

Chemical Mediators of Inflammation: Targets for Wound Repair

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Introduction

The ability of fighting infection, healing damages and the capability of energy storage for low nutrient obtainable and high energy need periods, aid the survival of a multicellular organism (Wellen and Hotamisligil, 2005). Healing can be defined as the attempt of the body to restore its regular structure and functions in response to an injury (Sarabahi and Tiwari, 2012). Wound is a constrained injury which is caused by external factor and it can involve any tissue and organ. Wound healing is a compound and sophisticated procedure, comprises a set of events that involve cellular and molecular interaction to restore function of the affected site (Ameh et al., 2020). Wound healing occurs in four main phases including inflammation phase (Stroncek and Reichert, 2008).

Defense mechanism of the body consists of an important part known as inflammation. This is when the healing process initiates by the immune system recognizing any harmful or foreign stimuli in the body (Pahwa et al., 2020). It is also defined as “the body’s immune system’s response to stimulus” by US National Library of Medicine (Bhatia et al., 2015).

The mechanism of inflammation will be facilitated by several chemical substances and signaling molecules, secreted by the defensive cells of the body (Abdulkhaleq et al., 2018). These soluble and diffusible substances are recognized as chemical mediators which are crucial in inflammatory response, hence in wound healing (Edwards, 2014).

Exploration of therapeutic target is the base of modern drug discovery. The ongoing studies have led to a growing interest in inventing new targets and more exploration of existing targets (Zheng et al., 2006). The chemical mediators are one of the known therapeutic targets in the instance of healing wounds.

This review mainly focuses on the processes of inflammation and wound healing. In addition, this

will also focus on how chemical mediators facilitate inflammation while acting as the therapeutic target of wound healing.

Chemical mediators and their types

Chemical mediators can be found in the body tissues; therefore, they are also known as endogenous or permeability factors (Oliviero and Scanu, 2017). While inflammatory response initiated by an injury, the chemical mediators secreted by plasma, cells or tissues in the injured site mediate the process (Anderson and Cramer, 2015).

According to the derivation sites of the mediator molecules, they are classified into two main groups;

1. Cell derived mediators, which are produced by the cells at inflammation site.
2. Plasma derived mediators, which are generally synthesized by the liver and can be found in the plasma as inactive precursors until inflammation occurs.

Different types of chemical mediators perform various functions in the case of inflammation. The table 1 below shows various actions of inflammation occurred due to by different chemical mediators.

Use of chemical mediators in the process of inflammation

Inflammation process

Inflammation is one of the vital processes required in defense mechanism of cells against injuries and infections (Nathan and Ding, 2010). The process of inflammation represents a chain of organized and dynamic responses consisting of cellular as well as vascular events with specific secretions known as chemical mediators (Akçay, Nguyen and Edelstein, 2009). The inflammatory response may consist of

Table 1: Actions of different types of mediators in inflammation

Type of Chemical Mediator	Mediator	Principal Source	Actions
Cell-Derived Mediators	Histamine	Mast cells, basophils, platelets	vasodilation, increased vascular permeability, endothelial activation
	Serotonin	Platelets	vasodilation, increased vascular permeability
	Prostaglandin	Mast cells, Leukocytes	vasodilation, pain, fever
	Leukotrienes	Mast cells, Leukocytes	increased vascular permeability, chemotaxis, leukocyte adhesion and activation
	Platelet-activating factor	Mast cells, Leukocytes	vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Plasma-Derived Mediators	Complement products (C5a, C3a, C4a)	Plasma (produced in the liver)	Leukocyte chemotaxis and activation, vasodilation (mast cell stimulation), increased vascular permeability, smooth muscle contraction, vasodilation, pain, endothelial activation, leukocyte recruitment
	Kinins		
	Proteases activated during coagulation		

several crucial events; Table 2 explains the use of chemical mediators in various inflammatory responses.

Table 2: Chemical mediators in Different Inflammatory responses.

Inflammatory Response	Chemical mediator
Increased vascular permeability	Vasoactive amines, Bradykinin, Leukotrienes
Fever	IL-1, TNF, Prostaglandins
Pain	Prostaglandins, Bradykinin
Tissue Damage	Neutrophil and macrophage, lysosomal enzymes,
Vasodilation	Prostaglandins, histamine, nitric oxide
Chemotaxis, leukocyte recruitment and activation	Leukotriene, chemokines, Bacterial products

The pathway involves migration of plasma, several white blood cells including monocytes, basophils, neutrophils and eosinophils in the inflammation site (Poher and Sessa, 2007). The mediators and several signaling molecules will be released by the immune defense cells to contribute in the process of

inflammation.

The indicators of inflammatory response can be divided as macroscopic and microscopic indicators. The Roman Physician, Celcius explained that macroscopic indicators typically categorized by four “Cardinal Signs” which may give rise to loss of function in the organism (Lotze and Thomson, 2005). Figure 1 illustrates the four cardinal signs.

**Figure 1:** Cardinal Signs of Inflammation

The inflammatory response may trigger through two phases, which are mediated through different mechanisms.

The immune responses which are involved in acute inflammation can be divided into vascular and cellular processes (Sattar et al., 2009). The responses occurring in microvasculature, commonly appear immediately following the injury or infection in the presence of vascular events known as inflammatory stimuli. These rapid processes sooner will lead to vasodilation and later makes the vessels additionally permeable. This will allow the inflammatory mediators to enter and

contribute to interstitial edema.

Etiology of inflammation

Inflammation may be a result of several factors including physical, chemical and biological agents (Siraj, 2020). Factors such as inappropriate immunological responses, tissue death, infectious agents also trigger inflammation.

Microbial infections are most common cause of inflammation. They give rise to inflammation by entering and destroying cellular components or even cells of the body. Bacteria can secrete a chemical substance known as endotoxins, which can initiate inflammation. Moreover, physical factors such as burn, radiation, injuries, corrosive chemicals and frostbites can also induce inflammation by tissue damage. Inflammation process can also take place when a tissue dies from lack of nutrients and oxygen, which can happen when the blood flow to the tissue is blocked (Nathanael et al., 2011). Apart from these exogenous causes, there are few endogenous factors which can also result in inflammation. Examples for some endogenous factors are; circulatory disorders, activation of several enzymes such as acute pancreatitis, metabolic products such as uric acid (Srikrishna and Freeze, 2009). Figure 2 below shows some of the causes of inflammation.

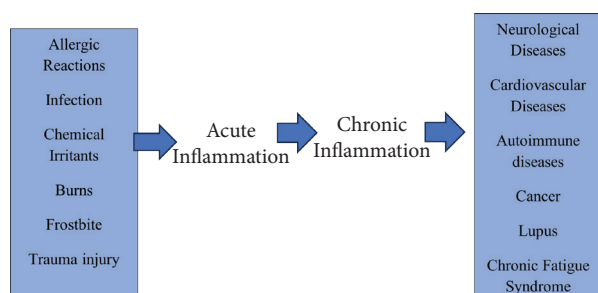


Figure 2: Etiology and cause of inflammation.

Chemical mediators as therapeutic target in progression of wound healing

Process of wound healing

Consequent to tissue damage or injury, a set of events occur in the body. That include inflammation, proliferation and maturation which promote wound closure and restoring of the tissue (Shukla et al., 2019).

The mechanism of wound healing involves two

distinct processes; regeneration and repair. They consist of a series of cellular and molecular actions which arise after the onset of a tissue abrasion to restore the injured tissue (Gonzalez et al., 2016). The process of proliferation of parenchymal cells occur during regeneration. Usually, regeneration of tissue results in a complete restoration of the original tissue (Koria, 2012).

The proliferation of connective tissue rudiments resulting in scarring and fibrosis is referred to as tissue repair. This includes granulation of tissue formation and contraction of the wound. Several cells are involved in the repair mechanism, such as; mesenchymal cells, macrophages, endothelial cells and platelets (Neuss et al., 2009).

The initial stage of wound healing is dedicated to hemostasis and the development of a temporary wound matrix, which happens instantly after injury and completed after several hours (Rosinczuk et al., 2018). Additionally, homeostasis will initiate the inflammatory process. Inflammation becomes activated during the phase of coagulation and may approximately get divided into an early stage with neutrophil cell recruitment and late stage with the appearance and alteration of monocytes (Shukla et al., 2019).

The recovery of the wound surface is the main target of proliferation stage. The granulation tissue formation and vascular network restoration also occurs in this phase. The neovascularization and angiogenesis will be stimulated by capillary sprouting, following the movement of fibroblast along the fibrin network and re-epithelialization initiating from the wound edge. When apoptosis take place, the formation of granulation tissues stops. For all the necessary actions to occur, the chemical mediators and all the components of extracellular matrix will undergo numerous changes (Johnstone et al., 2005).

The physical endpoint of wound repair mechanism is the formation of a scar, which is related to the extent of the process of inflammation during wound healing (Jackson, Nesti and Tuan, 2012).

Types of wounds and wound healing

There are two major types in wound healing, depending on the type of wound. They are primary and

secondary wound healing. The below Figure 4 shows the differences between the two types of wound healing.

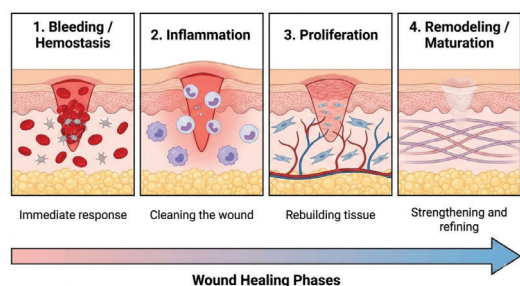


Figure 3: Phases of wound healing

Primary Healing

Wound is clean and uninfected.
Edges of wound are approximated by surgical sutures
Takes place in surgically incised wounds
Scar formation is neat and small
There is no granulation tissue formation
There is not much loss of cells and tissues
Healing is rapid

Secondary Healing

There is extensive loss of cells and tissues
Wound is open with large tissue defect and at times infected
Edges of the wound are not approximated by surgical sutures.
It forms the main bulk of secondary healing
Healing is slow
Healing takes place from base upwards besides from margins inward

Figure 4: Comparison of primary and secondary wound healing.

Various types of traumas may cause various kinds of wounds. The classification can be made according to the cause of injury, severity of the wound and healing time.

Factors affecting wound healing

There are four major phases of wound. Numerous factors play a huge role in facilitating the wound healing process (Guo and Pietro, 2010). The factors can affect any of the pathway of the healing, therefore causing improper wound healing or even halt the process in between. Table 3 shows few local and systemic factors, which can affect any phase of wound healing.

Table 3: Factors affecting wound healing process.

Local factors	Systematic factors
Tissue hypoxia	Senescence
Contamination from incontinence	Malnourishment
Pressure	Smoking
Tissue edema	Stress
Necrotic material	Comorbidity
Infection	Immune compromise
Dessication	Obesity
Maceration	Diabetes, Anemia

Evolution of wound healing in the medical industry

The major goal of treating wounds is to prevent infection and removing redundant tissues from the body. There are many problems impair with wound healing and recovery of the injured site. It can even result in systemic pathology. Proper techniques of wound care not only prevent infection but also lead to quick recovery and even result in minimize scarring (Han and Ceilley, 2017).

In order to deliver proper treatment, the medical sector needs to work on several areas, including diagnostic, therapeutic, the research on therapeutic target for further drug discovery, prognosis and the prospects of health hazard. Various diseases related to wounds such as skin wound, corneal wounds, diabetes foot ulcers and chronic wounds are becoming major cause of disability or even death globally; numerous studies are ongoing on more effective treatments and therapeutics (Siddiqui and Bernstein, 2010). There are several techniques and methods that have been discovered, such as stem cells to treat wounds.

The progress of fields such as proteomics, genomics, bioinformatic, pathophysiology has led to an increasing interest in finding new therapeutic targets and exploring pre-existing targets (Zheng et al., 2006). This has a positive impact on modern drug discovery and novel methods and techniques in the medical sector. Hence, treating wounds is also improving with more effective novel treatment methods (Baltzis, Eleftheriadou and Veves, 2014).

Conclusion

The evidence present in this review has shown that successful treatment of wounds would be one of the major improvements in the medical field globally. As an initial step for therapeutic discovery, scientists have already found a therapeutic target of wound healing. Chemical mediators are one of the crucial factors for the future therapeutic and medical aspects. Which are normally involved in the immunological approach of the body towards inflammation arises from injuries and other diseases.

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