Introduction

The earliest known description of inflammation comes from the Edwin Smith Papyrus, one of the Egyptian papyri found in a tomb near Thebes. The Papyrus dates from about 1550 B.C., but it is undoubtedly a copy of ancient tests of the archaic period of Egyptian history (3200-2780 B.C.) Documents from Egyptian and other early civilizations leave no doubt that the features of inflammation were recognized from very early periods; although the understanding of the process took a long time to happen.

Inflammation can be considered as the first response of a living tissue to injury and may be referred to as the innate immunity, and may appear due to microbial infections, physical factors (trauma, radiation, temperature), chemical substances (irritant and corrosive chemicals), as well as tissue necrosis and hypersensitivity reactions. It is didactically characterized by the following quintet: redness (rubor), heat (calor), swelling (tumor), pain (dolor) and dysfunction (functio laesa). The first four characteristics were drawn up by Celsus nearly 2000 years ago; function laesa was added to the definition of inflammation by Rudolf Virchow in 1858, considered the predecessor of modern pathology and social medicine. It was the latter who, in the field of inflammation, critically analyzed the changes which occurred in the living tissue when it is injured, provided that the injury is not of such a degree as at once to destroy its structure and vitality [1]. The inflammatory response consists of a vascular and a cellular component. The vascular component represents changes in vessel diameter (vasodilation) and consequently increased blood flow (causing redness and heat), and increased vascular permeability resulting in loss of plasma into the tissue and formation of fluid exudate. The exudate contains many valuable proteins such as fibrin and immunoglobulin but it also gives rise to edema. The swelling distends the tissues; it may compress nerve endings and thus cause pain.

According to its duration, inflammation is described as acute or chronic. Sometimes the acute process subsides but the stimulus persists sufficiently to evoke a subsequent chronic inflammation. In other cases, with a stimulus that typically induces chronic inflammation, the tissues response may be acute in type for the first day or so. Suffice it to say at this stage that the tissue response differs considerably in acute and chronic. The cellular component involves the movement of white blood cells (leukocytes) from the blood vessels into the inflamed tissue. They extra vasate from the capillaries into tissue, and act as phagocytes, picking up bacteria and cellular debris. They may also aid by walling off an infection and preventing its spread. Influx of neutrophils is one of the earliest stages of the inflammatory response. These cells mount a rapid, non-specific phagocytic response. Later, monocytes/macrophages and cells of other lymphocyte lineages (specific subsets of T cells and B cells) appear at the site of injury; cell types which are associated with antigen-specific and more tightly regulate immune responses and once activated also produce protective and inflammatory molecules.

The lymphocytes are the primary cells of the immunologic system, and have developed one of the more sophisticated intelligent defense mechanisms in the biological system. The review of ALAM and GORSKA [2], enlightens that the T lymphocytes play a major role in the organization of the immune response, eliminating intracellular pathogens (virus, and bacteria) through the generation of cytotoxic T lymphocytes. The B lymphocytes protect the organism against extracellular pathogens by the production of antibodies. The
natural killer cells (NK) are an important component of the innate immunity. The dendritic B cells begin the immunologic response by presenting antigens to the T lymphocytes. The authors resume that the interaction among the T lymphocytes, B lymphocytes, dendritic cells and the natural killer cells (NK) constitutes the fundamental defensive mechanism of the host.

The mechanism against pathogenic microbes demands different responses depending on the characteristic of the pathogen and on the attacked tissue. CHAPLIN [3], claimed that the organism of the host has developed innate and adaptive immune mechanisms of defense, being the former unspecific, attacking any nonself structure or antigen, and the latter, on the other hand, extremely specific. Both types of immune response act together in order to eliminate pathogenic antigens through the discrimination of what is self and what is not.

The changes described in blood flow, increased permeability of blood vessels and escape of cells from the blood into the tissues (diapedesis) are basically the same whatever the cause and wherever the site of inflammation is. Thermal injuries cause permanent occlusion of the blood vessels in a narrow zone of tissue immediately surrounding the burned site. Beyond the zone where the injury is less intense, blood flow is reestablished after a short initial period of vasoconstriction. Immediately after injury, there is transient ischemia due to vasoconstriction, particularly of the arterioles. The sequelae of acute inflammation depend upon the type of tissue involved and the amount of tissue destruction, which depend, in turn, upon the nature of the injurious agent. The possible outcomes of acute inflammation can be either healing or chronic inflammation. Chronic inflammation is characterized by a dominating presence of macrophages in the injured tissue. These cells provide a powerful defensive mechanism in the body, but the mediators they release are injurious to the organism’s own tissues, as well as invading agents. This is why chronic inflammation is almost always accompanied by tissue destruction [4].

Inflammation is referred to, didactically, as acute when it lasts two days or three weeks and as chronic when more prolonged. The typical case of acute inflammation is characterized by vasodilatation, by exudation of plasma and the emigration of neutrophilic leucocytes into the injured tissue. But not all the examples of acute inflammation exhibit neutrophilic infiltration and, conversely, neutrophils may be associated with prolonged and therefore chronic inflammation. Between acute and chronic there occurs a wide range of overlapping processes and those at halfway point are sometimes referred to as subacute inflammation. The main events in acute inflammation are vascular in origin and remarkably consistent for a wide range of stimuli. Nevertheless, the response exhibits considerable differences that depend, first, on factors related to the injury or infection and, second, on the condition of the host and nature of the tissue involved [5]. On the other hand, inflammation is said to be chronic when its duration is prolonged for months or years, or even indefinitely. Its prolonged course is due to persistence of the causative factor in the tissues, whether the factor be infection or inanimate foreign body. The tissues committed are infiltrated by macrophages, lymphocytes as well as plasma cells. In addition, there is a varying but often form substantial proliferation of fibroblasts forming collagen, blood vessels and of tissue histiocytes.

The role of cytokines

The immune system is a complex organ with both professional and non-professional cells involved, whose main objective is to allow the most developed organisms to endure in a world where microorganisms try to make use of them to survive. In short; it is a sophisticated and interconnected system that makes human existence possible; and so communication between its main components is a major issue. Therefore, the competent cells of the immune system make use of substances that may be unleashed in the blood stream to signalize the need of the cell recruitment or the production of specific substances. It is accomplished by direct cell-cell contacts, by contacts with non-self-factors; like pathogen compounds, and by soluble proteins. This immune response is obtained partially by the synchronized synthesis and function of the small cytokines called chemokines (CKs) and their action on their counterparts, the chemokine receptors (CKRs), without which the cells would never respond. In fact, CKRs define the subpopulation that will be recruited in each step of the immune responses. The name chemokines is derived from chemoattractant cytokines, and is related to their capacity of inducing directed chemo taxis in nearby responsive cells.

The cytokine family is large with still unanswered questions. It includes the Interleukins (IL), Interferon (IFN), Tumor Necrosis Factor (TNF), Coloning-stimulating Factor (CSF), Chemokines (CKs), and Growth Factor (GF) [3].

Interleukins – ranging from IL1 to IL32 - are different among each other, have different functions and are secreted by different cells. Interferon is subdivided in IFNα (leukocyte IFN - inhibitor of viral replication) IFNβ (fibroblast IFN – inhibitor of viral replication) and IFNγ (Secreted by lymphocytes – immune regulatory functions). Tumor Necrosis Factor is represented by TNFα (secreted more frequently by monocytes) and TNFβ (secreted by T cells). Colony-stimulating Factor (G-CSF, M-CSF, GM-CSF and others) – able to make bone-marrow cells differentiation into specific cell types, like monocytes, macrophages and neutrophils. Chemokines (Eotaxin and many others) are very important in controlling the migration of cells between and within tissues. Growth Factor (IGF, TGF and many others) was originally identified because of non-immune-related functions but may have effects on immune cells. Some of them are considered pro-inflammatory and can be induced during an immune response to promote cells of the immune system to a site of infection, whereas others are considered homeostatic and are involved in controlling the migration of cells during normal processes of tissue maintenance or development. The first cytokine identified to have chemotactic activity was interleukin-8 (IL-8), which proved to be a selective neutrophil chemoattractant [6].

Not only is the inflammatory bone destruction governed by local cytokine production but also the normal bone remodeling throughout the lifetime of an individual. Some of the factors which regulate physiologic bone remodeling are prostaglandins (PGs), IL-1, TNF-a and possibly IL-6 [7].

The production of cytokines at the sites of inflammation in the oral tissues is part of the host response which is essentially protective in nature. Both under-activity (hypo-responsiveness)
and over-activity (hyper-responsiveness) of the host response, such as unrestricted production of cytokine(s), may result in tissue destruction. Traditionally, the immune functions have been thought to be regulated by signals originating within the immune system. It is now evident that the immune system is regulated in part by the central nervous system (CNS), acting principally via the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) [8,9]. The pathways between brain and immune system seem to be bidirectional and the aim is maintenance of homeostasis. The SNS provides a major integrative and regulatory pathway for this communication. The sympathetic innervation of lymphoid tissue, the presence of adrenergic receptors on immune cells (B and T lymphocytes, macrophages) and studies of catecholamine interactions with the immune system [10], provide substantial evidence for the role of SNS in immune regulation. Furthermore, the cellular products of an activated immune system, namely cytokines, can signal to the brain. The cytokines TNF-α, IL-26 1 and IL-6 seem to be involved in the cross-talk between brain and immune system via corticotropin-releasing hormone (CRH) secretion and hence, they activate both the HPA and the SNS [11,12].

The development of methods for the study of leukocyte migration in vitro [13], facilitated the discovery of several chemoattractants, such as complement fragments C3a and C5a, arachidonic acid derivatives such as leukotriene B4 (LTB4) and 12-hydroxy-eicosanotetraenoic acid (12-HETE), and platelet activating factor (PAF) [14].

**Inflammation in the oral cavity**

The oral cavity is exposed in many ways to a number of potential microbial agents firstly because of its main functions: nourishment and communication. Other than these factors, some treatments applied on the teeth may favor the deposition of dental plaque associated with extra strength applied on the teeth, like orthodontics. Even more, inflammation in orthodontics also comes from the forces applied on the teeth, and the presence of osteoclasts at location of alveolar bone remodeling is antecedent to orthodontic tooth movement. Cell recruitment and clearance are the mechanisms by which osteoclast population are regulated [15]. During orthodontic force application, the periodontal ligament (PDL) undergoes hyalinization, a light microscope term describing the loss of cells from an area of the ligament because of necrosis. This tissue damage prevents the tooth from moving until the adjacent bone and the necrotic tissue are removed by osteoclasts. As a result, the tooth movement reaches a plateau which lasts about 10 to 20 days in humans [16,17].

Periodontitis and pulpsitis are the most common infections in odontology and are indeed commonly found in the daily practice in surgery offices. Periodontitis shares many pathologic features with other inflammatory diseases with concomitant bone resorption such as rheumatoid arthritis (RA), with accumulative evidence that both conditions manifest as a result of an imbalance between pro-inflammatory and anti-inflammatory cytokines [18]. The increased local production of pro-inflammatory cytokines either directly enhances the proliferation and/or activity of cells in the osteoclast lineage or indirectly affects the production of the essential osteoclast differentiation factor, receptor activator of NF-κB ligand, and/or its soluble decoy receptor, osteoprotegerin, by osteoblast/stromal cells [19].

As for what concerns root resorptions; one study showed that only interleukin-1α has a potent capacity, to increase it [20].

ESSAYAN, 1998 studied the role of the IL-1 cytokine family (interleukin-1), which represents a group of proteins that possesses synergic and contrasting biological responses. In agreement with their study, IL-1 and its precursory forms are strongly involved in the establishment of inflammation and host defense [21]. The continuous exposure too many sorts of biological, physical and chemical agents makes the mouth more prone to inflammation and infections, mainly caused by bacterial influence. Its main tissues are, in normal conditions, well adapted to endure; supporting even abrupt thermal changes, but sometimes, as a result of low immunity or high virulence of a determined agent (or even a combination of both), it may develop an inflamed site elsewhere in the mouth, where varieties of anaerobic gram negative bacteria exist and the LPS (lipopolysaccharide – a bacterial pathogenic element) of such bacteria is thought to be a virulence factor which plays a role in the development of dental diseases [22-24]. Once inflammation such as pulpitis, gingivitis, or periodontitis has been established, an inflammatory infiltrate is formed consisting of different cell types such as neutrophils, macrophages and lymphocytes which will produce different cytokine subtypes responsible for the immunopathology of the diseases.

Chronic marginal gingivitis is characterized clinically by gingival redness, edema, bleeding, changes in contour, loss of tissue adaptation to the teeth, and increased flow of gingival crevicular fluid (GCF) [25,26]. Its origins is usually associated with dental plaque which irritates the surrounding tissues because of the release of toxins produced by microorganisms and the natural course of the disease may times be modified by the action of hormones. Pregnancy is accompanied by an increase in the levels of both progesterone and estrogen which, by the third trimester, reaches levels 10-30 times than seen during the typical menstrual cycle. The changes in the levels of hormone lead to the conclusion that female steroid hormones may have dual effects on the pathogenesis of pyogenic granuloma in pregnancy.

Development of gingivitis necessarily requires the presence of plaque bacteria [27,28] which is believed to cause pathological changes in the tissues by both direct and indirect means [29]. Histopathologic observations have led to the subdivision of gingivitis into 3 stages, which are divided didactically for the understanding of the process. The first stage usually begins with an initial lesion which appears 2 or 4 days after initial injury, where there is a transitory period of vasoconstriction followed by vasodilatation and consequent increase of blood flow that brings along neutrophils (PMNs), progressively adhering to the endothelial walls getting ready for diapedesis. Vascular changes and collagen degradation represent the initial changes probably due to chemotactic attraction of neutrophils to the contaminated area by direct vasodilatory effects of bacterial products, as well as activation of host systems such as the complement and kinin systems and arachidonic acid pathways [30]. The second stage is a continuation of the process represented by the persistence of the
acute inflammatory response. Capillaries engorge and proliferate as a result of blood congestion, which increases the permeability and the inflow of plasma and the diapedesis, with a mixture of the first lineage of immune cells, which is unspecific, and the adaptive immunity, with the lymphocytes as their main representatives, preparing the area for a transition from acute to chronic. And finally the third stage would be the establishment of chronic gingivitis characterized by slow venous return and color change from red to blue hue and the intense population of lymphocytes B and the formation of granulation tissue rather than collagen bundles [31].

*In situ* production of pro-inflammatory cytokines is generally seen in inflamed pulp and/or gingiva as part of the inflammatory response [32,33]. The clinical signs and the discomfort of gingivitis have been attributed to pathological tissue changes which commit gingival microcirculation [34], a mechanism which involves capillaries and small venules right at the site of injury and the adjacent arterioles. Bacterial LPS and cytokines have only been implicated in the vascular component of edema formation [35], however their possible effect on the interstitium has not yet been explored. Following the expectable path of untreated gingivitis, it can progress to a more severe stage when the inflammatory process extends to the periodontal ligament and alveolar bone, compromising directly the anchoring apparatus of the teeth [36].

On the other hand, in periodontitis, bone resorption is mediated largely by the increased local production of pro-inflammatory cytokines, such as IL-1α, IL-1β, and TNF-α. The LPS released from the periodontopathic bacteria triggers the synthesis of IL-1 and TNF-α from macrophages. IL-1 and TNF-α stimulate the production of a variety of other inflammatory mediators (cytokines, nitric oxide and PGE2), matrix-degrading enzymes (metalloproteinases), and decrease the synthesis of glycosaminoglycans, enhancing bone destruction [37,38].

The degradation and removal of hard tissue are a cellular event brought about by giant multinucleated cells formed through asynchronous fusion of mononuclear cells belonging to the macrophage lineage and originating from the hematopoietic system [39]. They are called clasts and are easy to identify under the light microscope because of their size (50 to 100μm), their multinucleation (2 to 10 nuclei per cell), and their association with the surface of bone (occupying shallow depressions known as Howship’s lacunae). Such cells are also intermediated by cytokines which induce and stimulate their recruitment.

The field of odontology which deals with bone resorption and neoformation is orthodontics, for the fact that its basis is the application of mechanical forces which produce organized periodontal tissue remodeling generating tooth movement, with forces transmitted from the dental roots to the periodontium where cells are stimulated to remodel the surrounding matrices. The forces applied will necessarily cause an inflamed area in the surrounding tissues of a tooth, causing bone resorption in the pressure sites and bone deposition in the tension sites [40-43]. There seems to be a role of cytokines such as IL-1α, IL-1β, and TNF-α in the process [44,45].

As previously mentioned, several infectious, autoimmune, but also allergic and neoplastic diseases have been attributed to the imbalance between pro-inflammatory and anti-inflammatory cytokines and therefore, the regulation of pro/anti-inflammatory cytokines has attracted considerable interest [46]. Components of the innate immunity such as antigen presenting cells (APCs), dendritic cells, and monocytes/macrophages, as well as components of the acquired (adaptive) immunity such as T helper (Th) lymphocytes, are all involved in immunoregulation.

To mediate an effective response, leukocytes must find their way to sites of infection or inflammation. Leukocyte invasion of tissues can be induced by chemotactic activity of several substances—including interleukin-1 (IL-1), tumor necrosis factor- (TNF-α), and bacterial lipopolysaccharide (LPS)—that cause leukocyte emigration when injected *in vivo* [47]. All such compounds induce the production of chemoattractants, which in turn cause leukocyte migration. Therefore, chemotactic activity includes the receptor-mediated gradient perception and must be measured by the ability of a chemoattractant to induce directed leukocyte migration *in vitro* [47].

The antigen presenting cells (APC) are those that express high levels of class II MHC molecules; with internalizing ability to process and expose foreign antigens in the fitting MHC. Therefore, the immune response comes mainly from the action of four cellular types: T cells (fundamental in the elimination of intracellular pathogens such as virus and bacteria) through the generation of cytotoxic T cells. B cells, which defend the organism against extracellular pathogens by the production of antibodies. Natural killer cells (NK), which constitute a subspecies of positive cytotoxic lymphocytes CD56, which, in spite of belonging to the innate immunologic system for not presenting surface receptors, are fundamental for the recognition of pathogens, and Dendritic cells (DC), cells, which activate the immunologic response by the exhibition and consequent presentation of foreign antigens to the T cells [48,49].

Th lymphocytes are divided into two subclasses; Th1 and Th2. Th1 cells primarily secrete IFN-γ, and IL-2 which enhance cellular immunity, whereas Th2 cells secrete a different set of cytokines, primarily IL-4, IL-10, IL-13 and IL-9, which enhance humoral immunity [50,51]. The antigen –inexperienced (naïve) CD4+ Th0 cells can differentiate to either Th1 or Th2 and the differentiation is strongly dependent on the cytokines produced by cells of the innate immune system [51]. IL-12 produced by activated monocytes/macrophages, represents a major inducer of Th1 differentiation and hence cellular immunity. IL-12, together with TNF-α and IFN-γ act synergistically in inflammation and further promote Th1 responses and hence considered major pro-inflammatory cytokines [51]. Th1 and Th2 responses are mutually inhibitory. Thus IL-12 and IFN-γ inhibit Th2 and vice versa, IL-4 and IL-10 inhibit Th1 responses and the production of pro-inflammatory cytokines. IL-4 and IL-10 are the major anti-inflammatory cytokines and an increasing body of evidence suggests that catecholamines inhibit selectively the Th1 functions and pro-inflammatory cytokines and favor the Th2 responses and anti-inflammatory cytokines [8].

Cytokines and chemokines are redundant secreted proteins with growth, differentiation, and activation functions that regulate and
determine the nature of immune responses and control immune cell trafficking and the cellular arrangement of immune organs. Which cytokines are produced in response to an immune insult determines initially whether an immune response develops and subsequently whether such response is cytotoxic, humoral, cell-mediated, or allergic [52]. Cytokines act on cells through transmembrane cell surface receptors. Binding of the cytokine to the receptor elicits its cellular response by activating an intracellular signal transduction pathway that ultimately leads to induction of new gene transcription and synthesis of new cellular proteins. Most cytokine receptors signal using one of the Janus Kinase (Jak) family of proteins. Specific Jak proteins associate with the cytoplasmatic domains of cytokine receptors. When binding the cytokine activates the receptor, the Jak phosphorylates its respective STAT protein, causing the STAT to dimerize and translocate into the nucleus, where it initiates new gene transcription [3].

Increased vascular permeability can be induced by cytokines such as IL-1 and TNF-α acting either directly at the endothelial cells or indirectly by inducing other inflammatory mediators that affect the vascular endothelium [53,54]. In addition, LPS can increase vascular permeability not only through induction of pro-inflammatory cytokines, but also affecting directly the endothelial barrier [55,56].

The periapical lesion represents a product of the body’s immune response to bacterial infection of the pulp, with the purpose to wall-off the infection within the confines of the root canal system [57]. In many respects this periapical lesion recapitulates the pulpal response to infection, with the additional feature of periapical bone destruction. A mixed infiltrate of T and B lymphocytes, polymorphonuclear leukocytes (PMNs), macrophages, plasma cells, natural killer (NK) cells, eosinophils and plasma cells has been characterized [58-63]. NK cells are thought to represent a third lineage of lymphoid cells which, when activated, have the morphology of a large granular lymphocyte [3].

There are controversial results regarding the predominant infiltrating cell type in periapical lesions. Such periapical alterations are didactically postulated as chronic lesions with either lymphocytes [64,65], or macrophages [61,63] generally reported to be most numerous. T cells consistently outnumber B cells [65,66]. Of the T lymphocytes, both Th and T suppressor cells have been identified with temporal differences regarding their relative concentration [63,66]. The variety of inflammatory cells reveals that both non-specific and specific immune responses are mediated in the pulp and periapical tissues in response to infection. Therefore, the periapical lesion provides a suitable model for studying local immune responses. The superior cervical ganglion (SCG) supplies with sympathetic innervation the oral tissues [67,68]. By removal of the SCG, the local control of immune responses by sympathetic nerves can be studied in periapical lesions.

The interstitial fluid (IF) represents extracellular fluid located outside the blood vessels. Interstitial fluid bathes the cells of the tissues and it provides a mean of Delivering nutrients to the cells, intercellular communication and removal of metabolic waste. Plasma, the major component of blood, communicates with the interstitial fluid through pores and intercellular clefts in the capillary endothelium. Under physiologic conditions, the endothelium of the capillaries and proximal portion of the venules forms a semipermeable membrane that permits free movement of water and small molecules to and fro across the endothelium but normally restricts the passages of plasma protein. The capillary wall acts as a filtration “barrier”. Fluid equilibrium across this endothelial barrier is maintained by the hydrostatic pressure of the capillary blood being balanced by the equal and opposite restraint of the osmotic pressure of the plasma proteins. Most of the fluid within the capillaries is retained, but some fluid filters normally through pores between the cells, pushed by the pressure difference between the capillary blood and the IF. Water and small solutes can pass freely through these pores. The net effect of the hydrostatic pressure alone is a net loss of water and solutes from plasma to the IF. The capillary wall is, however, nearly impermeable to the plasma proteins and lipids but following inflammation, the capillary permeability for proteins increases. Because the capillary wall is permeable to water, but essentially impermeable to the plasma proteins, these molecules generate a colloid osmotic pressure gradient that draws water out of the interstitium and into the plasma. This pressure is proportional to the difference in protein concentration between the plasma and the IF.

Nevertheless, there is little information available regarding intra- and extra-vascular fluid volumes in dental tissues (oral mucosa, pulp) during health and disease. The absence of such information from the dental pulp is mainly due to the nature of the tissue that does not allow easy access to the interstitium. Its inextensible walls creates a hermetic cavity inside which blood runs bringing in nutrients and defense cells, while removes metabolic wastes from inside the pulp. However, attempts have been made to isolate dentinal fluid, which is a pulpal IF that moves across the dentinal tubules, in order to measure COP and protein concentration [69-71]. In order to collect dentinal fluid, it is mandatory to drill a deep cavity in the dentin and the consequent removal of the smear layer. These are rather invasive procedures that may affect the pulpal blood flow and subsequently the rate and direction of dentinal fluid flow [72,73]. The radius of the exposed tubules [74], and the disruption of the odontoblast layer as a result of the preparation trauma [75], may yet influence the dentinal fluid composition regarding plasma proteins. It is therefore evident that there is a need for a less invasive and traumatic method for the due isolation of pulpal IF in order to explore its microenvironment.

Conclusions

Inflammation is a complex process and a necessary defense strategy in search of the reestablishment of health. Its classification, cell types involved, cytokines and chemokines and other substances give us a hint of its nature and importance, although much more is to be discovered, mostly as for what concerns the oral cavity.

References


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