Chapter 7

Immunopathogenesis of Chronic Periodontitis

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Additional information is available at the end of the chapter

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Abstract

Periodontitis is a chronic inflammatory condition characterized by destruction of non-mineralized and mineralized connective tissues. The pathogenesis of periodontitis involves a complex interplay between periodontopathogens and the host immunity, greatly influenced by genetic and environmental factors. Failure in the inflammation resolving mechanism leads to establishment of a chronic inflammatory process, resulting in the progressive destruction of bone and soft tissue. The aim of this chapter is to summarize the role of innate and specific immune response involved in pathogenesis of periodontitis. Cells and inflammatory mediators, those participating in inflammatory process of the ligamentous supporting structure and in resorption of alveolar bone, will be presented.

Keywords: periodontal diseases, immune response, cytokines, chemokines, immune cells

1. Introduction

Periodontitis is one of the most common and a complex infectious disease of the oral cavity. Studies suggest that up to 60% of the population is affected by the common form of the disease, termed chronic periodontitis. Periodontitis is a multifactorial disease, with participation of bacterial, environmental, and host factors. The disease is characterized by an inflammatory response to commensal and pathogenic oral bacteria. Due to bacterial infection, gingival tissues become inflamed, characterizing gingivitis, and if left untreated, periodontal supporting tissues can be slowly destroyed by the action of the inflammatory process, which characterizes periodontitis. In the course of periodontitis, teeth lose their ligamentous supporting structure

to the alveolar bone, the alveolar bone is resorbed, and the teeth become mobile. In its severe form, it may lead to tooth loss.

There are two major forms of periodontitis, chronic periodontitis (CP) and aggressive periodontitis (AP). CP is a slowly progressing disease, which can be categorized as mild/early, moderate or severe based on clinical criteria, such as probing pocket depth (PPD) and clinical attachment loss (CAL). AP occurs in 1–3% of the population and is characterized by rapid rate of disease progression in an otherwise clinically healthy patient, absence of large accumulations of plaque, and familial inheritance.

Traditional and fundamental procedures for diagnosis of periodontitis include visual examination, tactile sensation, PPD, CAL, plaque index, bleeding on probing, and radiographic assessment of alveolar bone loss. Periodontal bleeding reveals the ulcerated area of subgingival tissue, whereas probing depth reveals the extent of the area of tissue covered by subgingival biofilm. Although different estimates for quantification of the area of periodontal injury have been reported in the literature, the inflammatory challenge of periodontal disease usually consists of an affected area of 15–72 cm^2 [1].

Bacteria have been considered to be the initiating factors to trigger periodontitis. Especially, Gram-negative anaerobic bacteria including *Porphyromonas gingivalis* (*P. gingivalis*) and *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) have been strongly implicated in disease. Localized aggressive periodontitis is associated with *A. actinomycetemcomitans*, while generalized forms of chronic disease involve *P. gingivalis*, and also *Tannerella forsythia*, *Prevotella intermedia*, *Treponema denticola*, and *Fusobacterium nucleatum* (*F. nucleatum*) [2]. *P. gingivalis* has been implicated to be one of the most important periodontal pathogens, and its important features in mediated CP include the ability to adhere to and invade host cells, to disseminate through host cells and tissues, and to subvert host immunological defense mechanisms. The cell wall components of *P. gingivalis*, especially lipopolysaccharide (LPS), can cause direct destruction of periodontal tissues and trigger a wide range of immune responses, including the production of proinflammatory cytokines, antiinflammatory cytokines and chemokines, which might be important in periodontitis development [3]. A distinct systemic response was observed among different strains of *P. gingivalis in vivo*: strains that induced expression of high levels of IL-4 were shown to induce alveolar bone loss, whereas strain that increased IL-10 did not significantly promote bone resorption in mice [4].

Current evidence supports the importance of several factors increasing onset and progression of periodontal diseases, including smoking, diabetes, hormonal changes, and osteoporosis. Other potential interactions with periodontal disease are those involving obesity, adverse pregnancy outcomes, cardiovascular diseases, psychosocial factors and socioeconomic status [5].

In this way, the aim of this chapter is to summarize the role of innate and specific immune response involved in pathogenesis of chronic periodontitis. The neutrophils, monocytes/macrophages, and T and B lymphocytes and inflammatory mediators, including cytokines, those participating in inflammatory process of the ligamentous supporting structure and in resorption of alveolar bone, will be discussed.

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2. Immunopathogenesis of chronic periodontitis

The host response during periodontitis involves the innate and adaptive immune system, leading to chronic inflammation and progressive destruction of tooth-supporting tissues. The pathogenesis of periodontal disease involves a complex interplay between periodontopathogens and the host immunity, greatly influenced by genetic and environmental factors (as smoking). Dental plaque is necessary, but not sufficient for disease, where an exacerbated, poorly specific and effective inflammatory response is mounted. Failure in the inflammation resolving mechanism leads to establishment of a chronic inflammatory process, resulting in the destruction of bone and soft tissue.

The host inflammatory response is mediated mainly by neutrophils, monocytes/macrophages, and T and B lymphocytes. Neutrophils are the first cells to arrive at the inflammatory infiltrate. The innate response involves the recognition of microbial components by Toll-like receptors (TLRs) expressed by host cells in the infected microenvironment. When the resolution of inflammation is not achieved, antigen-presenting cells are activated by bacterial products and interact with naïve T helper cells (Th0), driving their differentiation into several subsets, such as Th1, Th2, Th17, and Treg. T lymphocytes are central to adaptive immunity and provide help for B cells to generate specific antibodies. T cell receptor recognition of peptide antigen in the context of major histocompatibility complex can result in CD4 T cells activation. Activated Th0 may differentiate into either Th1 lymphocytes expressing Interleukin (IL)-2, interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α); or Th2 lymphocytes, expressing IL-4, IL-5, and IL-13; or Th17 expressing IL-17A, IL-17F, IL-21, and IL-22. Activated and effector T cells may become memory T cells. T regulatory (Treg) cells are responsible for mechanisms of tolerance: the T cells $CD4^+$ $CD25^+$ have been shown to be higher in periodontitis than gingivitis, suggesting the importance of immunoregulation in periodontitis.

2.1. The innate immune response

The innate immune response constitutes the first line of defense and is able to recognize non-self microorganisms trigging immune response to eliminate them.

Unlike adaptive immunity, innate immunity does not recognize every possible antigen. Instead, it recognizes a few highly conserved structures present in many different microorganisms such as LPS, peptidoglycans, bacterial DNA, double-strand RNA, N-formylmethionine found in bacterial proteins, the sugar mannose and proteases (named pathogen-associated molecular patterns, PAMPs). The defense cells have pattern-recognition receptors (PPRs) for these PAMPs and trigger immediate response against the microorganism. PPRs are found on inflammatory cells and on periodontal tissue resident cells, such as epithelial cells (ECs), gingival fibroblasts (GFs), periodontal ligament fibroblast (PDLF), dendritic cells (DCs), and osteoblasts (OBs). These receptors include TLRs, nucleotide-binding oligomerization domain (NOD) proteins, cluster of differentiation 14 (CD14), complement receptor-3, lectins, and scavenger receptors. PAMPs can also be recognized by a series of soluble pattern-recognition receptors in the blood that function as opsonins and initiate the complement pathways.

After bacterial challenge, the resident cells recognize PAMPS, via TLRs, and initiate an orchestrated signaling events resulting in the production of proinflammatory cytokines and chemokines, and recruitment of inflammatory cells. The TLR4 has been shown to specifically recognize LPS from gram-negative bacteria. Cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1β and IL-6, within periodontal lesions, orchestrate the cascade of destructive events that occur in the periodontal tissues. These events include the production of inflammatory enzymes and mediators (such as matrix metalloproteinases and prostaglandins), and osteoclast recruitment, and differentiation through receptor activator of nuclear factor-$\kappa\beta$ ligand (RANKL)-dependent and -independent pathways resulting in irreversible hard and soft tissue damage and in chronic periodontitis.

These cells involved in innate response and molecular factors involved in the local inflammatory reaction will be discussed later.

2.1.1. Cells involved in innate immune response

2.1.1.1. Neutrophils and monocytes/macrophages

Neutrophils, also called polymorphonuclear leukocytes (PMN), are one of the first responders of inflammatory cells to migrate toward the site of periodontal inflammation. The nucleus of neutrophils is segmented into three to five lobules, and the cytoplasm contains granules of two types: specific granules which are filled with enzymes such as lysozyme, collagenase, and elastase; and azurophilic granules which are lysosomes containing microbicidal substances as enzymes, defensins and cathelecidins. After periodontal pathogens successfully overcome epithelial barriers and invade soft tissues, signals from bacteria and gingival epithelial cells, human mesenchymal stem cells, connective fibroblast, and resident macrophages induce the production of cytokines and chemokines by the gingival epithelium. The chemoattractant molecules (such as IL-8 and IL-1β, and serum-derived plaque activated C5a) increase the expression of adhesion molecules, the permeability of gingival capillaries, and the migration of neutrophils through the junctional epithelium and into the gingival sulcus [6].

The interaction between the oral microbiota and neutrophils is a key determinant of oral health status. Neutrophils form a “wall” between the junctional epithelium and the pathogen-rich dental plaque providing a robust secretory structure (reactive oxygen species [ROS] and bactericidal proteins) and a phagocytic apparatus. However, this protection is not without cost because neutrophils from periodontitis patients are hyperreactive and contribute to tissue destruction: ROS and the enzymes released by cytoplasmic granules degrade the structural elements of tissue cells and extracellular matrix and cause tissue damage [7, 8]. A recently discovered innate defense strategy of neutrophils is the release of DNA to the extracellular environment, where the web-like DNA threads trap and kill microorganisms by means of DNA-bound antimicrobial proteins and peptides. These neutrophil extracellular traps (NETs) are also known to arise in periodontal tissues and purulent pockets. NETs represent a host defense mechanism but may also cause host tissue injury [9]. On the other hand, alterations in neutrophils function result in an acute, severe, and generalized clinical phenotype of periodontitis. These alterations can involve different functions, such as adhesion capabilities, chemotaxis response, and phagocytic function [10]. Added to this, neutrophils

with normal functions in individuals with alterations in the IL-8 production and/or mutations in Duffy antigen receptor chemokines (DARC) expression on erythrocytes predispose those individuals to periodontitis [11]. It occurs because adsorption of IL-8 onto erythrocytes by DARC leads to an increased recruitment of leukocytes from the blood to the tissue compared to individuals without DARC on the erythrocytes.

Monocytes/macrophages belong to mononuclear phagocytes system. They are also important innate immune cells at infection sites in patients with CP. These cells produce large amounts of proinflammatory cytokines, antiinflammatory cytokines, and chemokines, including TNF-α, IL-1β, IL-8, and IL-10. These chemokines produced by these cells attract neutrophils; however, neutrophils also produce chemokines, which attract macrophages to inflamed periodontal site. Thus, a crosstalk exists between these innate cells. Macrophages are important in triggering the specific immune response serving as antigen-present cells that display antigens to and activate T lymphocytes. Added, monocytes/macrophages can differentiate into osteoclasts [12].

2.1.1.2. Fibroblasts

Periodontal ligament fibroblast (PDLF) and gingival fibroblasts (GF) are the main cells of the soft connective tissue. In conjunction with infiltrating inflammatory cells, GFs take part in the inflammatory process in the periodontium and contribute to the disease persistence. After microorganisms breach the epithelial barrier, these cells produce cytokines and degradation molecules. Expression of matrix metalloproteinases (MMPs) became accentuated. Fibroblasts from periodontitis patients expressed higher mRNA of IL-1β, IL-6, and TIMP-3 and lower mRNA of IL-4 [13]. PDFL also produces IL-8, TNF-α, macrophage inflammatory protein (MIP)-1 alpha, and receptor activator of nuclear factor-$\kappa\beta$ ligand (RANKL), which are regulators on inflammation and alveolar bone loss. When in cell-cell contact with osteoclast precursors, PDFL upregulated osteoclastogenesis-related genes and significantly increased the number of osteoclast-like cells [14].

2.1.1.3. Dendritic cells

Dendritic cells (DCs) are the most important antigen-present cells for activating naïve T cells. These cells function in both innate and adaptive immune responses and are a link between these two components of host defense. They are part of myeloid lineage and arise from the same monocyte precursor. DCs have long membrane projections and phagocytic capabilities. Similar to macrophages, they express receptors that recognize bacteria and respond by secreting cytokines. They produce IL-12 and IL-18 that consequently promote interferon-gamma (INF-γ) secretion by natural killer (NK) cells and latter by T cells. In response to activation by microorganism, conventional DCs become mobile, migrate to lymph nodes, and display antigens to T lymphocytes.

2.1.2. Molecular factors involved in the local inflammatory reaction

In the innate immune response, the bacterial activation of resident cells culminates in a production of proinflammatory cytokines involved in periodontal immunopathogenesis. In order

to eliminate the bacteria, the inflammatory process is triggered; however, the inflammation culminates in periodontal tissue lesions and alveolar bone resorption [15].

2.1.2.1. Toll-like receptors (TLRs)

TLRs play an important role in the recognition of pathogens. TLRs are a family of transmembrane proteins expressed by immunologically competent cells. They recognize and bind to PAMPs derived from bacterial plaque. TLRs are evolutionarily conserved proteins with a highly conserved intracellular toll-interleukin receptor (TIR) domain involved in protein-protein interaction and signaling activation. The extracellular domain, with leucin-rich repeats (LRRs) is related to ligand recognition. LRR motifs vary among TLRs. After PAMPs recognizing, TLRs initiate the activation of several transcription factors including nuclear factor-kappa B (NF-κB) and activator protein 1 (AP-1) through the mitogen-activated protein kinase (MAK) cascade. NF-κB is a key transcription factor complex that appears to play a critical role in the regulation of an acute inflammation. NF-κB enters the nucleus of the cell and induces expression of proinflammatory mediators including adhesion molecules (ICAM-1, VCAM-1, and E-selectin), enzymes (COX-2, 5-LO, CPLA, and iNOS), cytokines (IL-1, TNF, IL-6, GM, and G-CSF), and chemokines (IL-8, RANTES, MCP-1, eotaxin, and MIP-1κ). An increase in the recruitment of leukocytes is generated [16, 17].

TLR-2, 3, 4 and 9 are much expressed in gingival tissues of periodontitis patients, and TLR-2 and TLR-4 expressions are increased in severe disease states, suggesting that these receptors have an increased capacity to signal and influence downstream cytokine expression. TLR-4 is present on antigen presenting cells, fibroblasts, and keratinocytes of gingival epithelium. TLR4 has been shown to specifically recognize LPS from gram-negative bacteria and thus recognize PAMPs of periodontopathogens such as *P. gingivalis, A. actinomycetemcomitans*¸ and *V. parvula*. Tool-like receptor-4 acts in cooperation with its coreceptors CD14 protein and MD-2 complex, as well as TLR4 adaptor proteins such as myeloid differentiation primary response gene 88 (MyD88) playing an important role in maintenance of periodontal healthy. However, over production of proinflammatory cytokines due to chronic stimulation of TLRs may lead to tissue damage. LPS-triggered TLR4 activation leads to an increased secretion of proinflammatory cytokines, mediators and matrix metalloproteinases (MMPs) from a variety of cells including monocytes, macrophages, neutrophils, lymphocytes, and gingival fibroblasts. Repeated stimulations of these receptors may also lead to development of tolerance to bacterial products. TLR-2 engagement has been shown to trigger production of proinflammatory and antiinflammatory cytokines [18, 19].

CD14 is a myeloid differentiation marker found primarily on monocytes and macrophages, although low levels are also found on neutrophils and endothelial cells. CD14 is a coreceptor for LPS. The CD14 gene is located on chromosome 5q31.3 and encodes two forms of protein: one is anchored to the membrane glycosylphosphatidylinositol (mCD14) and is a 55-kDa glycoprotein, and another is a soluble form (sCD14) found in body fluids. CD14 lacks the transmembrane domain and is unable to transmit LPS signaling. The major function of CD14 is to serve as an initial receptor for LPS and facilitate the binding of LPS to TLR4/MD-2 complex. In

addition, CD14 also recognizes other PAMPS such as lipoteichoic acid. Proinflammatory and antiinflammatory effect of CD14 has been shown indicating dual roles in response to Gram-negative bacteria [20, 21].

2.1.2.2. Matrix metalloproteinases (MMPs)

The matrix metalloproteinases (MMPs) are a structural and functional family of zinc-dependent extracellular proteinases, which are responsible for the remodeling and degradation of tissue extracellular matrix (ECM), including collagens, elastins, gelatin, matrix glycoproteins, and proteoglycans. To date, at least 26 members of MMPs have been identified and they are grouped according to their structural properties and substrate specificity in collagenases (MMP-1, -8, -13, -14), gelatinases (MMP-2 and -9), stromelysins, matrilysins, and membrane type matrix metalloproteinases. The balance between MMPs and their endogenous inhibitors (tissue inhibitor of matrix metalloproteinases, TIMPs) controls the MMP activity. MMPs play an important role in tissue degradation observed in periodontitis, and elevated levels of MMP-1, -2, -3, -8, and -9 have been detected in gingival crevicular fluid, peri-implant sulcular fluid, and gingival tissue of periodontitis patients. MMP-1 is produced by periodontal resident cells and is considered as central in the physiological remodeling of extracellular matrix in wound healing. MMP-8, mainly produced by neutrophils, is associated to periodontal collagen destruction and represents the major collagenase in gingival and crevicular fluids; its levels can differentiate periodontitis from gingivitis and healthy sites. MMP-9 has been associated with collagen breakdown and periodontal inflammation. MMP-13 is little or not expressed on normal tissues, but its upregulation has been involved in periodontitis progression and bone loss. MMPs can be released or activated during periodontal disease by proinflammatory cytokines, as TNF-α and IL-1β, reactive oxygen species, and proteases; IL-18 may be related to be involved in the regulation of MMPs [22–24].

2.1.2.3. Cytokines

The resident cells and migrating cells release cytokines during inflammatory response involving in chronic periodontitis. Endothelial cells and GF produce IL-8, a chemokine that is neutrophils chemoattractant and that increase the monocytes adhesion. Neutrophils (the migrant cells) and PDLF produce IL-1, IL-6, and TNF-α. GF also produces IL-6 and TNF-α. PDLF and also bacterial antigens could promote the expression of the RANKL by the osteoblasts. DC IL-12p40, IL-18, IL-6, and TGF-β (transforming growth factor beta) act as antigen-present cells to T lymphocytes. The role of this cytokines will be described later.

After this initial primary response, activation of T cells by APCs initiates the adaptive response. Subsequently, the effector mechanisms of innate immunity are improved by adaptive immunity involving an efficient loop for microbial clearance. Chronic periodontal inflammation perpetuates and amplifies itself through numerous autocrine and paracrine loops of cytokines, acting on cells within the periodontal tissue.

2.2. The adaptive immune response

When the resolution of inflammation is not achieved, adaptive immune response is initiated. Therefore, APCs are activated by bacterial products and interact with naïve T helper cells (CD4 T cells, Th0: CD45RA+), driving their differentiation into several subsets (CD45RO+), such as Th1, Th2, Th17, and Treg. Adaptive immune cells and their cytokines have important participation in pathogenesis of the chronic periodontitis, including the resolution of infection, tissue damages, and osteolytic process.

2.2.1. T cell subsets enrolled in the pathogenesis of CP

For a long time, periodontitis lesions were conceptually defined based on a Th1/Th2 paradigm. Currently, Th1 and Th2 responses, added to the Th17 subset, have been related to the disease progression and bone resorption. T cell lymphocytes (CTLs) are primarily involved in the cell-mediated immunity. CTLs were named because their precursors, which arise in the bone marrow, migrate and maturate in the thymus. The two major T cell subsets are CD4 (T helper) and CD8 CTLs, which express a highly diverse and clonally distributed antigen receptor called the $\alpha\beta$ receptor. Both effector cells usually express surface protein indicative of recent activation, such CD25, a component of the receptor for the T cell growth factor IL-2. Th cells express surface molecules as CD40 ligand (CD154) [25].

2.2.1.1. T-helper 1 (Th1 cells)

Th1 cells are generated under the influence of interleukin-12 and/or interferon-γ (INF-γ) signaling that leads to the activation of the transcription factor T-bet. In diseased gingival tissues, Th1 cells have been predominant. Activated Th1 cells secret INF-γ, present in high levels in human and experimental periodontal lesions. INF-γ is associated to onset and progression of lesions. Besides, INF-γ stimulates osteoclast formation and bone loss via antigen-driven T cell activation or through the chemoattraction of RANKL cells. Also, INF-γ can contribute to the migration of CD4/80+ cells, monocyte/macrophage-like phenotypes, a potential osteoclast precursor subpopulation [26, 27].

2.2.1.2. T-helper 2 (Th2 cells)

Th2 cells are generated under the influence of interleukin-4 and the activation of the transcription factor GATA-3. IL-4 secreted by Th2 exhibits antiinflammatory and suppressive properties related to the induction of IL-10 and suppression of Th1 response. In pathogenesis of periodontitis, it can be associated with the ability to inhibit the production of tissue degrading factors such as MMPs and the major osteoclastogenic factor RANKL. Therefore, IL-4 could attenuate the soft and mineralized tissue destruction. However, IL-4 levels were found lower in crevicular fluid from periodontitis patients.

Added to this fact, Th2 cells could be related to B cell function and humoral immunity in the periodontal lesion. B cells seem to contribute to periodontal disease development since B cell deletion prevented alveolar bone loss in mice after infection with *P. gingivalis* and because

the majorly of B cells in periodontal lesions are RANKL+ [28]. IgG is the more frequent antibody class present in the gingival crevicular fluid and gingiva of patients with periodontitis; therefore, IgA and IgM are also found. IgM and IgG classes were related to autoimmunity in periodontitis where high titers of anticollagen type I, antifibronectin and antilaminin were found [26, 27].

2.2.1.3. T-helper 17 (Th17 cells)

Th17 cells are generated under the influence of IL-6/IL-21/IL-23/TGF-β and the activation of the transcription factor RORγT. After TGF-β and IL-6 driver Th17, IL-23 amplifies the phenotype. Th17 cells have been linked to the development of pathological inflammatory disorders. Cytokines secreted by Th17, such as IL-17 and IL-22 are crucial for host protection against many extracellular pathogens. Furthermore, IL-17 contributes to innate and specific immunity by recruiting inflammatory cells and immobilizing macrophages in inflamed tissue. The consequence is an abundance of other inflammatory cytokines as IL-1β and TNF-α, and RANKL. Th17 cells have been linked to several autoimmune disorders and are also linked to the development of pathological inflammatory disorders, and their presence was demonstrated in the gingival tissue from patients with periodontitis [29, 30].

2.2.1.4. T regulatory cells (Treg cells)

Treg cells are generated under the influence of IL-10/TGF-β and the activation of the transcription factor forkhead box P3 (FOXp3). They also expressed as a $\alpha\beta$ antigen receptor. Treg cells specifically regulate the activation, proliferation, and effectuating functions of activated T cells. There are two types of Treg: (i) endogenous or natural (Treg), which are derived from the thymus and control autoreactivity; (ii) adaptive or induced (aTreg or iTreg), which regulate responses upon antigenic exposure in the periphery. In noninflammatory tissues, they are in resting state. The cytokines TGF-β, IL-10, and cytotoxic T lymphocyte-associated molecule 4 (CTLA-4) are supposed to mediate the suppressive activity in peripheral tissues and attenuate periodontal diseases progression and protect the bone resorption. Treg cells are shown to attenuate RANKL expression by other activated T cells. Treg cells were identified in periodontal tissues; however, deficiency of Treg cells was observed in periodontitis [31].

Another subset of Treg cells includes the Tcreg. In animal models and under noninflammatory conditions, murine osteoclasts can recruit naïve CD8 T-cells and activate these T-cells to induce CD25 and FoxP3 (Tcreg). Tcreg can potently and directly suppress bone resorption by osteoclasts. The activation of CD8 T cells by osteoclasts also induced the cytokines IL-2, IL-6, IL-10, and interferon (IFN-c). Individually, these cytokines can activate or suppress osteoclast resorption [32].

2.2.1.5. T CD8 cells

After naïve cells are activated, they became larger and proliferate, and are called lymphoblasts. Some of these cells differentiate into CD8 CTLs. CD8 cells have cytoplasmic granules filled with proteins that, when released, kill the cells that the CDLs recognize. They are also

called cytotoxic T cells. In an animal models, which allow investigating the stages of periodontitis, CD8 T cell knockout mice showed no significant change in bone loss after infection with *P. gingivalis* [33].

The activated T helper subsets, their produced cytokines and their general functions are summarized in **Table 1**.

2.2.2. The adaptive immunity in the pathogenesis of chronic periodontitis

Adaptive immune responses to most immunogens can begin only after the immunogen has been captured, processed, and presented by an APC to naïve T helper cells. The reason of this is that T cells only recognize immunogens that are bound to major histocompatiblity complex (MHC) proteins on the surfaces of other cells. There are two different classes of MHC proteins. Class I MHC proteins are expressed virtually in all somatic cell types and are used to present substances to CD8 T cells. Class II MHC proteins, on the other hand, are expressed only by macrophages, dendritic cells and a few other APCs, and are necessary for antigen presentation to T helper cells. The interaction of APC-T cells is dependent on other membrane receptors. The TCR complex confers specificity because it contains the antigen-specific receptor. The interaction is enhanced through coreceptors including CD27, CD28, CD40 ligand, or inhibited by coinhibitor receptors such as CTLA4, programmed cell death protein (PD1), and CD28 induced costimulator (ICOS) [25].

	Stimulating cytokines	**Differentiated T cells subsets and respective transcriptional factors (italic)**	**Produced cytokines ***	**Regulatory cytokines**	**Host defense**	**General roles in diseases**
Naive TCD4 T cells	IL-12 IL-18 INF-γ	**T_H1** *T-bet, STAT1, STAT4*	INF-γ LTA RANKL	IL-4 IL-10, TGF-β	Intracellular pathogens	Tissue damage associated with chronic infections
	IL-2 IL-4	**T_H2** *GATA-3, STAT6*	IL-4 IL-15 IL-13	INF-γ TGF-β	Extracellular pathogens Humoral immunity	Allergic diseases Autoimmune diseases
	IL-6 TGF-β	**T_H2** *2AHR*	IL-22	TGF-β	Extracellular pathogens	
	IL-6 TGF-β IL-21	**T_H17** *RORγT, STAT3*		IL-2 IL-4 IL-27 INF-γ	Homeostasis at mucosal sites/ inflammation	Organ-specific autoimmunity

*The cytokines produced by these T cells subsets determine their effector functions and roles in diseases. The cytokines also participate in development and expansion of the respective subsets.

Table 1. T cell subsets differentiation and general functions in immune response.

The acquired immune response is known to be important for periodontal disease development. Specific microbial components activate APCs, such as DC, and both migrate to local lymph nodes. In APC, immunogen become enclosed within membrane-lined vesicles in the cytoplasm and within these vesicles, undergo a series of alterations called antigen processing and a limited number of the resulting peptides are noncovalently associated to MHC class II proteins, and transported to APC surface, where it is detected by CD4 T cells. After specific antigen recognition, activation phase is initiated by the sequences of events induced in lymphocytes. The Th0 differentiation is dependent of the local cytokine milieu. Then, the CTL proliferate, leading to expansion of the clones of antigen-specific CTL and the amplification of the response. The pattern of cytokines expressed determines subsequent polarization of a distinct antigen-specific CTL response. Next, CTL differentiates to cells that function to eliminate foreign antigens: some T cells (CD4) differentiate into cells T helper subsets, that activate phagocytes to kill intracellular antigens, or in others T cells (CD8) that directly lyses cells that are producing foreign antigens, and also B cells, which transform to plasma cells that secreted specific antibodies. The effector phase is the stage that leads to antigen elimination. In this phase, inflammatory response is amplified after recruitment of specific and nonspecific effector cells (lymphocytes, macrophages, neutrophils) and their soluble products (lymphokines, monokines, complement, kinines, arachidonic acid derivates, mast cells—basophile products).

Characteristic markers of Th1, Th2, Th17 and Treg cell subsets have all been described in diseased periodontal tissues. Therefore, the exact crosstalk that occurs among Th cytokines in periodontal disease and its impact on disease outcome is still to be determined. However, it is clear that Th cells are essential for periodontal destruction because the absence of B cells does not impede LPS-induced bone resorption.

There are tissue resident memory cells within the oral mucosa. When compared with primary immune response, the recall of memory is faster and shows fewer requirements for antigen presentation by MHC and costimulation. In gingival tissues, IL-15 is found in abundance and seen to be responsible for the survival and proliferation of memory cells.

2.3. Cytokines in the pathogenesis of chronic periodontitis

Cytokines are low molecular weight water-soluble glycoprotein secreted by hematopoietic and nonhematopoietic cells in response to infection, and they are important key molecules and signal mediators in the pathogenesis of periodontitis. The cytokines involved in immunopathology of periodontal disease act in a highly complex coordinated network and play role in the maintenance of specific leucocytes on periodontal tissue, in the osteoclastogenesis activation and stimulation of bone resorption. Several of the cytokines have been demonstrated to serve either as proinflammatory (IL-1, IL-12, IL-17, IL-18, TNF-α) or antiinflammatory (IL-4, IL-10) mediators of the inflammatory process [34].

2.3.1. Interleukin-1 (IL-1)

IL-1 is a potent proinflammatory mediator and bone-resorbing cytokine formerly known as the osteoclast-activating factor. The *IL1* gene cluster is located on chromosome 2q13–q21

(https://www.ncbi.nlm.nih.gov/gene/3553) [35]. In the IL-1 superfamily members, two agonists and one antagonist members are highlighted: IL-1α and IL-1β (proinflammatory cytokines), and IL-1/IL-receptor antagonist (antiinflammatory cytokine). Between them, IL-1β is the most studied due its role in immunoinflammatory diseases. IL-1β, even as IL-1α, is able to bind and activate interleukin-1 receptors resulting in the recruitment of several intracellular adapter molecules, including MyD88, NFκB, AP-1, and mitogen activated protein kinase (MAPks). This interaction leads to transcription of genes of intercellular adhesion molecule-1 (ICAM-1) that incites the innate immune response, and genes of lymphocyte function associated antigen-1 (LFA-1) that culminates in a greater migration of leukocytes in tissue direction. Once secreted, IL-1 may activate lymphocytes, incite macrophage chemotaxis and prostaglandin production, and stimulate osteoclastic resorption of bone [36, 37].

In periodontitis, IL-1 is detected in the periodontal tissue and in the gingival crevicular fluid and is important in the metabolism of collagen, in bone destruction, and other inflammatory processes. IL-1β is secreted mainly by macrophages and resident cells. IL-1 could mediate the gingival and periodontal tissue destruction and bone resorption by different ways: (i) IL-1β and IL-1α stimulate the release of lysosomal enzymes such as metalloproteinase which degrades the extracellular matrix; (ii) IL-1β stimulates the production of prostaglandin E2 (PGE2) by fibroblasts and osteoblasts (OB). PGE2 stimulates bone resorption mediated by RANKL expression in OB; and (iii) IL-1β enhances RANKL expression on OB [38–40].

2.3.2. Tumor necrosis factor: alpha (TNF-α)

TNF-α is a very potent proinflammatory cytokine with a pleotropic effect on both immune and skeletal systems. It is encoded by *TNF* gene located on chromosome 6 (https://www.ncbi.nlm.nih.gov/gene/7124) [41] and is primary produced by activated T cells, monocytes/macrophages, and fibroblasts during inflammation. It is expressed as a transmembrane protein with 26 kDa or as a soluble TNF form with 17 kDa. When binding in the TNF receptors, TNF-RI of 55-kDa or TNF-RII of 75-kDa, the intracellular signaling pathways are activated via c-Jun, NF-kB, and calcium signaling leading to biological cellular response of inflammation. This response includes: (i) increase of adhesion molecules for leukocytes, as ICAM-1 and E-selectin; (ii) recruitment of leukocytes; (iii) increase of vascular permeability; (iv) increase the production of metalloproteinase and proinflammatory cytokines; and (v) osteoclasts differentiation dependent and independent of RANKL. The inappropriate or excessive TNF-α production can be harmful to tissue [42, 43].

TNF-α was detected in higher levels in saliva and crevicular fluid of patients with periodontal disease and its role and contribution to inflammation, loss of connective tissue attachment, and alveolar bone resorption has been well documented [44].

2.3.3. Interleukin-6 (IL-6)

IL-6 is a pleiotropic cytokine not only exerting immunological effect but also functioning in hematopoiesis, bone metabolism, and tissue regeneration. The human *IL6* gene is located in

the short arm of chromosome 7 (7p21; https://www.ncbi.nlm.nih.gov/gene/3569) [45]. IL-6 is a cytokine produced by T cells, B cells, monocytes/macrophages, endothelial cells, GF, OB and, periodontal ligament cells. It has multifunctional properties and is secreted in response to bacterial LPS or IL-1β and TNF-α stimulus. The IL-6 binding receptor (IL-6R) is located in membrane of cells and dimerizes with two gp130 subunits when IL-6 binds. Besides this, there is also a soluble form of receptor, and both receptors when activated are able to promote biological effects into the cells. IL-6 in promoting inflammation, it can also be involved in the regulation of tissue destruction. IL-6 induces the production of inhibitors of MMPs, suppresses IL-1β and TNF-α expression, and induces IL-1 receptor antagonist. Another positive point that favors the reduction of tissue damage is that IL-6 can stimulate fibroblasts to produce collagen and glycosaminoglycan. IL-6 plays role in B cells differentiation, T cell proliferation, and acute phase proteins expression. In addition, IL-6 in synergism with TNF-α is able to induce the differentiation of osteoclast progenitors directly or stimulate the stromal cells to produce RANKL.

This cytokine exerts an important effect in the pathogenesis of periodontitis, mainly in bone metabolism. During the development of CP, multiple biological actions could be mediated by the IL-6, including hematopoiesis, angiogenesis induction, immunocyte activation, and osteoclast differentiation. The presence of IL-6 in serum, gingival crevicular fluid, and saliva suggested an altered production of IL-6 in patients with CP [46, 47].

2.3.4. Interleukin-17 (IL-17)

The IL-17 family contains six members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (or IL-25) and IL-17F, and five receptors, IL-17RA-RD and SEF. Interleukin-17A is most homologous to IL-17F and the genes encoding them are proximally located on chromosome 6p12 (https://www.ncbi.nlm.nih.gov/gene/3605). The IL-17F activity is similar to IL-17A, but significantly weaker, and is related to induce the expression of various cytokines, chemokines, matrix metalloproteinases, antimicrobial peptides, and adhesion molecules by human fibroblasts, and airway epithelial cells and vein endothelial cells. IL-17A, IL-17B, IL-17C, IL-17D, and IL-17F are considered proinflammatory cytokines, and IL-17E is believed to have antiinflammatory properties. IL-17A, IL-17F and IL-22 are involved in neutrophilia, tissue remodeling, tissue repair, and production of antimicrobial products [48].

Many studies have demonstrated the presence of IL-17 in periodontal tissues, crevicular gingival fluid, saliva, and plasma of patients with periodontal disease. IL-17 contributes to inflammatory bone pathology and bone resorption by different ways: (i) stimulating the production and expression of TNF-α and IL-1β by human macrophages and IL-1β by OB; (ii) stimulating secretion of IL-6, CXCL8/IL-8, and PGE2 by fibroblasts, epithelial, and endothelial cells; (iii) increasing the expression of RANKL on OB; and (iv) stimulates the differentiation and activation of OC. In periodontal environment, IL-17 potentiates the innate immunity, mobilizing macrophages and neutrophils, and increasing TLR responsiveness in gingival epithelial cells. IL-17, when combined with IFN-γ, may modulate GF in periodontal disease by triggering the release of other proinflammatory, metalloproteinase and neutrophil-mobilizing cytokines [49].

2.3.5. Interleukin-18 (IL-18)

IL-18 is a member of IL-1 cytokine family and is codified by *IL18* gene located on chromosome 11q22 (https://www.ncbi.nlm.nih.gov/gene/3606) [50]. This proinflammatory cytokine is released at sites of chronic inflammation by APCs, such macrophages and DC, and non-immune cells, such epithelial and osteoblastic stromal cells. Its receptor IL-18RC is complex with two chains, the IL-18Rα and the IL-18Rβ chains; and the β protein contains the motif for sign-transducing. IL-18 has the property of stimulating both Th1/Th2 responses, depending on the immunological context. When the IL-12 is present, IL-18 drives to Th1 response, and in its absence, the Th2 cells' response is stimulated. IL-12 is able to increase the expression of IL-18Rβ. One of the major actions of IL-18 in Th1 response is to enhance the release of IFN-γ by $TCD4^+$ cells and natural killer (NK). INF-γ acts as a positive regulator of Th1 differentiation through increased transcription of T-bet. In addition, proinflammatory properties of IL-18 are due to promotion of the increase of cell adhesion molecules, nitric oxide synthesis, and chemokines production. IL-18 induces the production of Th2 cytokines such as IL-4, IL-5, IL-10, and IL-13, stimulating allergic inflammation, and inducing PGE_2 production [36, 51].

There are low evidences according IL-18 participation in periodontitis. Some studies show that IL-18 is an inhibitor of OC formation by indirect effects mediated by T cells and granulocyte macrophage colony-stimulating factor (GM-CSF). GM-CSF binds to preosteoclast and inhibits its proliferation and differentiation. The IL-18RC was found on T cells and OC. The concentration of IL-18 was found increased in the gingival crevicular fluid and serum of gingivitis, aggressive, and chronic periodontitis [52].

2.3.6. Interleukin-10 (IL-10)

IL-10 is considered an antiinflammatory cytokine playing a key role in the regulation of immune mechanisms. The *IL10* gene (https://www.ncbi.nlm.nih.gov/gene/3586) is mapped on chromosome 1q31-q32, in a cluster with closely related interleukin genes, including IL-19, IL-20, and IL-24, and has several regulatory promoter sequences within the 1.3 kb region upstream of the transcription start site [53].

IL-10 is produced by monocytes, macrophages, and T cells and plays a role in the regulation of proinflammatory cytokines such as IL-1 and TNF-α. During bone loss, IL-10 was correlated to inhibition of OC formation direct and indirectly. Directly, IL-10 inhibits osteoclast progenitors by an effect associated with decreased RANK-induced activation of nuclear factor-kappaB and expression of NFATc1, c-Fos, and c-Jun. Indirectly, by decreasing RANKL and increasing osteoprotegerin in dental folic cells. IL-10 also had protective role toward periodontal tissue destruction, inhibiting MMPs. However, it has stimulatory effect on B lymphocyte and may also stimulate the production of autoantibodies. Autoantibodies may play a role in periodontitis. The high production of IL-10 by Treg was found in gingival tissue [54].

2.4. Immunopathogenesis of bone resorption

Skeletal homeostasis depend on a dynamic balance between the activities of the bone forming osteoblasts (OB) and bone-resorbing osteoclast (OC). The RANK/RANKL/OPG regulating

system controls the bone resorption and deposition activity that occur during this bone remodeling. The receptor-activator of nuclear factor-kappaB (NF-κB) ligand (RANKL) binds to RANK on osteoclast precursors (monocyte/macrophage) causing them to differentiate into active cells (OC) that secrete enzymes that degrade bone. OPG (osteoprotegerin) is a soluble decoy receptor of RANKL that prevents the RANK-RANKL interaction. OPG inhibits the osteoclastogenesis and induces osteopetrosis when overexpressed [55]. In periodontitis, high levels of RANKL and low levels of OPG have been detected in gingival crevicular fluid. In response to LPS from periodontopathogens, for instances *P. gingivalis* and *A. actinomycetemcomitans*, RANKL expression has been increased in periodontal ligament fibroblasts; however, its major source is the activated immune cells, mainly Th1, Th17, and B cells [15, 56].

Several cytokines can synergize with RANKL in promoting osteoclastogenesis and increasing RANKL/OPG ratio. Cytokines, such as IL-1, TNF-α, IL-6, and IL-17, have the ability to stimulate bone resorption, whereas others, such as IL-4, IL-10, and TGF-β, act as inhibitors. TNF-α and also IL-1 have been shown to play an important role in periodontal bone loss in a dependent and independent RANKL pathway: TNF-α could promote the proliferation and differentiation of osteoclast precursors via NFATc1 activation. TNF-α also could lead to inhibition of OB differentiation. The TNF-related apoptosis inducing ligand (TRAIL) is expressed on OB after infection and induce the apoptosis of these cells. IL-17, when in high concentration, promotes osteoclastogenesis by enhanced RANKL expression on osteoblasts and CD4 T cells [57, 58].

The immune cells and cytokines produced by them involved in the protective and aggressive roles during CP are summarized in **Table 2**.

Immune response	Cells	Characteristic produced cytokines*	Protective actions	Deleterious actions
Innate immunity	Neutrophils	TNF-α IL-1 IL-6	No evidence	Proinflammatory RANKL inducers
	PDLFs	TNF-α IL-1 IL-6	No evidence	Proinflammatory RANKL inducers RANKL+
	Monocyte/ macrophage		No evidence	Proinflammatory RANKL inducers OC differentiation
Adaptive immunity	T_H1	INF-γ	Antiosteoclastogenic	Proinflammatory RANKL+
	T_H2	IL-4	Antiosteoclastogenic	B cells lesions and autoimmunity B RANKL+
	T_H17	IL-17	No evidence	Proinflammatory RANKL inducers RANKL+
	Tregs	IL-10 TGF-β	Antiosteoclastogenic	No evidence

PDLFs: periodontal ligament fibroblasts; OC: osteoclasts.

Table 2. Immune cells and their characteristic cytokines involved in tissue damage and bone resorption in chronic periodontitis.

3. Immunomodulation and therapeutic approaches

Therapeutic approaches in periodontitis attempt to eliminate the periodontal plaque, manage the inflammation and minimize the tissue damage. The conventional treatment of CP is the mechanical removal of infectious agents in gingival tissues, which resulted in bacteria resistance and disease recurrence. Considering the complexity of periodontitis, immunopathogenesis and clinical manifestations of disease, many different approaches could be considered in order to interfere during immunity response. Amongst them, blocking the cytokines activity may be a promissory intervention. The effect of TNF-α and IL-1 antagonists on periodontitis showed a significant reduction of inflammation and bone resorption when administered either systemically or locally in the gingiva. The administration of antiTNF-α or TNF-α/Fc fusion protein had demonstrated significant reduction of the clinical and radiographic signals in rheumatoid arthritis and periodontal diseases [59]. IL-11 has antiinflammatory effects by induction of inhibition of TNF-α and other proinflammatory cytokines, thus the use of recombinant human IL-11 in the animal models showed significant reduction in the rate of clinical attachment and radiographic bone loss [60]. Similarly, the use of RANKL inhibitors in periodontitis, although limited in animal models [61] or *in vitro* assays [62], demonstrates a protective effect on bone resorption. The inhibition of PGE2 formation by nonsteroidal antiinflammatory drugs decreases osteoclasts formation and alveolar bone loss in humans and in animal experiments [63]. The United State Food Drug Administration approved the host modulator drug denominated subantimicrobial dose doxycycline (SDD), which inhibits matrix metalloproteinases and results in reduced progression of disease [64].

4. Genetic variants and the periodontitis risk

The development of periodontitis relies on multiple factors, and it is estimated that 50% of the expression of periodontitis could be attributed to genetic factors. The multifactorial etiology of the periodontitis and the development of sequencing technology enabled us to discuss whether the variations of host's immunity affect the occurrence and development of the disease. Several immune response genes have been related to the protection or predisposition to CP, such as those responsible for bacterial antigens presentation to lymphocytes, as well as soluble mediators or membrane receptors that initiate or amplify the inflammatory process and bone loss.

4.1. Human leukocyte antigen (HLA)

HLA comprises of high polymorphic cell-surface molecules that have a key role in antigen presentation and activation of T cells. Because of the capability to bind periodontopathogens peptides, HLA represents an important factor of risk or resistance to CP development. A metaanalysis focusing on Caucasian case-control studies demonstrated no associations between HLA and CP, although for aggressive periodontitis, HLA-A*09 and B*15 appeared to represent susceptibility factors, and HLA-A*02 and B*05 were potential protective factors

[65]. However, other studies provide evidence that class I and II HLA polymorphisms are associated with chronic periodontitis [66].

4.2. Pattern recognition receptors (PRRs)

PRRs play an important role in the recognition of periodontopathogens and genetic variations within the genes encoding them. They may have an important influence on immune response and in the pathogenesis of periodontal diseases [67].

TLR polymorphism may alter host susceptibility to periodontitis. The main studied polymorphism was related to *TLR4* gene because TLR-4 is responsible for LPS recognition. *TLR4* was associated with susceptibility of the periodontitis, although conflicting results are related [68]. *TLR2* and *TLR9* (except some TLR9 haplotypes) were not associated to CP development [69].

The *CD14* −159C>T and −260 C>T promoter polymorphisms are located upstream from the major transcriptional site, affecting the transcriptional activity and CD14 density. Individuals homozygous for the mutation have increased serum levels of soluble sCD14 and an increased density of CD14 in monocytes. Thus, patients without mutation lead to a reduced expression of the CD14 receptor and may be more susceptible to CP. No association of CD14 polymorphism and CP was found in a metaanalysis study [70].

Mannose-binding lectin (MBL) polymorphisms were also associated to the severity of CP. Therefore, it is possible to affirm that periodontitis susceptibility was partly controlled by PRR polymorphisms involved in the innate immunity [71].

4.3. Cytokines

4.3.1. IL1

The *IL1* genotypes appear to be the most studied genetic polymorphisms in CP. Associations between *IL1* family polymorphisms and CP were initially assessed by Kornman et al. [72]. The authors observed that the simultaneous occurrence of *IL1A* −889 and *IL1B* +3953 polymorphisms was associated with severe periodontitis in nonsmokers. To date, the following *IL1* genetic polymorphisms have been studied in association with CP: *IL1A* −889 (in linkage disequilibrium, LD, with +4845), *IL1B* −511 (in LD with −31), *IL1B* +3954 (also mentioned as +3953), and *IL1RN* VNTR (in LD with +2018). Different from others *IL1* SNPs, *IL1RN* VNTR variant-alleles seem to decrease gene transcription or the protein production levels. Taken altogether, the *IL1* gene cluster polymorphisms cannot be considered as risk factors for CP in the worldwide population. However, in Caucasians, an association between CP and *IL1A* −889 and *IL1B* +3953 mutate-allele may be genetic risk factors. The *IL1* promoter SNPs and periodontitis might reflect subpopulation effects and have to be interpreted with care [72–74].

4.3.2. TNF

Several case-control studies in both Caucasians and nonCaucasians have investigated genetic polymorphisms in the *TNF* gene as putative risk factors for periodontitis. SNPs in the gene

encoding *TNF* are mainly studied in the promoter region at positions 1031, 863, 857, 376, 308, and 238 and also in the first intron at position +489. *TNF* −308 G/A and A/A genotypes were associated with increased CP risk in Asians, Caucasians, and nonsmoking Asians [75].

4.3.3. IL6

The *IL6* −174G>C was found to influence IL-6 expression and production, and the individuals with carrier mutation present low *IL6* gene transcriptional activity and low plasma levels of IL-6. Thus, the polymorphism may hamper individual's defense against periodontal pathogens. Many studies had been found that *IL6* −174 polymorphism may be associated with CP susceptibility and *A. actinomycetemcomitans* infection. However, a metaanalysis that included this polymorphism did not show any association for this polymorphism with CP [76, 77].

4.3.4. IL17

Two *IL17* polymorphisms had been found associated to diseases: *IL17A* G197A (rs2275913) and *IL17F* T7488C (His161Arg, rs763780). The *IL17A* 197A allele correlates to more efficient IL-17 secretion and higher affinity for the nuclear factor activated T cells (NAFT), which is a critical regulator of the *IL17* promoter gene. IL-17F activity is similar to IL-17A, but weaker, and the variant form of IL-17 protein suppresses the expression and the activity of wild type. *IL17A* AA genotype and A allele were associated with worse clinical and inflammatory periodontal parameters. *IL17F* polymorphisms were not associated to CP [78].

4.3.5. IL10

Several promoter polymorphisms have been described in the *IL10* gene: −1087 (−1082), −819 (−824), −627, −592 (−597), and −590. There is strong linkage disequilibrium between *IL10* 1082G>A, 819C>T, and 592C>A, and they form two common haplotypes on the basis of *IL10* −592 polymorphism. The allele A of the −592 has been associated with decreased synthesis of IL-10 *in vitro* and *in vivo*, and when present could modify the synthesis of IL-10 in response to inflammation. IL-10 has a protective role toward periodontal tissue destruction; therefore, the *IL10* −592 polymorphism may be less protected against bacterial challenge and contribute to a relative increase in the risk for CP [79].

5. Conclusion

Chronic periodontitis is an inflammatory disease of the teeth-supporting tissues. The imbalance between periodontopathogens and host factors is responsible for the transition of gingivitis into periodontitis and is estimated that 50% of the expression of periodontitis could be attributed to genetic factors. The genetic polymorphisms may in some situations cause a change in the protein or its expression possibly resulting in alterations in innate and adaptive immunity and may thus be deterministic in disease outcome. Thus, development and regulation of the immune response influence disease progression or resolution, and each person may have an individual response to the bacterial challenge. Most individuals are

resistant to the disease and will not develop CP. The disease progression depends on the increased production of proinflammatory cytokines (IL-1α, IL-1β, IL-6, IL-8, and TNFα), metalloproteinases, and prostaglandins or decreased production of antiinflammatory cytokines (IL-10, TGFβ) and inhibitors of metalloproteinases. The knowledge of the immunopathogenesis mechanisms in the chronic periodontitis could contribute to new therapeutic approaches.

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