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REVIEW ARTICLE

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Innate and adaptive immunity of periodontal disease. From etiology to alveolar bone loss

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Abstract

Periodontal disease refers to inflammation of the tissues that support the tooth. It is of multifactorial etiology. Innate and adaptive immune cells participate jointly through the release of their molecules and mechanisms of action in order to maintain homeostasis in periodontal tissues, so the host's immune response plays an essential role in defense against microorganisms. However, bacterial persistence and the dysregulation of the immune system as an exaggerated response can lead to the worsening of periodontal disease, leading to loss of gingival tissue and alveolar bone and thereby loss of teeth. Therefore, a better understanding of the cellular mechanisms involved in the development of periodontal disease is necessary to design new treatments and prophylactic measures in order to decrease the prevalence of this disease that afflicts a large part of the world population.

KEYWORDS

bone loss, immunity, periodontitis

1 | INTRODUCTION

The term periodontal disease describes inflammation of the tissues that offer support to the teeth. In this paper, we will focus on the etiology and immunopathology of the two most common diseases, which are dental biofilm-induced gingivitis and periodontitis.

Periodontal disease represents a significant public health problem. The Global Burden of Disease (GBD) reported that the number of people affected by severe chronic periodontitis reached 538 million in 2015. In Latin America, the prevalence of periodontal disease in adults has been reported in only a few countries. The prevalence of gingival inflammation was 96.5% for Argentina and Chile, whereas in Costa Rica and Colombia was 99.6%. In the case of periodontitis, Argentina reported that 40.7% of adults over the age of 18 were affected, Chile reported 58.3% for subjects aged 35 to 44 years, 81.4% for subjects aged 65 to 74 years, and Colombia reported for 61.8% of adults. Brazil reported 19.4% in subjects aged 35 to 44 years based on the CPI/ CPITN index (Carvajal et al., 2020). In Mexico, the Epidemiological Surveillance System for Oral Pathologies 2018 (SIVEPAV 2018) reported that 57.9% of the population between 20 and 99 years of age presented with some kind of periodontal damage (Salud, 2020).

2 | ETIOLOGY

Periodontal disease is a multifactorial disease in which genetic, microbial, and environmental factors are involved. For the onset of periodontitis, a large number of genetic loci participate in this process, which vary according to ethnic populations and may be influenced by environmental factors (Wu et al., 2015).

Various scientific disciplines are working in a multidisciplinary way to acquire a better understanding of diseases. The relationship between oral diseases and nutrition has a strong association,

with various factors linked in a bidirectional relationship (Barrios et al., 2014). Low-grade inflammation, a characteristic of obesity, could lead to oral alterations through dysregulated immune responses (Ramírez-De Los Santos et al., 2020).

The microbial interactions with each other and with the host play an essential role in the appearance and progression of periodontal disease. Among them, bacteria are the most abundant, and around 500 species may be present in the gingival plaque. Sequencing studies of the 16s rRNA gene have shown the concomitant participation of different bacterial species in healthy conditions, dominated by bacteria from the green complex. There may also be bacteria from the orange and red complex, although in smaller quantities. In part, gingivitis comprises species of the green and specifically the orange complex. Finally, when biomass increases further, periodontitis can develop, leading to the red species becoming more dominant in the now dysbiotic microbiota. For this reason, periodontitis is now considered a multimicrobial inflammatory disease in which the initiation and progression of the disease will be determined by the susceptibility of the host and its interaction with the microbiota of the biofilm (Curtis et al., 2020; Fragkioudakis et al., 2021).

3 | THE NATURAL HISTORY OF THE PERIODONTAL DISEASE

The initial stage of biofilm formation on the surface of the teeth consists of an extracellular matrix made up of different components that facilitate the development of microbial associations through adhesive and fixing factors for surfaces between bacteria (Senpuku et al., 2019). Because dental biofilm is not yet mineralized, some particles in the oral cavity continue to adhere to the layer until it is finally mineralized with calcium phosphate mineral salts (Sakaue et al., 2018). As the biofilm grows and matures, there is a gradual depletion of oxygen, and anaerobic microorganisms increase in abundance (Velsko et al., 2019).

In the transition from periodontal health to the disease, the modification of a symbiotic microbial community composed of facultative bacteria toward a dysbiotic community; this dysbiosis is rich in virulence factors with the ability to thrive an inflammatory environment (Abusleme et al., 2013).

Under normal conditions, this subgingival environment is rich in immune and inflammatory mediators, which imposes a challenge on the survival of pathogenic bacteria. However, when the host's immune response is dysregulated due to changes in the microbial community or due to immune-regulatory defects, it is difficult to restrict bacterial growth, thus manifesting the pathogenicity (Borilova Linhartova et al., 2020).

4 | IMMUNE SYSTEM

The immune system is classified into the innate and adaptive system. The former includes cells of the myeloid line such as macrophages, neutrophils, natural killer cells (NK cells), and dendritic cells (DCs). Additionally, non-hematopoietic cells, such as oral epithelial cells, gingival, and fibroblasts, are involved (Liu et al., 2013).

In the adaptive immune system, the cells that participate are mainly B and T lymphocytes. There is a link between these two immunities, since the innate system activates the adaptive system through the route of antigen presentation through DCs or other antigen-presenting cells (Guo et al., 2005). Cytokines provide a communication system between cells. Cytokines exert their function at low concentrations, but when the oral levels of these molecules are modified, they can lead to the appearance of oral pathologies (Sánchez-Hernández et al., 2011).

4.1 | Innate immunity

In the oral cavity, the protective mechanism of saliva against microorganisms is due to salivary antimicrobial peptides (AMPs), as well as immunoglobulin A (IgA) that binds to microbes, resulting in an amalgamated mass that is ingested by phagocytes, thereby minimizing microbial populations (Zainab et al., 2019).

One defense system of innate immunity is the complement system, which generates effectors that opsonize microbial pathogens so that antibodies and phagocytic cells cooperate to eliminate them. Additionally, the membrane attack complex (MAC) induces the lysis of microbial targets (Grande et al., 2021).

Due to genetic factors, the homeostatic environment of tissues can be deregulated, causing excess activation of some immunity cells. This leads to damage and degradation of connective tissue and the loss of alveolar bone, which serves as nutrients for the dysbiotic microbial population (Hajishengallis et al., 2019). Once microbial factors come into contact with periodontal tissues, the immune response is initiated through PRRs such as TLRs; these receptors are expressed on the membranes of gingival epithelial cells, fibroblasts, DCs, and macrophages (Li et al., 2014).

PPRs recognize highly conserved regions in microbes, such as lipopolysaccharides (LPS), peptidoglycans, bacterial DNA, and lipoproteins, which are known as pathogen-associated molecular patterns (PAMPs) (Ghaderi et al., 2014). When TLRs recognize PAMPs, the mitogen-activated protein kinase cascade (MAPK) is activated inside immune cells, which culminates in the activation of transcription factors. This leads to the production of specific cytokines and chemokines that recruit non-resident leukocytes such as neutrophils to the site of infection (Lewkowicz et al., 2016).

Neutrophils are a type of leukocyte and one of the first to respond to chemokines released by migrating to the site of the periodontal lesion. However, neutrophils are short-lived cells and die in large numbers at periodontal sites, so accumulation and mass death of this type of leukocyte is one of the leading causes of tissue degradation in periodontitis (Nicu et al., 2018). Neutrophil extracellular traps (NETs) are released, which consist of a network of chromatin fibers combined with elastases, cathepsin G, myeloperoxidases, and peptidoglycan recognition proteins; these granular proteins bind to pathogens and destroy them (Moonen et al., 2019). Aggressive localized periodontitis is

characterized by a high number of hyperactivated neutrophils that can contribute to tissue destruction and antimicrobial defense due to the production of high levels of reactive oxygen species (ROS). An investigation showed that subjects with periodontal disease had higher levels of 8-hydroxy-20-deoxyguanosine (8-OHdG), a product of oxidative DNA damage caused by ROS (Zamora-Perez et al., 2015).

Activated mast cells produce nitric oxide (NO), acid phosphatases, metalloproteinases (MMP), and some cytokines such as TNF-α. Previous studies have shown that periodontitis patients have elevated levels of mast cells and that these levels increase according to the evolution of the disease, so they could be involved in bone loss (Shahsavari et al., 2020), although other researchers report contrasting results (Silveira et al., 2018).

NK cells induce DCs to mature so that they eventually produce TNF-α and IL-2. In this way, NK cells contribute to the specific immune response by exerting action on DCs, causing responses in T cells (Krämer et al., 2013). After NK cells bind to the oral pathogen, they secrete TNF-α, a cytokine involved in the pathogenesis of periodontitis (Y. Wang et al., 2016).

Macrophages are resident cells with phagocytic abilities. The classic phenotype (M1) facilitates bacterial destruction and is characterized by the expression of IL-6 and TNF-α and the promotion of inflammation. Macrophages can promote periodontal connective tissue damage and bone resorption when they secrete matrix metalloproteinases and collagenases along with pro-inflammatory cytokines (Yang et al., 2017).

DCs recognize microbial antigens through their TLRs and travel to the lymph nodes to present the antigen to T and B lymphocytes. Activation of DCs occurs through the recognition of infected cells by bacteria, apoptotic cell debris, and microorganisms (Di Benedetto et al., 2013). While traveling to the Lymph node, DCs mature and express major histocompatibility complex (MHC) class II molecules through which they present antigen to CD4+ T cells (Wilensky et al., 2014).

The type of antigen presented in the TLR provides information to the lymphocytes about the invading pathogen so that they stop the infection through a suitable effective response (Pasare & Medzhitov, 2004).

4.2 | Adaptive immunity

Specific immunity is orchestrated by B and T cells. There are different classes of T lymphocytes. CD4+ T (helper) cells amplify the immune response and are subdivided according to the type of cytokines they release as Th1 cells that produce interleukin-2 (IL-2) and interferon-gamma (IFN-γ), and Th2 cells that produce IL-4, IL-5, IL-6, IL-10, and IL-13. It is essential to mention that both types produce TNF-α. Another subgroup of CD4+ T cells includes Th17 cells that produce IL-17. The final subset is made up of regulatory T (Treg) cells (Sommer et al., 2019).

It is believed that CD8+ T cells could play a suppressive role since they can regulate other cells of the immune system. Research carried out in Sprague-Dawley rats analyzed the role and presence of CD8+ regulatory T cells in the gums, spleens, and cervical lymph nodes of healthy animals or those with induced periodontitis. It was clarified that CD8+ regulatory T cells affect the homeostasis of alveolar bone and protect it by reducing osteoclastogenesis and modulating the local immune response (Han et al., 2018a).

It has been described that non-susceptible subjects to periodontal disease have increased Th1 cell activation. In contrast, subjects with periodontitis have mainly activated Th2 cells (Bártová et al., 2000). However, an investigation showed that the proportions of Th1 cells, together with Th17, were more abundant in subjects with chronic periodontal disease, suggesting that these cells could be involved in the pathogenesis of chronic periodontitis (Chen et al., 2016). Another investigation carried out on Wistar rats concluded that the evolution of gingivitis to the next stage is related to an increase in activated Th1 lymphocytes, associated with an increase in IL-17 (Sommer et al., 2019).

Th17 cells produce IL-17. This molecule is a pro-inflammatory cytokine that aggravates inflammation of the gingival tissue and the loss of alveolar bone. IL-17 induces the expression of RANKL, IL-1β, and TNF-α. A recent study carried out in mice showed that IL-17 facilitates the differentiation of osteoclasts and bone resorption in vitro and in vivo (Song et al., 2019). In a study conducted in rhesus monkeys, overexpression of Th17 versus Treg (Th17/Treg axis) was observed at the beginning of periodontal disease with successive permanence of the Th17-mediated response with the progression of periodontitis (Ebersole et al., 2014).

The primary cytokines produced by the Th1 and Th17 subgroups promote the production of TNF-α and IL-1β, which in turn activate the nuclear factor-κB receptor ligand (RANKL), which binds to its receptor located on the membrane of osteoblasts, and with this, there is more significant bone resorption (Monasterio et al., 2018).

The main functions of Treg are to suppress the release of cytokines, the proliferation of T cells, and the innate response. A study conducted on mice about the role of Treg in periodontal disease suggests that Treg suppresses excess inflammation and tissue damage, thereby playing a protective role (L. Wang et al., 2014).

B cells constitute adaptive humoral immunity and participate in the secretion of antibodies and cytokines (S. Liu, 2018). It has been described that B cells facilitate the elimination of bacteria by stopping the progression of the disease and therefore play a protective role in the chronic phase of periodontal disease. Plasma cells are abundant in inflammatory infiltrates and produce cytokines such as TNF-α, IL-6, IL-10, and metalloproteinases (MMP), so they may contribute to the degradation of periodontal tissue when expressing MMP (Zouali, 2017). A study demonstrated that gingival tissue memory B cells promote osteoclastogenesis by producing RANKL, revealing a possible way by which B cells participate in alveolar bone erosion, independently of antibody production during periodontitis (Han et al., 2018b).

5 | BONE RESORPTION

Many factors can affect bone loss; among them, the RANKL stands out, causing the activation of osteoclasts by binding to RANK

expressed on the membrane of osteoclast precursors. Patients with periodontitis have been shown to have elevated levels of RANKL. There is a soluble decoy receptor for RANKL, osteoprotegerin (OPG), predominantly produced by osteoblast and inhibits osteoclastogenesis (Kim et al., 2017).

The interaction of TLR with LPS can increase the expression of RANKL and promote the process of osteoclastogenesis. This process occurs by different mechanisms. 1) Complete RANKL-dependent osteoclastogenesis initiated by LPS/TLR interaction, and 2) RANKL-dependent partial osteoclastogenesis also initiated by LPS/TLR interaction promoted by RANKL and maintained by other pro-inflammatory cytokines. When the LPS interacts with TLR4 on macrophages or DCs, they upregulate pro-inflammatory cytokines such as TNF-α and IL-6. This can stimulate the expression of RANKL; TNF-α can also induce T and B cells to produce RANKL. In addition to this, fibroblasts participate in the secretion of RANKL when exposed to bacteria. Thus, the RANKL in the microenvironment binds to its receptor RANK expressed on the osteoclast precursors membrane, promoting the activation of these cells into mature osteoclasts (AlQranei & Chellaiah, 2020). An investigation carried out in rats with induced experimental periodontitis demonstrated the role of other pro-inflammatory molecules such as substance P (SP) concerning the RANKL/OPG ratio and showed that SP positively regulated the expression of RANKL and reduced the expression of OPG in gingival fibroblasts with or without 1 ug/ml of LPS, and they also showed that the RANKL/OPG ratio was increased in the group with LPS+SP (Yan et al., 2020). Thus, alveolar bone loss depends on RANK expression, increased levels of RANKL, or a decrease in soluble OPG receptor (Gibertoni et al., 2017). The alteration of RANKL concentrations induces osteoclast formation, and the presence of TNF-α has been shown to increase the effects of RANKL (Marahleh et al., 2019).

Research has shown that the IFN-γ released by Th1 prevents RANKL signaling and, consequently, osteoclastogenic processes (Takayanagi et al., 2000). Another investigation showed that concentrations in the gingival tissue of IFN-γ were significantly higher in cases than in controls and found a positive correlation between IFN-γ levels and some clinical parameters. In addition, it was concluded that IFN-γR expression showed an increase only in the beta chain (IFN-γR2) in endothelial cells of the gingival tissue of subjects with periodontal disease compared to the control group (Franco-Topete et al., 2018). In addition, the mechanism through which activated osteoclasts degrade bone is through reabsorption gaps by causing a pH gradient between the surface of the bone and the cell (Hienz et al., 2015).

6 | CONCLUSIONS

The participation of the innate and adaptive immune system in periodontal disease is outlined in Figure 1. It is generally accepted that the presence of bacteria is responsible for triggering the onset of gingivitis, and if the host's immune response is not adequate, it will progress to periodontitis. Therefore, a better understanding of the cellular and molecular mechanisms involved in the development of periodontal disease is necessary to design new treatments and prophylactic measures of this disease.

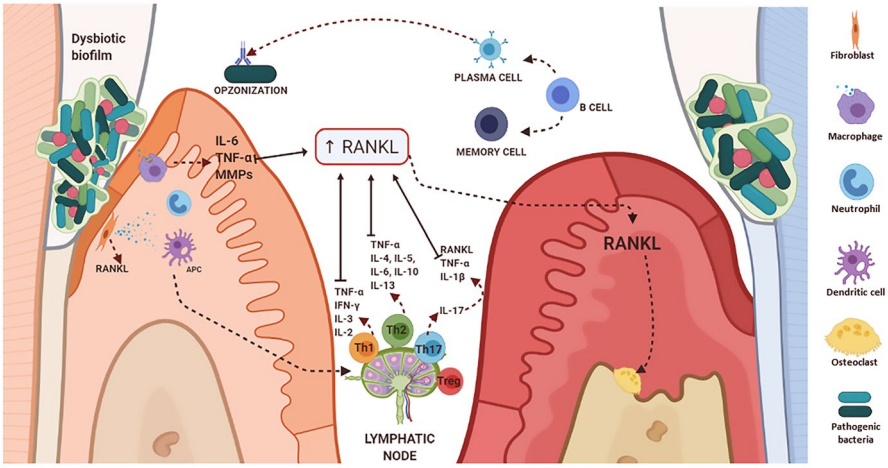

FIGURE 1 Participation of adaptive and innate immunity in the periodontal disease process. When a dysbiotic biofilm occurs with periodontopathogenic bacteria, the cells, such as fibroblasts, release cytokines to attract other immune cells like neutrophils and macrophages, in order to fight infection. In turn, these cells release pro-inflammatory cytokines. Dendritic cells recognize antigens and travel to the lymph nodes to present the antigen to T lymphocytes, which differentiate into subtypes depending on the antigen and the cytokines present. T cells induce cytokine secretion to regulate the immune response. In sequence, B cells produce antibodies or become memory cells. When TLRs recognize LPS, the expression of RANKL is induced; likewise, an increase of TNF-α induces the expression of RANKL. The alteration of RANKL concentrations induces the formation of osteoclasts, which will ultimately destroy the alveolar bone

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

Julieta Sarai Becerra-Ruiz: Conceptualization; Investigation; Writing – original draft; Writing – review & editing. **Celia Guerrero-Velázquez:** Conceptualization; Investigation; Writing – review & editing. **Fernando Martínez-Esquivias:** Investigation; Writing – original draft. **Luz Andrea Martínez-Pérez:** Investigation; Writing – original draft. **Juan Manuel Guzman-Flores:** Conceptualization; Investigation; Supervision; Writing – review & editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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