation- redness, heat, swelling and pain.

Cellular events:

Important function of inflammatory response is to deliver leukocytes to the site of injury and to activate them. Leukocytes ingest offending agents, kill bacteria and other microbes and eliminate necrotic tissue and foreign substances.[1]

Exudation of leukocytes:

Loss of fluid from the blood thickens it, slowing flow and allowing the normally fast flowing white blood cells to make contact with, and adhere to, the vessel wall. In the acute stages, the most important leukocytes is the neutrophil, which adheres to the blood vessel lining, squeezes between the endothelial cells and enter the tissues.[7] The polymorphonuclear neutrophils (PMN's) comprise the first line of body defence, followed by monocytes and macrophages. The changes leading to migration of leukocytes are as:

- Changes in the formed elements of blood.
- Rolling and adhesion
- Emigration
- Chemotaxis.[3]

Changes in the formed elements of blood: Rate of flow is increased due to vasodilation, subsequently slowing or stasis of blood stream leading to the changes in normal axial blood flow. The normal axial flow comprises leukocytes and RBCs in centre and free plasma at the periphery. Slowing or stasis widens the central stream and peripheral plasma zone becomes narrower because of loss of plasma by exudation. This phenomenon is known as Margination.

Rolling and adhesion: As a result of margination the neutrophils come close to vessel wall, known as pavementing. These neutrophils slowly roll over the endothelial cells lining the vessel wall (rolling phase), followed by transient bond between the leukocytes and endothelial cells becoming firmer (adhesion phase).

Following molecules bring about the rolling and adhesion phase:[3]

- **Selectins:** Selectins are receptors expressed on leukocytes and endothelium that contain an extracellular domain that binds sugars. The three members of this family are E-selectin (also called CD62E), expressed on endothelial cells; P-selectin (CD62P), present on endothelium and platelets and L-selectin (CD62L), on the surface of most leuckocytes.[1]
- **Integrins:** on the endothelial surface are activated during the process of loose and transient adhesions between receptors for integrins on the neutrophils are also stimulated. This brings firm adhesion between leukocyte and endothelium.[3]
- Immunoglobulin gene superfamily adhesion molecule: such as intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) allow a tighter adhesion and stabilise the interactin between leukocytes and endothelial cell adhesion molecule-1 (PECAM-1) or CD31 may also be involved in leuckocyte migration from the endothelial surface.

Emigration:

Within an hour after the inflammatory process starts, phagocytes appear on the scene. As large amount of blood accumulate neutrophils begin to stick to the inner surface of the endothelium (lining) of the blood vessels. Then the neutrophils begin to squeeze through the wall of the blood vessels to reach the damaged area. This process is called emigration, depends on chemotaxis. Neutrophils attempt to destroy the invading microbes by phagocytosis. A steady stream of neutrophils is ensured by the production and release of additional cells from red bone marrow. Such an increase in white blood cells in blood is termed leukocytosis.

Although neutrophils predominate in the early stage on infection, they die off rapidly. As the inflammatory response continues, monocytes flow the neutrophils into the infected area. Once in the tissue, monocytes transform in wandering macrophages already present. True to their name, macrophages are much more potent phagocytes than neutrophils. They are large enough to engulf damaged tissue, Worn out neutrophils, and invading microbes.[8]

Pus consists of dead phagocytes, dead cells, cell debris, fibrin inflammatory exudates and living and dead microbes. It is contained within a membrane of new blood capillaries, phagocytes and fibroblasts. The most common causative pyogenic (pus forming) microbes are Staphylococcus aureus and Staphylococcus pyogenes.

Chemotaxis: - This is the chemical attraction of leukocytes, including neutrophils and macrophages, to an area of inflammation.[6] Chemicals that attract phagocytes might come from invading microbes, white blood cells, damaged tissue cells, or activated complement protein.[8] This results from the appearance of certain chemical substances in the tissues. Any chemical substance that causes chemotaxis to occur is called a chemotactic substance.[9]

Both exogenous and endogenous substances can be chemotactic for leukocytes, including

- Bacterial products, particularly with N-formylmethionine termini;
- Cytokines, especially those of the chemokine family;
- Components of the complement system, particularly $C5_a$; and
- Products of the lipoxygenase pathway of arachidonic acid (AA) metabolism, particularly leukotriene B_4 (LTB_4).[1]

In addition to neutrophils, other inflammatory cells too responds and partake in inflammation and there are chemokines for them, e.g. monocyte chemoattractant protein (MCP-1), eotaxin chemotactic for eosinophil, NK cells for recognizing virally infected cells etc.

Phagocytosis: - It is the process of engulfment of solid particulate material by cells (cell eating). The cells performing this function are called phagocytes. There are two main types of phagocytic cells;

- Polymorphonuclear neutrophils (PMNs) which appear early in the

acute inflammatory response, sometimes called microphages.

- Circulating monocytes and fixed tissue mononuclear phagocytes, commonly called as macrophages.[3]

Phagocytosis consists of three distinct but interrelated steps:

- Recognition and attachment of the particle to the ingesting leukocyte;
- Engulfment, with subsequent formation of a phagocytic vacuole; and
- Killing and degradation of the ingested material.

Leukocytes bind and ingest most microorganisms and dead cells via specific surface receptors, which recognize either components of the microbes and dead cells, or host proteins called opsonins, that recognize microbes and target them for phagocytosis (a process called opsonisation). The most common important opsonins are antibodies of the immunoglobulin G (IgG) class that bind to microbial surface antigens, breakdown products of the complement protein C3, and plasma carbohydrate binding lectins called collectins.

Binding of opsonised particles triggers engulfment; in engulfment pseudopods are extended around the object, eventually forming a phagocytic vacuole. The membrane of the vacuole then fuses with the membrane of a lysosomal granule, resulting in discharge of the granule's contents into the phagolysosome.

The culmination of the phagocytosis of microbes is killing and degradation of the ingested particles. The key steps in this reaction are the production of microbicidal substances within lysosomes with phagosomes, thus selectively exposing the ingested particles to the destructive mechanism of the leukocytes. The dead microorganisms are then degraded by the action of lysosomal acid hydrolases.[1]

Chemical Mediators of Inflammation

These are also called permeability factors or endogenous mediators of increased vascular permeability; these are a large and increasing number of endogenous compounds which can enhance vascular permeability. The substances acting as chemical mediators of inflammation may be released from the cells, the plasma, or

damaged tissue itself. They are broadly classified into 2 groups:

- Mediators released by cells; and
- Mediators originating from plasma.[3]

Histamine:[12-17]**-** Histamine was one of the earliest mediators of the inflammatory process identified.[9] It is stored in the granules of tar mast cells. Histamine is produced by many cell types, particularly mast cells adjacent to vessels, as well as circulating basophils and platelets. Histamine is a hydrophilic molecule, it is synthesized from histidine by virtue of its content of L-histidine decarboxylase. The chief site of storage in most tissues is the mast cells; in the blood, it is the basophil.[10] Histamine is released from these cells by various agents as under:

- Stimuli or substances including acute inflammation e.g. heat, cold, irritation, trauma, irritant chemicals, immunologic reactions etc.
- Anaphylotoxins like fragments of complement $C3_a$, and $C5_a$, which increase vascular permeability and cause oedema in tissues.
- Histamine- releasing factors from neutrophils, monocytes and platelets.
- Interleukins.

There are three types of histamine receptors viz. H_1, H_2 and H_3.

The main actions of histamine are vasodilation, increased vascular permeability, itching and pain.

Eiconasoids:- Two distinct families of autocoids derived from membrane phospholipids have been identified: the eiconasoids, which are formed from certain polyunsaturated fatty acids (principally arachidonic acid), include the prostaglandins, prostacyclins, thromboxane A_2, and the leukotrienes.[9] Products derived from metabolism of arachidonic affect a variety of biologic processes, including inflammation and hemostasis. These can mediate virtually every step of inflammation, their synthesis is increased at sites on inflammatory response, and agents that inhibit their synthesis also diminish inflammation.

Arachidonic acid is a 20-carbon polyunsaturated fatty acid (with four double bonds) derived primarily from dietary linoleic acid and present in the body mainly in its esterified form as a component of cell membrane phospholipids via cellular

phosholipases that have been activated by mechanical, chemical, or physical stimuli, or by inflammatory mediators such as $C5_a$. Arachidonic acid metabolism proceeds along one of the two major enzymatic pathways: cyclooxygenase stimulates the synthesis of prostaglandins and thromboxanes, and lipoxygenase is responsible for production of leukotrienes and lipoxins.[1]

Prostanoids: - Cyclo-oxygenase-1 is present in most cells it is the enzyme that produces prostanoids which act as homeostatic regulators, where as COX-2 is not normally present but it is strongly induced by inflammatory stimuli. Arachidonic molecule, forming the highly unstable endoperoxides PGG_2 and PGH_2. These are rapidly transformed by isomerase or synthase enzyme to PGE_2, PGI_2, PGD_2, $PDF_{2\alpha}$ and TXA_2 , which are the principal bioactive end products of this reaction.

Catabolism of the prostanoids: - After carrier-mediated uptake, most prostaglandins are rapidly inactivated by 'prostaglandin-specific' enzymes, and the inactive products are further degraded by general fatty acid-oxidising enzymes.

The prostaglandin-specific enzymes are present in high concentration in the lung, and 95% of infused PGE_2, PGE_1 and PGF2α are activated on first passage. The half life of most prostaglandin in the circulation is less than 1 minute. Prostaglandin I_2 and TXA_2 are decay rapidly into inactive 6-keto-$PGF_{1\alpha}$ and TXB_2.

Prostanoids receptors: - There are five main classes of prostanoids receptors all of which are typical G- protein-coupled receptors. They are termed DP, FP, IP, EP and TP receptors, respectively, depending on whether their ligands are PGD_2, PGF2α, PGI_2, PGE_2 and TXA_2.

The prostanoids affect most tissues and exert a bewildering variety of effects

- PGD_2 causes vasodilation, inhibition of platelet aggregation, relaxation of gastrointestinal and uterine muscle, and modification of release of hypothalamic / pituitary hormones. It has a bronchoconstrictor effect through an action on TP receptors.
- $PGF_{2\alpha}$ causes myometrial contraction in humans, luteolysis in some species (e.g. cattle) and bronchoconstriction in other species (cats and dogs).

- PGI_2 causes vasodilation, inhibition of platelet aggregation, rennin release and natriuresis through effect on tubular reabsorption of Na^+.
- TXA_2 causes vasoconstriction, platelet aggregation and bronchoconstriction.
- PGE_2 has the following actions:

  - ❖ On EP_1 receptors, it causes contraction of bronchial and gastrointestinal smooth muscles
  - ❖ On EP_2 receptors, it causes bronchodilation, vasodilation, stimulation of intestinal fluid secretion and relaxation of gastrointestinal smooth muscles
  - ❖ On EP_3 receptors, it causes contraction of intestinal smooth muscles, inhibition of gastric acid secretion, increased gastric mucus secretion, inhibition of lipolysis, inhibition of autonomic neurotransmitter release, and stimulation of contraction of the pregnant human uterus.[11]

Leukotrienes:- Leukotrienes (leuko because they are made by white cells, and trienes because they contain a conjugated triene system of double bonds) are synthesised from arachidonic acid by lipoxygenase-catalysed pathways. The main enzyme in this group is 5-lipoxygenase.

Receptors for the leukotrienes are termed leukotriene receptors: BLT if the ligand is LTB4, and CysLT if the cysteinyl-leukotrienes. Cysteinyl-leukotrienes have important actions on the respiratory and cardiovascular systems, and specific receptors for LTD_4 have been defined on the basis of numerous selective antagonists

- **The respiratory system: -** Cysteinyl-leukotrienes are potent spasmogens, causing dose-related

contraction of human bronchiolar muscle in vitro. LTE_4 is less potent than LTC_4 and LTD_4, but its effect is much longer lasting. All cause an increase in mucus secretion. Given by aerosol to human volunteers, they reduce specific airway conductance and maximum expiratory flow rate, the effect being more protracted than that produced by histamine.

- **The cardiovascular system: -** Small amounts of LTC_4 or LTD_4 given intravenously because a rapid, short-lived fall in blood pressure, and significant constriction of small coronary resistance vessels. Given subcutaneously, they are equipotent with histamine in causing weal and flare. Given topically in the nose, LTD_4 increases nasal blood flow and increases local vascular permeability.

The role of leukotriene in inflammation: - Leukotriene B_4 is found in inflammatory exudates and tissues in many inflammatory conditions, including rheumatoid arthritis, psoriasis and ulcerative colitis. The cysteinyl-leukotrienes are present in the sputum of chronic bronchitis in amounts that are biologically active. On antigen challenge, they are released from samples of human asthmatic lung in vitro, and into nasal lavage fluid in subjects with allergic rhinitis. There is evidence that they contribute to the underlying bronchial hyper reactivity in asthmatics, and it is thought that they are among the main mediators of both the early and late phases of asthma.[2, 18]

Conclusion:

A complex interplay of inflammatory cells and chemical mediators is responsible for allergic inflammation. The understanding of how the mast cell-mediated events of the early-phase response lead to the late-phase response and chronic inflammation indicates that effective management of allergic diseases must address the inflammatory component. However, the numbers of mediators, their multiple effects and sites of action, and the interplay among the mediators and effector cells in the inflammatory process suggest that no single mediator can be targeted. The most effective therapies will combine the receptor antagonist approaches of the antihistamines with the anti-inflammatory properties of corticosteroids.

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