

Mechanisms and substances involved in inflammation in the oral cavity – Literature review

Mecanismos e substâncias envolvidas na inflamação na cavidade oral – Revisão da literatura

Mecanismos y sustancias involucradas en la inflamación de la cavidad oral – Revisión de la literatura

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Pedro Guimarães Sampaio Trajano Dos Santos

ORCID: <https://orcid.org/0009-0001-5720-603X>

Faculdade de Odontologia do Recife, Brazil

E-mail: pedroguimaraessampaio@gmail.com

Luciano Barreto Silva

ORCID: <https://orcid.org/0000-0002-1508-4812>

Faculdade de Odontologia do Recife, Brazil

E-mail: lucianobarreto63@gmail.com

Paula Andréa de Melo Valença

ORCID: <https://orcid.org/0000-0002-1433-5632>

Faculdade de Odontologia do Recife, Brazil

E-mail: valensa@gmail.com

Rodolfo Scavuzzi Carneiro Cunha

ORCID: <https://orcid.org/0000-0001-7110-848X>

Faculdade de Odontologia do Recife, Brazil

E-mail: scavuzzi@gmail.com

Ailton Coelho de Ataíde Filho

ORCID: <https://orcid.org/0000-0002-8105-4259>

Faculdade de Odontologia do Recife, Brazil

E-mail: ailtonataide@hotmail.com

Fabiana Moura da Motta Silveira

ORCID: <https://orcid.org/0000-0001-8905-2373>

Faculdade de Odontologia do Recife, Brazil

E-mail: fabianamottamsn@hotmail.com

Caíque Silveira Martins da Fonseca

ORCID: <https://orcid.org/0000-0002-6812-3811>

Faculdade de Odontologia do Recife, Brazil

E-mail: caiquesmfonseca@gmail.com

Abstract

Objective: The aim of the paper is to research through literature review the features of inflammation in the oral cavity and the cellular and humoral mediators involved in its development towards healing. **Methodology:** The searches were carried out using descriptors in PubMed Central, VHL/BIREME, Web of Science, SciELO, The Cochrane Library and Google Scholar. Furthermore, considering that this article is a narrative literature review, the vision of Rother (2007) was used to structure this work. **Results:** Our search resulted in 36 articles. **Conclusion:** The immune response in relation to the oral cavity can be considered an integrated process that involves a complex network of substances and signaling pathways to activate different cell types. The interaction between APCs, lymphocytes, NK cells and DCs, together with the regulatory effects of cytokines and chemokines, directs the final outcome of inflammatory responses in the hard and soft tissues of the oral cavity.

Keywords: Inflammation; Tooth resorption; Root resorption; Cytokine-induced killer cells.

Resumo

Objetivo: O objetivo do artigo é pesquisar por meio de revisão de literatura as características da inflamação na cavidade oral e os mediadores celulares e humorais envolvidos no seu desenvolvimento rumo à cura. **Metodologia:** As buscas foram realizadas utilizando descritores no PubMed Central, BVS/BIREME, Web of Science, SciELO, The Cochrane Library e Google Scholar. Além disso, considerando que este artigo é uma revisão narrativa da literatura, utilizou-se a visão de Rother (2007) para estruturar este trabalho. **Resultados:** Nossa busca resultou em 36 artigos. **Conclusão:** A resposta imune em relação à cavidade oral pode ser considerada um processo integrado que envolve uma complexa rede de substâncias e vias de sinalização para ativar diferentes tipos celulares. A interação entre APCs, linfócitos, células

NK e DCs, juntamente com os efeitos regulatórios de citocinas e quimiocinas, direciona o resultado final das respostas inflamatórias nos tecidos duros e moles da cavidade oral.

Palavras-chave: Inflamação; Reabsorção dentária; Reabsorção radicular; Células assassinas induzidas por citocinas.

Resumen

Objetivo: El objetivo del artículo es investigar a través de la revisión bibliográfica las características de la inflamación en la cavidad bucal y los mediadores celulares y humorales involucrados en su desarrollo hacia la curación. **Metodología:** Las búsquedas se realizaron mediante descriptores en PubMed Central, BVS/BIREME, Web of Science, SciELO, The Cochrane Library y Google Scholar. Además, considerando que este artículo es una revisión narrativa de la literatura, se utilizó la visión de Rother (2007) para estructurar este trabajo. **Resultados:** Nuestra búsqueda resultó en 36 artículos. **Conclusión:** La respuesta inmune en relación con la cavidad bucal puede considerarse un proceso integrado que involucra una red compleja de sustancias y vías de señalización para activar diferentes tipos de células. La interacción entre APC, linfocitos, células NK y DC, junto con los efectos reguladores de citocinas y quimiocinas, dirige el resultado final de las respuestas inflamatorias en los tejidos duros y blandos de la cavidad bucal.

Palabras clave: Inflamación; Reabsorción dental; Reabsorción radicular; Células asesinas inducidas por citocinas.

1. Introduction

Extensive literature has explored root resorptions and their association with osteoclasts, the principal cellular entities responsible for the resorptive processes that lead to the degradation of dental roots. It was not until a decade ago that the immunological dimensions and mechanisms underlying this pathology were initially elucidated, heralding a new epoch in research (Santos, 2007). Similarly, other oral infections are also deeply linked to immunological interaction, affecting the whole oral cavity.

Inflammation represents the initial response of living tissues to aggression, and is a fundamental component for the first lineage of immunity: the innate one. This complex physiological process is triggered by a number of stimuli, including microbiological infections, and diverse situations such as trauma and radiation, chemical substances like irritants and corrosives. Necrosis in different tissues and allergic reactions are also included. Historically, inflammation has been associated with specific and well known signs such as: redness, heat affecting the area involved, swelling and pain, and some authors have also included the dysfunction of the affected organ.

The classical description of inflammation, encompassing redness, heat, swelling, and pain, was articulated by Aulus Cornelius Celsus approximately 2000 years ago. Scientific literature has provided evidence regarding the role of the immune system in the initiation and progression of all kinds of inflammatory conditions in the oral cavity, including root resorptions, irrespective of their categorisation (Alam & Gorska, 2003). Regardless of their origin, chemotactic factors must be generated to signal the immune system that a specific region of the organism is undergoing injury. This communication is mediated by peptides known as cytokines, particularly interleukins (ILs), and more recently, evidence has emerged regarding the role of prostaglandins (PGs) in this process. The aim of the paper is to research through literature review the features of inflammation in the oral cavity and the cellular and humoral mediators involved in its development towards healing.

2. Methodology

For the accomplishment of this work, online searches were carried out by searching the database available from BVS/BIREME and PUBMED Central. Other portals such as Web of Science, Science Direct, Periodic Portal from CAPES, The Cochrane Library and PROSPERO were also used. This article is a narrative review of the current literature, with the aid of a study by Rother (2007), where the author addresses how this type of work should be constructed, the structure it should compose and how the methodology should work.

3. Results

3.1 Modulating Substances Involved in Root Resorptions

Pathological root resorptions are invariably linked to some form of trauma inflicted upon the teeth, whether singularly or in groups. The extent of the damage—be it temporary or permanent—plays a crucial role in determining the onset and progression of various types of root resorptions. The inflammatory response of the organism, particularly the exudate resulting from subsequent vascular changes, is a primary, if not the most critical, factor in the initiation of root resorptions (Félix, 1976). The inflammatory exudate contains a high concentration of leukocytes, plasma and tissue proteins, as well as local traditional and stem cells. Frequently, it also includes the offending agent, especially if of biological origin, such as bacteria, at the injury site, alongside other substances often overlooked in the literature addressing dental resorption pathologies (Limeback, 1991).

Following trauma, especially mechanical injuries where the tooth is extracted from the alveolar bone and subsequently replanted, several factors may influence the outcome for both the affected tooth and the surrounding dentition (Pohl, 2005). Mechanical impacts, foreign bodies, microbial contamination, delays in dental intervention, and the conditions under which the tooth is transported to a dental practice all contribute to the extent of the damage and the prognosis of the case. When these factors converge at a single site, reciprocal interactions occur in an attempt to restore homeostasis (Shioi, 1994). Notably, this process is accompanied by an increase in cytokine production, including interleukin-1 α and β , interleukin-2, and interleukin-6, as well as tumor necrosis factor-alpha (TNF- α). Additionally, there is an elevation in Epidermal Growth Factor (EGF) and an indirect increase in lipopolysaccharides (LPS) or endotoxins, which induce intense cellular stress and the release of substantial amounts of local mediators (Arsenault, 1999).

3.2 Nitric Oxide (NO) as a Mediator in Inflammation

Nitric oxide (NO) is a key mediator in inflammatory processes and functions as a signaling molecule released in response to injury, playing a crucial role in modulating inflammation. Under normal physiological conditions, nitric oxide (NO) generally plays an anti-inflammatory role within tissues. Nevertheless, it may also function as a proinflammatory mediator due to its effect on molecules during cellular injury (Banick, 1997). NO also seems to influence the release of various inflammatory mediators from a wide range of cells involved in inflammatory responses, including leukocytes, macrophages, and platelets (Beckman, 1996). Furthermore, NO also seems to be involved in the regulation of blood flow, leukocyte adhesion to the vascular endothelium in order to promote diapedesis, and also in the modulation of the activity of many enzymes involved directly on the inflammatory response (Clancy, 1992).

Nitric oxide is released as a gas and is generated by cellular stress, which subsequently leads to the formation of arachidonic acid. This acid is essential for the synthesis of prostaglandins and leukotrienes. Besides modulating prostaglandin activity as a lipid second messenger capable of regulating signaling enzymes such as phospholipase C- δ (PLC- δ) and protein kinase C- α and - β (PKC- α and PKC- β), arachidonic acid also functions as a vasodilator, enhancing blood flow and thereby augmenting pro-inflammatory effects (Davies, 1997).

The process initiates trauma inflicted on the teeth, where NO release significantly exacerbates the cardinal signs of inflammation, thus acting as a pro-inflammatory mediator. As the injury persists, fibroblasts from the periodontal ligament (PDL) initiate the healing steps, while neurovascular components from the root canal often sustain permanent damage. The extent of pulp damage will depend on some factors including the width of the apical foramen. Additionally, healing is also influenced by the release of prostaglandins, as well as serum calcium availability.

3.3 Prostaglandins (PGs) and Systemic Calcium in Root Resorptions

Prostaglandins (PGs) are a group of physiologically active lipid compounds known as eicosanoids, which exert hormone-like effects in animals. They play a significant role in bone metabolism, with Prostaglandin E2 (PGE2) being particularly influential. PGE2 modulates bone metabolism by promoting morphological changes in osteoclasts and osteoblasts through the elevation of intracellular cyclic adenosine monophosphate (cAMP) levels (Shanfeld, 1986; Kalaizic, 2014). Notably, PGE2 also enhances the synthesis of messenger RNA (mRNA) and the protein secretion of the Receptor Activator of Nuclear factor kappa- β Ligand (RANKL), which is fundamental to bone remodeling (Mayahara, 2012). Despite this, elevated concentrations of PGE2, often administered through injections, have been associated with an increased incidence of root resorptions (Cağlaroğlu, 2012; Yamasaki, 1980). PGE2 functions as a local vasodilator and inhibits platelet aggregation, which facilitates greater blood influx to the affected area. One of its primary functions is to prevent unnecessary clot formation by being synthesized within blood vessel walls and regulating smooth muscle contraction (Kurzrock, 1930).

Initially, prostaglandins were thought to be released from cells via passive diffusion, given their high lipophilicity, which theoretically would allow them to traverse the cell membrane. However, the discovery of specific transporters, such as the prostaglandin transporter (PGT, SLCO2A1), which mediates their cellular uptake, has demonstrated that passive diffusion alone cannot account for their cellular entry. Recent research has also identified the multidrug resistance protein 4 (MRP4, ABCC4), a member of the ATP-binding cassette transporter family, as a key mediator of prostaglandin release. While it remains uncertain whether MRP4 is the sole transporter involved, its role appears crucial for the intracellular accumulation of prostaglandins (Moreno, 2017). The effects of prostaglandins on root resorptions, particularly following impact trauma, involve significant vasodilation (Rivera & Hancock, 2022; Teixeira et al., 2023).

3.4 Cytokines in Inflammatory Processes

Cytokines are undoubtedly the principal proteins involved in inflammatory processes in mammals. They play essential roles in nearly all aspects of inflammation regulated by the immune system, exerting direct effects on the recruitment, proliferation, and infiltration of cells into the inflamed tissue. Among the extensive cytokine family, interleukins have been particularly implicated in hard tissue resorptions. Since the initial reports in 1979 on inflammatory research, interleukins have been recognized as secreted polypeptides released by leukocytes to recruit other lymphoid cells to the site of tissue damage.

The immune system constitutes a highly intricate network comprising both specialized and non-specialised cells, with its principal objective being the facilitation of organismal survival in an environment where microorganisms seek to exploit their hosts. In essence, it is the system that underpins human existence, and as such, effective communication within this system is paramount.

The term "chemokines" comes from "chemoattractant cytokines," and reflects their fundamental role in inducing target chemotaxis in nearby responsive immune competent cells. The cytokine family is vast and can be exemplified as Chemokines (CKs), Interferons (IFNs), Interleukins (ILs), Tumor Necrosis Factors (TNFs), Colony-Stimulating Factors (CSFs), and Growth Factors (GFs), with ongoing research addressing numerous unresolved questions. Basically, cytokine's function involves lymphocytes and leukocytes communication.

Up to now there are 32 known types of interleukins (IL-1 up to IL-32), usually distinct from one another, with varied functions especially the fact of being secreted by diverse cellular sources. One example to illustrate their modulating feature is the relationship of Interferons, classified into IFN- α (leukocyte interferon, which inhibits viral replication) and TNF- α (fibroblast interferon, also inhibiting viral replication). Cytokines' modulation implies stimulating inflammation on one hand, and inhibiting it on the other. For so, immune competent cells utilize various substances to be unleashed right into the bloodstream in order to

signal cellular recruitment or the production of specific factors. For each situation, a particular group of them are activated or inhibited. Such communication takes place through direct cell-cell interactions, engagement with non-self-entities, as well as the release of soluble proteins. Such coordination also includes the synthesis of small cytokines, named chemokines (CKs), exerting their effects through interaction with corresponding receptors (CKRs), crucial for initiating cellular responses. CKRs play a pivotal role in determining the specific subpopulations of cells recruited at each stage of the immune response.

The interactions between the immune system and the brain appear to be bidirectional, with the overarching goal being the maintenance of homeostasis. The SNS serves as a crucial integrative and regulatory conduit for this communication. The presence of sympathetic innervation in lymphoid tissues, the expression of adrenergic receptors on immune cells (such as B and T lymphocytes and macrophages), and research into the interactions between catecholamines and the immune system (Madden, 1995) collectively underscore the role of the SNS in immune regulation.

3.5 Microbial Exposure and Inflammatory Responses in the Oral Cavity

The oral cavity is continually exposed to a variety of potential microbial agents, primarily due to its fundamental functions of nourishment and communication. Beyond these inherent factors, dental treatments, particularly those involving mechanical interventions such as orthodontics, can exacerbate microbial accumulation by facilitating dental plaque deposition. Additionally, orthodontic treatments induce inflammation through the forces applied to the teeth, which subsequently stimulate osteoclastic activity in the alveolar bone during the remodeling process associated with tooth movement. The regulation of osteoclast populations is mediated through mechanisms of cell recruitment and clearance (Noxon, 2001).

Periodontitis and pulpitis are prevalent infections encountered in clinical dental practice, and they frequently present with significant inflammatory responses. Periodontitis shares many pathological characteristics with other inflammatory diseases that involve concomitant bone resorption, such as rheumatoid arthritis (RA). There is accumulating evidence that both conditions arise from an imbalance between pro-inflammatory and anti-inflammatory cytokines (Bartold, 2005). The local overproduction of pro-inflammatory cytokines can either directly stimulate the proliferation and activity of osteoclast precursors or indirectly influence the production of critical osteoclast differentiation factors, such as the receptor activator of NF- κ B ligand (RANKL) and its soluble decoy receptor, osteoprotegerin, by osteoblasts or stromal cells (Boyce, 2005).

3.6 Susceptibility to Inflammation and Infections in the Oral Cavity

The continuous exposure to a diverse array of biological, physical, and chemical agents renders the oral cavity particularly susceptible to inflammation and infections, predominantly driven by bacterial influences. Under normal conditions, the primary tissues of the oral cavity are well-adapted to withstand various insults, including abrupt thermal changes. However, when there is a compromise in immune function or an increase in the virulence of a pathogenic agent—whether individually or synergistically—an inflammatory response may develop in various sites within the mouth. Anaerobic Gram-negative bacteria, which often inhabit such sites, possess lipopolysaccharides (LPS)—a bacterial pathogenic component—that is believed to play a significant role in the pathogenesis of dental diseases (Slots & Genko, 1984; Warfvinge, 1985; Larjava, 1987).

3.7 Inflammatory Conditions in the Oral Cavity: Pulpitis, Gingivitis, and Periodontitis

Pulpitis, gingivitis, and periodontitis are the principal inflammatory conditions observed within the oral cavity. Chronic marginal gingivitis is clinically characterized by gingival erythema, oedema, bleeding, alterations in contour, loss of tissue adaptation to the teeth, and an increase in the flow of gingival crevicular fluid (GCF) (Cimasoni, 1983; Greenstein, 1984). This condition is typically associated with dental plaque, which irritates the surrounding tissues through the release of microbial toxins.

The natural progression of gingivitis may be influenced by hormonal changes, such as those occurring during pregnancy, which are accompanied by elevated levels of progesterone and estrogen. By the third trimester, these hormone levels can be 10-30 times greater than those observed during the typical menstrual cycle. These hormonal fluctuations suggest that female steroid hormones may exert dual effects on the pathogenesis of pyogenic granuloma during pregnancy.

Histopathological studies have led to the classification of gingivitis into three distinct stages, which are delineated didactically to aid in understanding the disease process. **Stage One:** This initial stage commences approximately 2 to 4 days after the onset of injury. It is marked by a transient phase of vasoconstriction, followed by vasodilatation and an increased blood flow, which recruits neutrophils (PMNs). These cells adhere progressively to the endothelial walls in preparation for diapedesis. The initial vascular changes and collagen degradation are likely due to the chemotactic attraction of neutrophils to the infected area, mediated by bacterial vasodilatory products, as well as activation of host systems such as the complement and kinin systems, and arachidonic acid pathways (Attström, 1970). **Stage Two:** This stage represents the continuation of the acute inflammatory response. Capillary engorgement and proliferation occur due to blood congestion, increasing permeability and plasma influx. This is accompanied by diapedesis and the infiltration of both nonspecific immune cells and lymphocytes, marking the transition from acute to chronic inflammation. **Stage Three:** In this final stage, chronic gingivitis is established, characterized by diminished venous return, a change in tissue color from red to a bluish hue, and a significant increase in B lymphocytes. Granulation tissue formation becomes predominant over collagen bundle formation (Payne, 1975).

Conversely, in periodontitis, bone resorption is predominantly driven by the elevated local production of pro-inflammatory cytokines, including IL-1 α , IL-1 β , and TNF- α . The LPS released by periodontopathic bacteria stimulates the synthesis of IL-1 and TNF- α by macrophages. These cytokines, in turn, promote the production of additional inflammatory mediators (e.g., cytokines, nitric oxide, and prostaglandin E2), matrix-degrading enzymes (such as metalloproteinases), and reduce the synthesis of glycosaminoglycans, thereby exacerbating bone destruction (Meyer, 2003).

The degradation and removal of hard tissues are cellular processes mediated by giant multinucleated cells, known as osteoclasts, which are formed through the asynchronous fusion of mononuclear cells from the macrophage lineage, originating from the haematopoietic system (Silva, 2008). Osteoclasts, easily identifiable under a light microscope due to their large size (50 to 100 μ m), multinucleation (2 to 10 nuclei per cell), and association with bone surfaces in shallow depressions called Howship's lacunae, are regulated by cytokines that induce and stimulate their recruitment.

In the field of orthodontics, which concerns bone resorption and neof ormation, mechanical forces are applied to produce organized periodontal tissue remodeling and facilitate tooth movement. These forces, transmitted from the dental roots to the periodontium, stimulate cells to remodel the surrounding matrices. The application of such forces inevitably causes inflammation in the surrounding tissues of the tooth, resulting in bone resorption at pressure sites and bone deposition at tension sites (Reitan, 1954).

3.8 Antigen Presenting Cells and Immune Responses

Antigen presenting cells (APCs) are characterized by their high expression of class II major histocompatibility complex (MHC) molecules. These cells are adept at internalizing, processing, and presenting foreign antigens in conjunction with MHC class II molecules. Consequently, the immune response primarily involves four key cellular types: T cells, B cells, natural killer (NK) cells, and dendritic cells (DCs).

T cells are pivotal in the elimination of intracellular pathogens, such as viruses and bacteria, through the generation of cytotoxic T cells. **B cells** defend the organism against extracellular pathogens by producing antibodies. **NK cells**, which belong to the innate immune system and are characterized by their positive cytotoxic lymphocyte CD56 marker, play a crucial role in

pathogen recognition despite lacking surface receptors. **Dendritic cells** are essential for activating the immune response by presenting foreign antigens to T cells (MÜNZ, 2005).

T lymphocytes are subdivided into two main subclasses: Th1 and Th2 cells. Th1 cells primarily secrete interferon-gamma (IFN- γ) and interleukin-2 (IL-2), which enhance cellular immunity. Conversely, Th2 cells secrete a distinct set of cytokines, including IL-4, IL-10, IL-13, and IL-9, which bolster humoral immunity (ABBAS, 1996). Naïve CD4⁺ Th0 cells can differentiate into either Th1 or Th2 cells, with differentiation strongly influenced by the cytokines produced by innate immune system cells (FEARON, 1996). Interleukin-12 (IL-12), produced by activated monocytes and macrophages, is a major inducer of Th1 differentiation and thus cellular immunity. IL-12, together with tumour necrosis factor-alpha (TNF- α) and IFN- γ , acts synergistically in inflammation and promotes Th1 responses, marking these cytokines as major proinflammatory factors (Fearon & Locksley, 1996).

4. Discussion

The intricate mechanisms underlying the immune responses within the oral cavity, particularly in the context of pulpitis, gingivitis, and periodontitis, highlight the complex interplay between various immune cells, cytokines, and signaling pathways. The antigen-presenting cells (APCs), pivotal in initiating and modulating these immune responses, utilize class II major histocompatibility complex (MHC) molecules to present foreign antigens to T lymphocytes. This process is critical for orchestrating both the cellular and humoral aspects of the immune response.

In the context of oral diseases such as pulpitis, gingivitis, and periodontitis, the local production of pro-inflammatory cytokines is a fundamental aspect of the inflammatory response. Cytokines such as IL-1 α , IL-1 β , and TNF- α are integral in mediating tissue destruction and bone resorption. In periodontitis, the interaction between bacterial lipopolysaccharides (LPS) and macrophages triggers the synthesis of these cytokines, which in turn stimulates the production of additional inflammatory mediators, including nitric oxide (NO) and prostaglandin E2 (PGE2). These mediators, along with matrix-degrading enzymes, contribute to the degradation of bone and connective tissue, illustrating the detrimental effects of unchecked inflammatory responses.

The role of giant multinucleated osteoclasts in bone resorption, driven by cytokine-induced recruitment, further exemplifies the cellular mechanisms involved in tissue destruction. These osteoclasts, originating from mononuclear cells of the macrophage lineage, are essential for the removal of damaged bone tissue. Their activity is regulated by cytokines that promote their differentiation and function.

5. Conclusion

The immune response within the oral cavity is a multifaceted process involving a complex network of cells, cytokines, and signaling pathways. The interplay between APCs, T and B cells, NK cells, and DCs, alongside the regulatory effects of cytokines and chemokines, dictates the nature and outcome of inflammatory responses in dental tissues. Understanding these mechanisms is crucial for developing targeted therapeutic strategies to mitigate inflammation and promote tissue repair in oral diseases.

Therefore, it is necessary to carry out new studies that seek to understand more about the complex network of cells involved in the process, about the ways that cause this response and its forms of inflammation and tissue repair, together with case reports, which will show clinical results to provide a greater basis for studies of what happens in practice.

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