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Biochemical mediators of inflammation and basic principles of wound healing in the skin

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Abstract
Biochemical mediators released during inflammation intensify and propagate the inflammatory response. These mediators are soluble, diffusible molecules that can act locally and systemically. Mediators derived from plasma include complement and complement-derived peptides and kinins. Released via the classic or alternative pathways of the complement cascade, complement-derived peptides (C3a, C3b, and C5a) increase vascular permeability, cause smooth muscle contraction, activate leukocytes, and induce mast-cell degranulation. C5a is a potent chemotactic factor for neutrophils and mononuclear phagocytes. The kinins are also important inflammatory mediators. The most important kinin is bradykinin, which increases vascular permeability and vasodilation and, importantly, activates phospholipase A_2 (PLA_2) to liberate arachidonic acid (AA). Here, we review mediators of inflammation and process of wound healing.

Keywords: biochemical mediators, inflammatory response, complement cascade, wound healing

Introduction

The inflammatory response is a crucial aspect of the tissues' responses to deleterious inflammogens. This complex response involves leukocytes cells such as macrophages, neutrophils, and lymphocytes, also known as inflammatory cells [1]. In response to the inflammatory process, these cells release specialized substances which include vasoactive amines and peptides, eicosanoids, proinflammatory cytokines, and acute-phase proteins, which mediate the inflammatory process by preventing further tissue damage and ultimately resulting in healing and restoration of tissue function [2, 3]. This review discusses the role of the inflammatory cells as well as their by-products in the mediation of inflammatory process.

A brief insight into the role of natural anti-inflammatory agents is also discussed.

The significance of this study is to explore further and understand the Potential mechanism of inflammatory processes to take full advantage of vast and advanced anti-inflammatory therapies [4].

Mediators of inflammation

- **Vasodilation:** Histamine, nitric oxide (NO), prostaglandin: PGI_2, PGE_2, PGD_2.
- **Increased vascular permeability:** Histamine, bradykinin, reactive oxygen species, leukotrienes, platelet activating factor, complement.
- **Chemotaxis:** leukotrienes: LTB_4, LTC_4, Complement: C5a
- **Fever:** prostaglandin, TNF, IL-1, IL-6
- **Pain:** bradykinin, PGF2
- **Tissue damage:** NO, lysosomal enzyme [5]

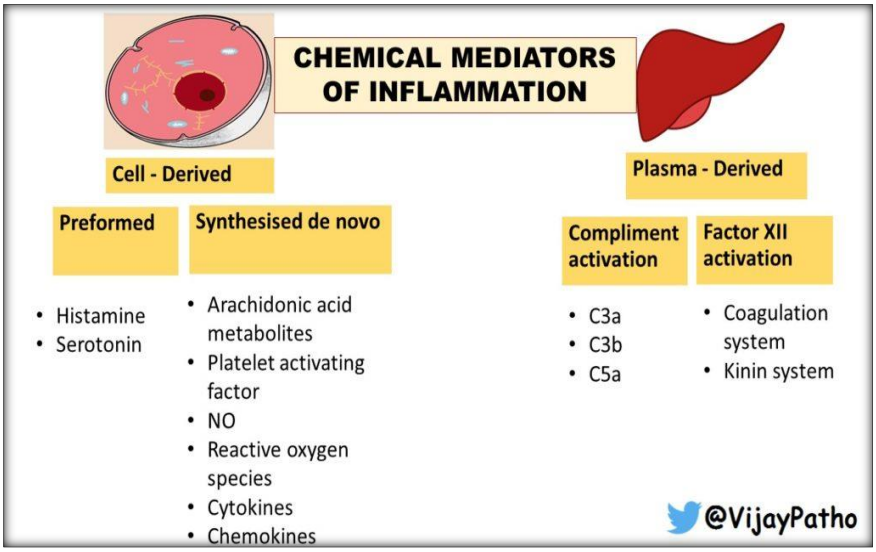

Fig 1

Information about chemical mediators/ their groups/ pathways is mentioned below:

Vasoactive amines

Histamine and serotonin are known to increase vascular permeability. They are stored in cells for immediate release.

Histamine:

Histamine is present in granules of basophils and platelets. Its main source is mast cells, present in perivascular connective tissue. It is important in early inflammatory responses and in type I hypersensitivity reactions. It promotes contraction of smooth muscles in bronchi and stimulates stromal cells to synthesize and release toxins. Following agents are known to stimulate release of histamine from mast cells.

- Physical injury, mechanical trauma, heat, chemical agents.
- Antigen binding to IgE on mast cells.
- Anaphylotoxins: C3a and C5a.
- Neuropeptides[6]

Serotonin

It is present in platelets.It sends signals between your nerve cells. Serotonin is found mostly in the digestive system, although it's also in blood platelets and throughout the central nervous system[7].

Plasma proteases

Three interrelated systems, important in the inflammatory response, are located within plasma.

They are: Compliment system, Kinin system, Clotting system

Compliment system:

The compliment system, also known as compliment cascade, is a part of the immune system that enhances (compliments) the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promote inflammation, and attack the pathogen's cell membrane.

- Kinin system:

The kinin system generates its vasoactive peptides called kininogens. Specific proteases called killikreins lead to activation of bradykinin from kininogens.

Bradykinin has following actions:

- Vasodilation and stimulation of histamine leading to increased vascular permeability.
- Contraction of non-vascular smooth muscle.
- Generation of pain[8-9].

Clotting system

Homeostasis involves three basic steps: vascular spasm, the formation of a platelet plug, and coagulation, in which clotting factors promote the formation of a fibrin clot. Fibrinolysis is the process in which a clot is degraded in a healing vessel. Thrombin binds to a receptor on platelets on endothelium, smooth muscle and causes them to:

- Produce chemokines
- Change endothelial shape

Arachidonic Acid metabolites

When cells are activated by various stimuli, their lipid membranes are remolled to generate biologically active lipid mediators. These lipid mediators are formed rapidly, exert their effects locally and are then inactivated. Oxygenated arachidonic acid dervatives have role in inflammation. Arachidonic acid is derived from linoleic acid and has 20-carbon polyunsaturated composition[9-10].

Following activation, there are two major pathways:

- Cyclooxygenase pathway
- Lipo oxygenase pathway
- Cyclooxygenase pathway:

Two enzymes are able to produce products related to this pathway: COX-1 and COX-2. COX-1 is normally present for activities, it is also synthesised at sites of inflammation. COX-2 is present only in special circumstances like inflammation. There are three main products resulting from this pathway. They are as follows:

Thromboxen A_2: It is found in platelets ant other cells. It is potent vasoconstrictor.

Prostacyclin (PGI_2): It is predominantly in endothelial cells. It is potent inhibitor of vasodilator.

Prostaglandins (PGE_2, PGD_2, $PGF_{2\alpha}$): They cause vasodilation, increased vascular permeability and pain.

Lipooxygenase pathway: It leads to production of leukotrienes and lipoxins, which have opposing effects.

Leukotrienes: they exacerbate acute inflammatory response by actions like vasoconstriction and bronchoconstriction.

Lipoxins: they are secreted by platelets and have both pro- and anti-inflammatory effects [11, 13].

- **Oxygen derived free radicals**

Superoxide anion (O_2^-) and hydroxyl radical (OH) are two mains oxygen derived free radicals. When released into tissues, they cause following effects: Endothelial cell damage resulting in increased vascular permeability. Injury to various types of cells. E.g tumour cells, red cells and parenchymal cells.

- **Platelet activating factor (PAF)**

PAF is of phospholipid origin. It is derived from the cell membranes of leucocytes, endothelial cells and platelets. It has following anti-inflammatory effects:

- Broncho-constriction and vasoconstriction.
- Increased leucocyte adhesion to endothelium, chemotaxis, degranulation and oxidative burst.
- Vasodilation and increased vascular. permeability at low concentrations; it is much potent than histamine [14].

IL-1 and TNF-α (interleukins and tumor necrosis factor)

These are the master cytokines produced by monocyte-macrophages.

They are distinct proteins in terms of biochemical and immunological structure. However, they are similar in biological activities, which are listed below: On endothelial cells, they increased leucocytes adhesion, stimulate synthesis of PGI2 and PAF and increase pro-coagulant activity. They include systemic acute phase responses e.g. fever, neutrophilia and hemodynamic effects causing shock [15].

- IL-5: It is produced by helper T-lymphocyttes (CD4 and Th2) and mast cells. It affects proliferation, chemotoxins and activation of eosinophils.
- IL-6: It is produced by T-lymphocytes and macrophages. Its major activites include proliferation of B and T cells.
- IL-8: It is produced by leucocytes and endothelial cells. It is powerful chemo-attractant and activator of neutrophils.

- IFN-γ (interferon): It is produced by T lymphocytes and NK (natural killer) cells. It activates macrophages and T-lymphocyte, particularly against viral infections.
- PGDF (platelet derived growth factor): It is produced by leucocytes, endothelial cells ajnd fibroblasts. It is important in chronic inflammation [16].

Nitric oxide (NO)

It is produced in endothelial cells, neurons and macrophages.

NO relaxes smooth muscles in vessels i.e. vasodilation.

Superoxide anion can convert NO to its own free radical called as peroxynitrite; which is bactericidal in nature [17, 20].

$$NO + O_2^- \longrightarrow ONOO \text{ (peroxynitrite)}$$

Basic Principles of Wound Healing In the Skin

Wound healing is a complex process in which the skin, and the tissues under it, repair themselves after injury. In undamaged skin, epidermis (surface layer) and dermis (deeper layer) form a protective berrier against external environment. When the barrier is broken a series of biochemical events are set in motion to repair the damage. This event is called as wound healing [21, 22].

It is divided into following four stages:

- Hemostasis (blood clotting
- Inflammatory phase
- Proliferation (growth of new tissue)
- Remodelling (maturation)

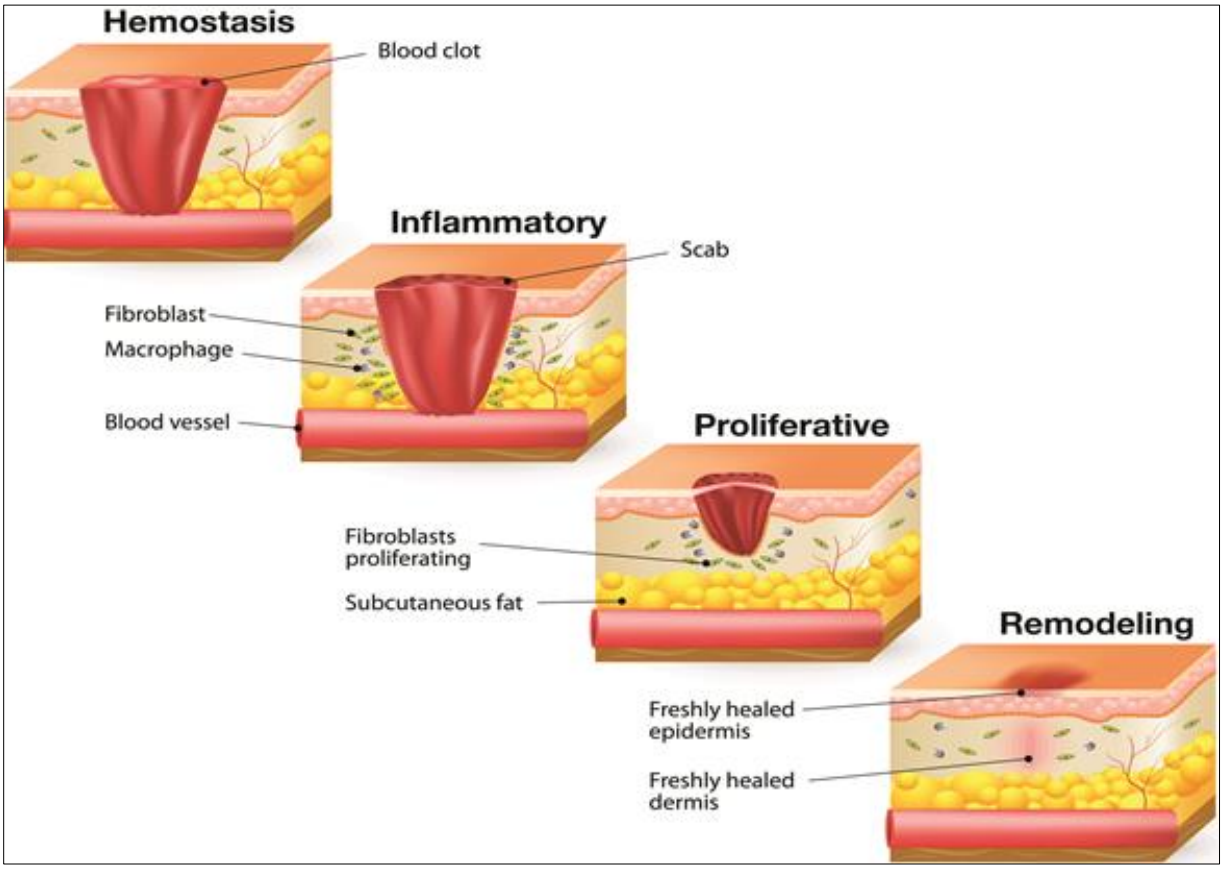

Fig 2

Hemostasis (blood clotting)

Within the first few minutes of injury, platelets in the blood begin to stick to the injured site. This activates the platelets, causing a series of events. Platelets change into an amorphous shape, more suitable for clotting and they release chemical signals to promote clotting. This results in activation of fibrin, which forms a mesh and acts as glue to bind platelets to each other. This makes a clot which serves to plug the break in the blood vessels slowing/ preventing further bleeding [23, 24].

Inflammatory phase

Just before the inflammatory phase is initiated, the clotting cacade occurs in order achieve hemostasis or stop blood loss. Inflammatory phases is divided into following sub-components:

a. Clotting cascade
b. Vasoconstriction and vasodilation
c. Polymorpho nuclear neutrophils

a. Clotting cascade: The coagulation pathway is a cascade of events that leads to hemostasis. The intricate pathway allows for rapid healing and prevention of spontaneous bleeding. Two paths, intrinsic and extrinsic originates separately but converge at a specific point, leading to fibrin activation [25].
b. Vasoconstriction and vasodilation: Immediately after the blood vessel is broken, ruptured cell membranes release inflammatory factors like thromboxanes and prostaglandins which cause vessels to contract to prevent blood loss and to collect inflammatory cells and factors in the area.' This vasoconstriction lasts for 5-10 minutes; it is followed by vasodilation i.e relaxation of blood vessels, which peaks at about 20 minutes after wounding.

Poly morpho nucleuar neutrophils: Within an hour after wounding, Poly morpho nuclear neutrophils arrive at wound site and become the predominant cells for two after the injury, the number is highest during second day. Macrophages: one of the important role of macrophagesis to phagocytise other expended phagocytes, bacteria and damaged tissue. When the process of healing results in incomplete repair, scar contraction occurs, bringing various grades of structural imperfections, deformities and problems with flexibility. Decline of inflammatory phase: As process of inflammation declines, fewer inflammatory factors are secreted; existing ones are broken down and number of neutrophils and macrophages are reduced [26].

Proliferation (growth of new tissue)

After 2-3 days after the wound, fibroblasts begin to enter the wound site. This is the beginning of the proliferative phase even before the end of inflammatory phase. Steps in the proliferative phase do not occur in a series but partially overlap in time.

- Angiogenesis: It is also called neov as cularisation. It occurs concurrently with fibroblast proliferation when endothelaial cells migrate to the area of the wound. It is divided into following components
- Latent period
- Endothelial activation
- Degradation of endothelial basement membrane
- Vascular sprouting
- Vascular maturation
- Fibroplasias and granulation tissue formation:

Along with angiogenesis, fibroblasts begin accumulating near the wound site. Fibroblasts start entering the wound site within 2-5 days wounding when inflammatory phase ending. By the end of first week, fibroblasts are the predominant cells in the wound. The deposited fibroblastic connective matures by secreating ECM into the extracellular space, leading to formation of granulation tissue. Granulation tissue works as a rudimentary tissue and begins to appear during inflammatory phase [27].

- Collagen deposition: Collagen deposition is important because it increases the strength of the wound before it is laid down.
- Epithelialisation: Formation of granulation tissue in an open wound allows the re-epithelialisation to take place; since epithelial cells migrate across the new tissue form a barrier between the wound and the environment [28].

Remodelling (maturation)

When levels of collagen production and degradation equalize, the maturation phase of tissue repair has already begun. During maturation, type III collagen is replaced by type I collagen. The phase can last even for a year or longer, depending on type of wound. As the maturation phase progresses, the tensile strength of the wound increases. Activity at the wound site is reduced, the scar loses its red appearance because bold vessels, which are not needed are removed by apoptosis [29, 30].

Conclusion

This review has highlighted the important roles of inflammatory mediators in the inflammatory process. Although inflammation is very important in the elimination of pathogens and other causes of inflammation, a prolonged inflammatory process has been shown to results in chronic disease processes that may eventually result in organ failure or damage. Thus, limiting the inflammatory process by the use of anti-inflammatory agents is important in controlling this process and limiting its course. However, while a handful of synthetic anti-inflammatory agents exist, they all seem to have adverse effects with prolonged usage. Hence, there is still the need to discover newer and better anti-inflammatory agents from natural products.

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