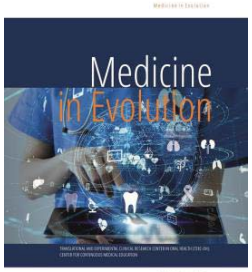
Inflammation and its relationship to oral cavity



Cosoroaba R.M.[1], Todor L.[2], Olariu I.[3], Gaje P.N.[4], Ceausu R.A.[4], Popovici R.A.[1], Matichescu A.M.[1]

[1]Department 1, Faculty of Dental Medicine, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania
[2]Department of Dental Medicine, Faculty of Medicine and Pharmacy, University of Oradea, Romania
[3]Department of General Medicine, Faculty of Medicine "Vasile Goldis" Western University of Arad
[4]Department of Microscopic Morphology/Histology, Angiogenesis Research Center Timisoara, Victor Babes University of Medicine and Pharmacy, Timisoara, Romania

Correspondence to:
Name: Iustin Olariu
Address: No 96 Liviu Rebreanu Street, Arad, Romania
Phone: +40 723423263
E-mail address: iustin_olariu@yahoo.com

Abstract

The inflammation process was described in science and literature a long time ago, but the understanding of the process took a long time. Inflammation is a complex reaction to harmful agents and includes vascular responses, migration and activation of leukocytes. Inflammation begins with an acute reaction, which evolves into a chronic phase if left to persist. Acute inflammation is a rapid process characterized by fluid exudation and leukocyte migration and primarily neutrophils. Chronic inflammation, on the other hand, extends over a longer period of time and is associated with the infiltration of lymphocytes and macrophages, the proliferation of blood vessels and fibrosis. Inflammation ceases when the invader is eliminated and secret mediators are removed. However, many factors change the course and morphological appearance, as well as the pattern of termination and duration of inflammation. Chronic inflammatory diseases are now seen as problems that could have an impact on the periodontium. The reciprocal effects of periodontal diseases are potential factors that change the severity of the progression of systemic inflammatory diseases.

This review aims to review studies in the literature on the processes, interactions, classification and morphological, and clinical characteristics of inflammation, relating it to the oral cavity and describing the main cell types and chemical mediators used for its occurrence. As a research source we used the PubMed database.

Keywords: Innate immune system, macrophage, mast, cells, oral disease, inflammation

INTRODUCTION

The oldest known description of the inflammation comes from the Edwin Smith papyrus, one of the Egyptian papyri that was found in a tomb near Thebes. Papyrus dates approximately from 1550 BC. This document is undoubtedly a copy of the ancient tests of the archaic period of Egyptian history (3200-2780 BC.). Documents from Egyptian civilizations and other early civilizations leave no doubt that the features of inflammation were recognized from those periods, but the understanding of the process took a long time.

Inflammation is didactically characterized by the following quintet: redness (rubor), heat (calor), swelling (tumor), pain (dolor) and dysfunction of the organs involved (functionio laesa). The first four characteristics were described by Celsus almost 2000 years ago. Functio laesa was added to the definition of inflammation by Rudolf Virchow in 1858, considered the predecessor of modern pathology and social medicine. The latter was the one who, in the field of inflammation, critically analyzed the significance of the four key symptoms and postulated that inflammation could not be represented as a single process, but rather as consisting of various inflammatory processes.

Inflammation is a protective, inherent response that is evolutionarily preserved in all multicellular organisms. As a crucial function of the innate immune system, it cleanses infectious agents and degenerate cells and repairs damaged tissue [1]. Acute inflammation is an auto-limitative, transient response that facilitates tissue repair and is beneficial for the body. However, chronic inflammation could lead to the development of various pathologies, including degenerative diseases associated with aging, fibrosis and cancer [2,3]. Inflammation involves the activation and chemotactic migration of leukocytes (neutrophils, monocytes and eosinophils) and mast cells to the site of the lesion. These cells secrete growth factors, cytokines and other inflammatory mediators, ie histamine, heparin, metalloproteases and serum proteases, which profoundly affect endothelial and mesenchymal cells, stimulating proliferation, differentiation and migration.

In acute inflammation, platelet aggregation and activation occurs immediately after tissue damage and helps to accelerate coagulation by forming a thrombus followed by a fibrin matrix to prevent bleeding and infection with microorganisms pathogenic. Fibrin clot also acts as a reservoir of growth factors released by platelets, such as platelet-derived growth factor (PDGF) and transformer-β growth factor (TGF-β), which are essential to attract neutrophils, monocytes, fibroblasts and myofibroblasts. These cells, together with the formation of a new extracellular matrix and the induction of angiogenesis, facilitate the appearance of granulation tissue. In tissues, monocytes are differentiated into macrophages and, once activated, macrophages are the main source of growth factors and cytokines that modulate tissue repair. The final phase of healing consists of re-epithelizing the wound by proliferating and migrating epithelial cells to its edge, a process that requires the dissolution of the fibrin clot and the degradation of the underlying collagen by serum proteases and metalloproteases. Persistence of causal factors or failure to resolve the inflammatory response could lead to chronic inflammation and a large number of clinical and experimental studies have linked inflammation and cancer. In fact, many malignancies occur in places of persistent infection and inflammation [4].

The oral cavity is one of the most complex ecological microenvironments in the human body, where the interactions between the host and the microbes define health and disease. The teeth are the only functional hard tissues that extend from the inside to the outside of the human body, crossing a series of other hard tissues (meaning bones) and soft (meaning connective tissue and epithelium), surrounded by a tight biofilm consisting of the richest collection of bacteria outside the colon. Such an architecture creates several areas, which

operate in concert during inflammatory responses in the oral cavity. The regulation of immuno-inflammatory mechanisms in oral diseases is partly governed by the patient's susceptibility and environmental factors [5].

Aim and objectives

This article presents a review of studies in the literature that report the processes, interactions, classification and morphological and clinical characteristics of inflammation, relating it to the oral cavity and describing the main cell types and chemical mediators used for its occurrence.

Vascular and cellular component of inflammation

A definition of inflammation is complicated because local vascular and tissue reactions are often accompanied by systemic effects. These effects include fever, leukocytosis, malaise, metabolic disorders and shock. The inflammatory response consists of a vascular and a cellular component.

The vascular component of the inflammatory response is characterized by vasodilation and, consequently, increased blood flow and vascular permeability. Increased blood flow causes, clinically, redness and heat in the inflamed tissue, and increased vascular permeability results in plasma loss and the formation of inflammatory exudate. Exudate contains many proteins (fibrin, immunoglobulin) and is responsible for edema. They can compress nerve endings and thus cause pain.

The cellular component involves the migration of leukocytes from the blood vessels to the inflamed tissue. They are extravasated from capillaries and reach the inflamed tissue where they phagocytic bacteria and cellular debris. Neutrophil influx is one of the first stages of the inflammatory response. These cells generate a fast and nonspecific phagocytic response. Later, macrophages and lymphocytes (specific subsets of T and B lymphocyte) appear at the site of inflammation.

Lymphocytes are the primary cells of the immune system and have developed one of the most sophisticated defense mechanisms in the biological system. T lymphocytes play a major role in organizing the immune response, eliminating intracellular pathogens (viruses and bacteria) by generating cytotoxic T lymphocytes. B lymphocytes protect the body against extracellular pathogens by producing antibodies. Natural killer cells (NK) are an important component of innate immunity. Dendritic B cells begin the immune response by presenting T lymphocyte antigens. The interaction between T lymphocytes, B lymphocytes, dendritic cells and natural killer cells (NK) is the fundamental defense mechanism of the host [6].

The mechanism against pathogens requires different responses depending on the characteristic of the pathogen and the attacked tissue. Chaplin's study and collaborators claim that the host body has developed innate and adaptive immune defense mechanisms. The first mechanism is non-specific, attacking any structure or antigen non-self, and the second mechanism is extremely specific [7]. Both types of immune response work together to eliminate pathogenic antigens.

The sequelae of acute inflammation depend on the type of tissue involved and the size of the destroyed area, which in turn depend on the nature of the harmful agent. Possible results of acute inflammation are either healing or evolution towards chronic inflammation. Chronic inflammation is characterized by the predominant presence of macrophages in the injured area. These cells provide a strong defensive mechanism in the body, and the mediators they release are harmful to both the body's tissues and invading agents. This is why chronic inflammation is almost always accompanied by tissue destruction [8]. In addition to macrophages, inflamed tissue is infiltrated with lymphocytes and plasmocytic. In

addition, in chronic inflammation there is a proliferation of fibroblasts that form collagen fibers.

The role of cytokines in inflammation

The cytokine family includes interleukins (IL), chemokines (CKs), interferon (IFN), growth factors (GF), tumor necrosis factor (TNF) and colony stimulating factor (CSF colonization stimulating factor) [7].

Interleukins (IL1 - IL32) are different from each other, have different functions and are secreted by different cells. Chemokines are very important in controlling the migration of cells between and inside tissues. Interferon has several subunits: IFNα (leukocyte IFN, a viral replication inhibitor), IFNβ (IFN fibroblast, a viral replication inhibitor) and IFNγ (lymphocyte secret, with immune control functions). Growth factors (TGF, IGF and many others) were initially identified due to functions that are not related to the immune system but can have effects on immune cells.

Tumor necrosis factor includes TNFα (more frequently secreted by monocytes) and TNFβ (secreted by T cells). Colony stimulating factor (G-CSF, M-CSF, GM-CSF and others) is able to differentiate bone marrow cells into different types of specific cells, such as monocytes, macrophages and neutrophils. Interleukin-8 (IL-8) was the first cytokine identified as having chemotactic activity. It has been shown to be a selective chemo-attractor for neutrophils [9].

The study by Essayan et al, (1998) showed the role of the family of IL-1 cytokines, which are a group of proteins that possess synergistic and contrasting biological responses. According to their study, IL-1 and its precursor forms are strongly involved in determining the inflammation and defense of the host [10].

The production of cytokines at the site of inflammation in the oral tissues is part of the host's response, which is essentially protective in nature. Unrestricted production of cytokines can lead to the destruction of oral tissues. It is traditionally believed that immune functions are regulated by signals from the immune system. It is now obvious that the immune system is partially regulated by the central nervous system, acting mainly through the hypothalamic-pituitary-suprarenal axis and through the sympathetic nervous system [11,12]. The pathways between the immune system and the brain seem to be two-way, and the goal is to maintain homeostasis. The sympathetic nervous system provides a major integrative and regulatory path for this communication. Sympathetic lymphoid tissue innervation, the presence of adrenergic receptors on immune cells (B and T lymphocytes, macrophages) and studies of catecholamine interactions with the immune system [13], provides substantial evidence for the role of the sympathetic nervous system in immune regulation. In addition, the cellular products of an activated immune system, namely cytokines, can send signals to the brain. Cytokines, such as IL-6 and TNF-α, appear to be involved in the dialogue between the brain and the immune system through the secretion of corticotropin-releasing hormone (CRH) and therefore, activates both the hypothalamic-pituitary-suprarenal axis, but also the sympathetic nervous system [14,15].

Inflammation in the oral cavity

The oral cavity is an open cavity, which is thus exposed to various potential microbial agents. In addition to these factors, some treatments applied to the teeth may favor the deposition of the dental plaque associated with additional resistance applied to the teeth, such as orthodontics. Moreover, inflammation in orthodontics also comes from the forces applied to the teeth.

Pulpitis and periodontitis, the most common infections in dentistry, are common in daily practice in surgery offices. Periodontitis shares many pathological features with other inflammatory diseases with concomitant bone resorption, such as rheumatoid arthritis, with evidence that both conditions are manifested as a result of an imbalance between proinflammatory and anti-inflammatory cytokines [16]. In both forms of inflammation, the pathological consequences are associated with the accumulation of bacteria leading to a host response that generates the infiltration of inflammatory cells [17]. Because the soft and hard tissues of the oral cavity are part of the same functional and physiological organ, the separation of the host's response to several components is artificial and does not recognize the dynamic relationship between cells, bacteria and extracellular structures. Also, although practical and instructive, the assumption of a linear change in lesions from acute to chronic is unclear. Recent discoveries that define resolution pathways in inflammatory processes challenge the concepts of compartmentalization and linearity in acute and chronic responses [18,19].

Once oral inflammation, such as pulpitis, gingivitis or periodontitis, an inflammatory infiltrate of various cell types, such as neutrophils, lymphocytes, macrophages, is formed, mast cells that will produce different subtypes of cytokines responsible for the immunopathology of diseases.

The role of leukocytes in inflammation of the oral cavity

To mediate an effective response, leukocytes must find their way to places of infection or inflammation. Leukocyte invasion of tissues can be induced by the chemotactic activity of several substances, such as interleukin-1 (IL-1), tumor necrosis factor (TNF-α) and bacterial lipopolysaccharide (LPS), which causes leukocyte migration when injected in vivo. All such compounds induce the production of chemo-attractors, which in turn cause leukocyte migration. Therefore, chemotactic activity includes receptor-mediated gradient perception and should be measured by a chemo-attractor's ability to induce targeted leukocyte migration in vitro [20].

Th lymphocytes are divided into two subclasses: Th1 and Th2. Th1 cells secrete mainly IFN-γ and IL-2 that increase cellular immunity. Th2 cells secrete a different set of cytokines, mainly IL-4, IL-10, IL-13 and IL-9, which increase the humoral immunity [21]. CD4 cells + can be differentiated in either Th1 or Th2, and the differentiation is strongly dependent on cytokines produced by cells of the innate immune system. IL-12 produced by activated monocytes / macrophages is a major inducer of Th1 differentiation and therefore of cellular immunity. IL-12 together with TNF-α and IFN-γ act synergistically in inflammation and further promote Th1 responses and are therefore considered major proinflammatory cytokines [22]. 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 proinflammatory cytokines. IL-4 and IL-10 are major anti-inflammatory cytokines and an increasing number of evidence suggest that catecholamines selectively inhibit Th1 functions and proinflammatory cytokines and promote Th2 responses and anti-inflammatory cytokines [23].

The role of macrophages in inflammation of the oral cavity

Macrophages are essential for coordinated resolution of oral inflammation and return to tissue homeostasis. In the first stage of the oral inflammatory process directed against microorganisms, bacteria and their virulence factors trigger the receptor-mediated production of cytokines by epithelial cells with the simultaneous release of neuropeptides, which causes

vasodilation of local blood vessels. The generation of chemo-attractant proteins (chemokine) at this stage results in the attraction of the first line of defense, neutrophils, which leave the vessels and migrate to the site of the microbial invasion. This step is critical and plays a key role in generating an effective defense system. Neutrophils are followed by macrophages. This is usually the stage where clinical signs of oral inflammation are detectable, including bleeding, swelling and redness of the gums. Inflection can be either limited and eliminated by neutrophil and macrophage function at this early stage, or it can be extended to include other cells and structures. Being myeloid cells of hematopoietic origin, the overall role of macrophages is to limit the pathological changes of soft tissues or to raise the inflammatory response to the next level. Major macrophage functions include the elimination of invasive bacteria, the recruitment of other cells at the site of infection, the elimination of excess neutrophils, the production of cytokines and chemokines, and the activation of the lymphocyte-mediated adaptive immune response. The net result of these functions can be either complete healing, limiting the resulting fibrosis infection and healing with the formation of scar tissue, or failure to eliminate infection by establishing a chronic inflammatory lesion. If the oral inflammatory process is prolonged and chronic, the destruction of soft and hard tissues, including alveolar bone, is observed due to direct destruction of inflammatory-mediated tissues [24].

Macrophages along with neutrophils are responsible for the phagocytosis and digestion of microorganisms and foreign substances through surface receptors that recognize and bind certain surface molecules of bacteria, such as lipopolysaccharides. These receptors are the key components to distinguish between host and invader and are defined as recognition receptors, called TLR receptors, which mediate the elimination of pathogens by phagocytosis. TLR receptors regulate apoptosis, inflammation, and immune responses. Evidence is accumulated that supports a role of TLR-mediated macrophages in the resolution of oral inflammation [25].

It now becomes obvious that the cells of the innate immune system are the determining factors of tissue and organ destiny and are more than transient, and their role is not limited to the phagocytosing of microbes. Neutrophils and macrophages are the key cells of the host's response where their role exceeds „defense" and are involved in tissue homeostasis, where protection, healing-repair and regeneration are encoded.

The role of mast cells in inflammation of the oral cavity

Numerous studies have investigated the participation of mast cells in inflammation and other pathologies. Such studies have been useful, for example, in documenting changes in the number of mast cells in different anatomical areas that also have a specific pathology.

Once activated, the mast cells secret many vasoactive and proinflammatory mediators [26-29]. These include preformed molecules such as histamine, serotonin, TNF, kinins and proteases stored in secretory granules. Leukotrienes (LT), prostaglandins and PAF (activated flat facto) are synthesized during the activation of mast cells from arachidonic acid released by the action of phospholipases. In addition, a number of cytokines (for example, IL-1, 2, 5, 6, 8, 9, 13 and TNF) and vascular endothelial growth factor (VEGF) are synthesized de novo and released a few hours after stimulation [30].

Mature mast cells vary considerably in their cytokine content (Bradding, 1995) and proteolytic enzymes. Mastocytes in the presence of SCF produce predominantly proinflammatory cytokines, while in the presence of SCF and IL-4, they mainly produce Th2 cytokines [31].

More and more evidence indicate that mast cells are critical to the pathogenesis of inflammatory diseases. Genetical analysis of IgE-activated human mast cells showed

overexpression of many genes, mainly related to inflammation [32]. Prostheses released from mast cells could act on plasma albumin to generate histamine-releasing peptides [33] which would further propagate mast cell activation and inflammation. Proteases could also stimulate protease-activated receptors (PAR) inducing widespread inflammation [34,35]. However, unlike allergic reactions, mast cells are rarely seen as degranulating during inflammatory processes. The only way to explain the involvement of mast cells in non-allergic processes would be through the „ differential" or „selective" secretion of non-granular mediators [36,37].

Mastocytes are present in oral tissues and appear to be involved in the initiation of a number of inflammatory conditions in the oral cavity. In inflammatory processes in the oral sphere, cytokines activate and stimulate mast cells to secrete proinflammatory molecules. These molecules play a crucial role in inducing inflammation [38]. Mastocytes are responsible for releasing elevated levels of proinflammatory cytokines, such as IL-1, IL-6 or TNF. In acute oral inflammation, mast cells release proinflammatory cytokines, such as histamine, proteoglycans, metabolites of arachidonic acid, TNF and tri-phase that promote the inflammatory process.

After activation, MC induces T lymphocyte migration, either directly by releasing chemokines (lymphactin, IL-16 and MIP-1), or indirectly by inducing the expression of the adhesion molecule on endothelial cells [39]. Histamine increases vascular permeability through structural changes that include endothelial contraction and the formation of intercellular spaces. In addition, histamine promotes leukocyte adhesion to endothelial by transient mobilization of the selectin P-adhesion molecule to the surface of endothelial cells. This functional relationship between mast cells and T lymphocytes has proven to be two-way, fulfilling mutual regulatory and / or modulatory roles, including influences on cellular processes such as growth, proliferation, antigen activation and presentation. In addition, mediators derived from T lymphocytes, such as β-chemokines, directly induce mast cell degranulation. These findings led to the proposal of a functional relationship between these two cell populations that could facilitate the emergence of an immune response that contributes to the onset of pathogenesis of periapical inflammatory lesions [40].

Studies in the literature show an increase in the number of mast cells in the inflamed place compared to healthy places and have suggested important dynamic changes in the migration and location of mast cells in the evolution of periodontal disease. The significance of mast cell distribution in tissue compartments refers to their influence on nearby cells, with stimulating, inhibitory or toxic effects. The participation of mast cells in the defense mechanism and destructive events both as effect cells and receptive to chronic inflammation, as well as possible functional populations in periodontal lesions are still debatable. Thus, it was concluded that periodontitis is not unidirectional, but rather interactive. Mastocytes that produce destructive proinflammatory cytokines can also produce mediators that activate the healing process [41].

Future prospects

Oral inflammatory processes involve microbial etiological factors, induce a number of host responses that mediate an inflammatory cascade of events in an attempt to protect and / or heal tissues. It is becoming increasingly clear that the macrophage phenotype is very important for the evolution of the lesion for resolution or chronicity. Because the response of the macrophage is essential for health and disease, it is important to achieve a more complete understanding of the molecular events in this complex system.

Mastocytes play a critical role in the development of inflammation in the oral cavity, both in the early stages and during the transition from acute to chronic inflammation.

Mastocytes in these inflammatory lesions are associated with increased vascular permeability, angiogenic response, collagen synthesis, inflammation regulation, bone resorption and destruction of the extracellular matrix. Based on the concept that mast cells play an important role in chronic inflammation, it is possible to use drugs therapeutically to influence the release of cytokines by mast cells and therefore, to counteract the inflammation. In the future, it may be possible to develop new approaches that influence the release of proinflammatory or neuropeptide molecules to relieve inflammation caused by mast cells. Because mast cells play a key role in inflammation, therapies aimed at mast cell function may have value in managing oral inflammation.

The classification of inflammation, cell types, cytokines and chemokines involved gives us an indication of its nature and importance, although much remains to be discovered, especially in terms of the oral cavity.

REFERENCES

1. Karin M, Clevers H. Reparative inflammation takes charge of tissue regeneration. Nature. 2016;529:307–315.
2. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860–867
3. Zinger A, Cho WC, Ben-Yehuda A. Cancer and Aging—The Inflammatory Connection. Aging Dis. 2017;8:611–627.
4. Mueller MM. Inflammation in epithelial skin tumours: Old stories and new ideas. Eur. J. Cancer. 2006;42:735–744.
5. Uitto VJ, Overall CM, McCulloch C. Proteolytic host cell enzymes in gingival crevice fluid. Periodontol. 2003;31:77–104.
6. Alam R, Gorska M. Lymphocytes. Allergy and Clinic. Immunol. 2003;111(2 Suppl):S476-85.
7. Chaplin DD. Overview of the immunologic response. J Allergy Clin Immunol. 2010;125: S3-23.
8. Trowbridge HO, Emling RC. Inflammation. A Review of the Process (5th ed). Quintessence Publishing. 1997;200
9. Yoshimura T, Matsushima K, Tanaka S, Robinson EA, Appella E, et al. Purification of a human monocyte-derived neutrophil chemotactic factor that has peptide sequence similarity to other host defense cytokines. Proc Natl Acad Sci USA. 1987;84:9233-9237.
10. Silva LB, Guimaraes CS, Santos RA. Immunology of root resorption: a literature review. Indian J Dent Res. 2008;19(4):340-343.
11. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve-an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 2000;52:595-638.
12. Haddad JJ, Saadé NE, Safieh-Garabedian B. Cytokines and neuroimmune-endocrine interactions: a role for the hypoth ALAMic-pituitaryadrenal revolving axis. J Neuroimmunol. 2002;133:1-19.
13. Madden KS, Sanders VM, Felten DL. Catecholamine influences and sympathetic neural modulation of immune responsiveness. Annu Rev Pharmacol Toxicol. 1995;35:417-448.
14. Del Rey A, Besedovsky H, Sorkin E, Dinarello CA. Interleukin-1 and glucocorticoid hormones integrate an immunoregulatory feedback circuit. Ann N Y Acad Sci. 1987;496:85-90.
15. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immunemediated inflammation. N Engl J Med. 1955;332:1351-1362.
16. Silva L. A Literature Review of Inflammation and Its Relationship with the Oral Cavity. Glob J Infect Dis Clin Res. 2016;2(1):001-007.
17. Socransky SS, Haffajee AD. Periodontal microbial ecology. Periodontol 2000. 2005;38:135-187.
18. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat. Rev. Immunol. 2008;8:349–361.
19. Pruss H, Kopp MA, Brommer B, Gatzemeier N, Laginha I, Dirnagl U, Schwab JM. Nonresolving aspects of acute inflammation after spinal cord injury (SCI): indices and resolution plateau. Brain Pathol. 2011;21:652–660.

20. Silva TA, Garlet GP, Fukada SY, Silva JS, Cunha FQ. Chemokines in Oral Inflammatory Diseases: Apical Periodontitis and Periodontal Disease. JDR 2007;86:306-319.
21. Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. Nature. 1996;383:787-793.
22. Fearon DT, Locksley RM. The instructive role of innate immunity in the acquired immune response. Science. 1996;272:50-53.
23. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve-- an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 2000;52:595-638.
24. Li Q, Yu H, Zinna R, et al. Silencing mitogen-activated protein kinase-activated protein kinase-2 arrests inflammatory bone loss. J Pharmacol Exp Ther. 2011;336(3):633-642.
25. Hasturk H, Kantarci A, Van Dyke TE. Oral Inflammatory Diseases and Systemic Inflammation: Role of the Macrophage. Front Immunol. 2012;3:118.
26. Galli SJ. New concepts about the mast cell. N Engl J Med. 1993;328(4):257-265.
27. Holgate ST. The role of mast cells and basophils in inflammation. Clin Exp Allergy. 2000;30 Suppl 1:28-32.
28. Galli SJ, Kalesnikoff J, Grimbaldeston MA, Piliponsky AM, Williams CM, Tsai M. Mast cells as "tunable" effector and immunoregulatory cells: recent advances. Annu Rev Immunol. 2005;23:749-786.
29. Bradding P, Okayama Y, Howarth PH, Church MK, Holgate ST. Heterogeneity of human mast cells based on cytokine content. J Immunol. 1995;155(1):297-307.
30. Grützkau A, Krüger-Krasagakes S, Baumeister H, et al. Synthesis, storage, and release of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) by human mast cells: implications for the biological significance of VEGF206. Mol Biol Cell. 1998;9(4):875-884.
31. Bischoff SC, Sellge G, Manns MP, Lorentz A. Interleukin-4 induces a switch of human intestinal mast cells from proinflammatory cells to Th2-type cells. Int Arch Allergy Immunol. 2001;124(1-3):151-154.
32. Jayapal M, Tay HK, Reghunathan R, et al. Genome-wide gene expression profiling of human mast cells stimulated by IgE or FcepsilonRI-aggregation reveals a complex network of genes involved in inflammatory responses. BMC Genomics. 2006;7:210.
33. Carraway RE, Cochrane DE, Boucher W, Mitra SP. Structures of histamine-releasing peptides formed by the action of acid proteases on mammalian albumin(s). J Immunol. 1989;143(5):1680-1684.
34. Schmidlin F, Bunnett NW. Protease-activated receptors: how proteases signal to cells. Curr Opin Pharmacol. 2001;1(6):575-582.
35. Molino M, Barnathan ES, Numerof R, et al. Interactions of mast cell tryptase with thrombin receptors and PAR-2. J Biol Chem. 1997;272(7):4043-4049.
36. Theoharides TC, Kempuraj D, Tagen M, Conti P, Kalogeromitros D. Differential release of mast cell mediators and the pathogenesis of inflammation [published correction appears in Immunol Rev. 2007 Oct;219:204]. Immunol Rev. 2007;217:65-78.
37. Theoharides TC, Alysandratos KD, Angelidou A, et al. Mast cells and inflammation. Biochim Biophys Acta. 2012;1822(1):21-33.
38. Fattahi S, Sadighi M, Faramarzi M, Karimifard E, Mirzaie A. Comparison of mast cell counts between the patients with moderate and severe periodontitis. J Adv Periodontol Implant Dent. 2019;11(1):34-38.
39. de Oliveira Rodini C, Batista AC, Lara VS. Comparative immunohistochemical study of the presence of mast cells in apical granulomas and periapical cysts: possible role of mast cells in the course of human periapical lesions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;97(1):59-63.
40. Sheethal HS, Kn H, Smitha T, Chauhan K. Role of mast cells in inflammatory and reactive pathologies of pulp, periapical area and periodontium. J Oral Maxillofac Pathol. 2018;22(1):92-97.
41. Kak MM, Bharali J, Rastogi P, Chaubey KK. Role of mast cells in periodontal health and disease: A comparative study. International Journal of Applied Dental Sciences. 2021;7(4):113-116.