



Role of Lipids in the Etiopathogenesis of Periodontal Diseases

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Abstract

This review article summarizes current knowledge on the association between lipid metabolism and periodontal diseases as well as the role of lipids in the realization of the etiologic and metabolic role of periodontogenic bacteria in this process. Extremely high prevalence of infectious inflammatory periodontal diseases and their currently established impact on the development of systemic conditions is a prerequisite for this paper. The role of lipids as an important factor of the vital activity of micro- and macroorganisms is much addressed in published sources. However, a systemic approach (in particular, in clinical stomatology) is yet to be fully established. Meanwhile, the advances in molecular biology allow for better understanding of the mechanisms of lipid involvement in the development of the virulent properties of periodontogenic bacteria, the modulating the process of bioadhesion of these bacteria to the solid tissues of the oral cavity, their influence on the composition and ultrastructure of the original biofilm of the oral cavity, the specificity of the interaction between periodontitis causative agents and host cells, the regulation of inflammatory and immune processes, pathogenically relevant bone tissue resorption, and the development of systemic effects. As a result, this knowledge may be potentially applied for designing the innovative approaches to the evaluation of the diagnostic markers of pathological periodontal tissues, the treatment and prevention of periodontal diseases.

Keywords: Lipid metabolism; Periodontal disease; Periodontogenic bacteria; Systemic effects

Abbreviations: OMVs: Outer Membrane Vesicles; LPSs: Lipopolysaccharides; MHC: Major Histocompatibility Complex.

Introduction

Periodontal diseases are characterized by a complex etiopathogenesis and result from a number of factors which lead to periodontal tissue destruction, irreversible bone resorption, and tooth loss [1]. Periodontal diseases are common, i.e., severe periodontitis ranks 6th globally [2]. They have a significant impact on public health due to a high prevalence but are also related to many systemic disorders including diabetes, cardiovascular disorders (i.e., atherosclerosis) etc [3,4]. Given a global burden of periodontitis, the identification of novel therapeutic targets

for the treatment and prevention of periodontal diseases is an important issue [5].

Polymicrobial nature of periodontitis is currently recognized. Human inflammatory response has a crucial role in the development and progression of periodontitis thus forcing the researchers to focus on identifying the determinants of the local response to etiologically important bacteria and bacterial products [6]. Recent progress in microbial culture techniques allowed for the identification of about 250 bacterial and fungal species within the dental plaques which can more or less affect the development of periodontitis. The emergence of highly effective methods of molecular biology expanded this list to 750 species [7]. Despite such species diversity, most researchers agree that gram-negative anaerobic bacteria (e.g., Porphyromonas

gingivalis, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia*, *Treponema denticola*, *Fusobacterium nucleatum* etc.) are the leading etiology of periodontal tissue damage [8,9]. Either of these bacteria have a unique set of virulence factors whose interactions provide the synergism of the periodontogenic effect of emerging microbial associations [10].

Meanwhile, the involvement of general tissue metabolic changes and associated elevation of the levels of proinflammatory mediators (as factors determining the local response to pathogens) are clear. Considering this, systemic conditions related to the development and progression of periodontal diseases are of great interest [11,12].

Among systemic conditions associated with periodontal diseases, lipid metabolism disorders are particularly important [13,14] while hyperlipidemia as a risk factor for the inflammatory destruction of periodontal tissues is inferior only to smoking [15]. Meta-analysis of clinical trials has demonstrated that the development of periodontal diseases is largely associated with low blood levels of high-density lipoproteins and high levels of low-density lipoproteins and cholesterol. Hence, the status of periodontal tissues directly correlates with systemic lipid metabolism [16].

Since the mechanisms of the relationship between lipid metabolism and periodontal diseases as well as the etiologic and metabolic role of periodontogenic bacteria in this process are extensively studied in recent years, this paper aims to analyze the latest available data on this issue.

Lipids and Oral Biofilm Formation

Biofilm formation on the teeth and gingival mucosa is fundamental to periodontal diseases [17]. The first step is the formation of a pellicle which is largely composed of adsorbed proteins and other macromolecules of the oral cavity (saliva and gingival crevicular fluid) and is different in composition from the oral biofilm/dental plaque [18,19]. Pellicle is an acellular layer deposited on solid surfaces which are exposed to oral fluid. It is composed of proteins, glycoproteins, and lipids [20]. Lipids amount one quarter of the dry weight of pellicle and are likely to be of crucial importance for implementing its protective properties though very limited data are now available on the nature of pellicle lipids [17]. Thus, it is known that lipophilic components modulate bioadhesion to the solid tissues of the oral cavity and also the composition and ultrastructure of the initial biofilm of the oral cavity or pellicle, respectively. Lipids on tooth surface can provide pellicle with hydrophobic properties thus preventing bacterial colonization and ultimately reducing the susceptibility to caries. Lipid-enriched pellicle is more resistant to acids that can reduce mineral loss by erosion.

Lipids as fatty acids have anti-inflammatory effects on the soft tissues of the oral cavity [21]. Fatty acid profiles of pellicle samples obtained from various individuals are rather similar [20]. Pellicle contains eleven fatty acids, of them, palmitic (32%), stearic (21%), oleic (14%), erucic (10%), and linoleic (5%) acids are the most common ones [17]. Therefore, lipids are exactly the components which are responsible for the early steps of biofilm formation, i.e., its attachment to tooth surface or oral mucosa.

Classic biofilm life cycle involves several stages, i.e., bacterial attachment and microcolony formation, biofilm growth/maturation, and dispersion. In addition to microorganisms, biofilm contains multiple assemblies of extracellular polysaccharides which enmesh microorganisms to produce diffuse-modifying matrix. Biofilm matrix being a non-cleaved structure greatly affects the chemical and physical microenvironment and species composition of biofilm microbes [22]. Matrix formation is regulated by signaling molecules produced by biofilm bacteria [23]. Over the last decade, it was demonstrated that both structural and protective properties of biofilm matrix are accounted for by exopolysaccharides as well as glycolipids [24].

The role of lipid-containing structures when periodontogenic bacteria (primarily *P. gingivalis*) are integrated into the biofilm should be addressed. This phenomenon was described by Gui MG, et al. [25]. Many gram-negative bacteria are able to generate so-called "outer membrane vesicles" (OMVs), asymmetric single-layer membrane nanostructures containing virulence factors of these microbes (i.e., toxins or aggression enzymes). A pathogen distantly damage the surrounding bio-environment by releasing OMVs. The initial step of the integration of *P. gingivalis* into the biofilm is the production of OMVs containing gingipains (aggressive proteases) of these bacteria that easily surmount the biofilm due to their small sizes and contribute to the damage of periodontal tissues, the suppression of immune mechanisms, and the invasion of less virulent biofilm constituents before periodontogenic microbes reach epithelial barrier. The formation and separation of OMVs from a bacterial cell require special conditions since vesicle membrane curvature is 14-times greater than external bacterial membrane curvature. As a result, vesicle membrane synthesis requires much greater energy. *P. gingivalis* lipopolysaccharide deacetylation and its anionic fraction release account for greater curvature. The results are the generation of OMVs and the modulation of periodontogenic microbe properties (see below).

Lipids as Virulence Factors of Periodontogenic Bacteria

Porphyromonas gingivalis is the key periodontal

pathogen identified in the biofilm of the gingival sulcus. It is widely recognized that *P. gingivalis* can greatly affect the properties of the whole microbiome of this epitope and ultimately initiate the development of periodontal diseases [26]. These bacteria are among the pathogenic microbes which particularly affect the microecology of periodontal tissues and are a model for studying the etiopathogenesis of periodontal infectious inflammatory conditions [27]. One of the major virulence factors of *P. gingivalis* determining its involvement in periodontal disease pathogenesis and closely related to antibiotic resistance mechanisms are bacterial cell wall lipopolysaccharides (LPSs) [28,29].

LPS is a fundamental structural element of cell membrane of gram-negative bacteria which can induce host innate immune reactions. LPS is composed of three elements, i.e., O-antigen, core, and lipid A. O-antigen has a strain-, group-, type-, and variant-specific structure and consists of monosaccharide repeating units. Core includes keto-deoxy-octanoic acid, heptoses, and neutral saccharides (e.g., galactose). Lipid A is an endotoxin which contains two acylated residues of glucose-N-acetyl phosphate [30,31].

Lipid A is the most active biological component that provide LPS with the properties of endotoxin. Lipid A is composed of di-glucosamine with 1'- and 4'-phosphate residues and attached acyl chains [32,33]. Lipid A structure varies greatly among the species of gram-negative bacteria depending on the differences in the composition of attached fatty acids, the number of phosphorylation sites and replaced groups attached to phosphate residues [34]. However, *P. gingivalis* can deceptively change its lipid structure as a result of dephosphorylation or deacetylation to orchestrate host immune response and to promote chronic inflammation [34-36]. Among heterogeneous patterns of the acetylation of *P. gingivalis* lipid A, two variants are predominant, i.e., tetra-acylated and penta-acylated ones.

Hence, *P. gingivalis* can express two LPS isoforms, i.e., penta-acylated LPS1690 and tetra-acylated LPS1435/1449 which are generated via the changes in lipid A structure in different microecological conditions such as hemin level or culture temperature [35,37]. In fact, *Porphyromonas gingivalis* cannot produce hemin (which is an important factor of the increased virulence of these bacteria) that, therefore, should be received from the host. Meanwhile, *P. gingivalis* expresses several protein hemin-binding sites which are essential for hemin binding and transport from the host and also have an impact on the formation of lipid A structure [38].

It was demonstrated that LPS1690 and LPS1435/1449 of *P. gingivalis* differentially modulate host immune response, e.g., the expression of human β -defensin-2 with its antimicrobial properties, proinflammatory cytokines, and

E-selectin which determines leukocyte adhesion to vascular endothelium [36,38,39]. Thus, it was shown that LPS1690 of *P. gingivalis* can stimulate the expression of specific LPS-binding protein (LBP) by gingival epithelial cells while LPS1435/1449 of *P. gingivalis* lacks these properties [40,41].

LPS/LBP complex interacts with CD14 on monocytes via CD14-binding site. This results in the activation of Toll-like receptor (TLR) 4 [42]. Penta-acylated lipid structures (LPS1690) act as TLR4 agonists while tetra-acylated lipid structures (LPS1435/1449) act as TLR4 antagonists [36,43]. LPS/LBP complex can thereby modulate the expression of proinflammatory cytokines (IL-1, IL-6, and IL-8) by periodontal monocytes induced by various isoforms of *P. gingivalis* LPS [44]. Similar process occurs in gingival fibroblasts [38].

This mechanism is typical of the LPS of most gram-negative bacteria although various species of p-Periodontogenic bacteria are characterized by a different set of fatty acids within the lipid A. Thus, *A. actinomycetemcomitans* LPS contains predominantly myristic acid [45] while *F. nucleatum* lipid A contains hexa-acylated lipid A similar to that of *Escherichia coli* [46]. Structural differences in the LPS of periodontogenic bacteria account for a more potent stimulation of IL-1 β secretion under the effect of *F. nucleatum* LPS as compared with *P. gingivalis* LPS [47].

Meanwhile, unlike other periodontogenic bacteria, *P. gingivalis* LPS is also a potent activator of TLR2 [43]. The nature of this phenomenon was discovered recently. A unique fatty acidic component of *P. gingivalis* lipid A, phosphorylated dihydroceramides (sphingolipid derivatives), is characterized by this activity [48,49].

P. gingivalis synthesizes at least four major ceramides and two of them are selectively adsorbed on damaged tooth surfaces and can penetrate damaged gingival tissues [50]. In addition, these bacteria produce two serine lipids (lipid 654 and lipid 430) which play an important role as inflammatory reaction mediators both in periodontal tissues and other tissues accumulating these lipids [51].

P. gingivalis phosphorylated dihydroceramides are currently recognized to facilitate inflammatory reactions and fibroblast morphological changes [52]. These constituents are isolated from the gingival samples of the patients with manifest periodontitis [53]. Phosphorylated dihydroceramides as well as serine dipeptides of *P. gingivalis* interact with TLR2 and stimulate IL-6 production by dendritic cells [54], inhibit osteoblast functions and mineral deposition in bone tissue both *in vivo* and *in vitro* [55,56]. As a result, *P. gingivalis* contributes to bone tissue loss in experimental animals and modulates osteoclastogenesis

[57].

It was also demonstrated that the lack of sphingolipid synthesis in *P. gingivalis* leads to the reduced expression of cell-associated arginine- and lysine-gingipains and trypsin-like proteases as well capsule formation by this microbe [58,59].

Therefore, the lipids of periodontogenic bacteria (as well as other prokaryotes) are among their virulence factors. The lipids of most periodontogenic bacteria are endotoxins (lipid A) that can affect host immune system. Their toxic effects and the manner of their interaction with host immune system depend on microecological conditions. The structure of the lipid A of major periodontogenic bacteria can be changed depending on the presence of hemin and temperature. In these conditions, major periodontogenic bacteria demonstrate mainly proinflammatory properties and the ability to induce the resorption of the alveolar ridges of the jaws that results in tooth loss. Moreover, the variability of lipid A structure contributes to the chronicity of periodontal disease course. The production of the structurally different molecules of sphingolipids by major periodontogenic bacteria is less studied. Sphingolipids as virulence factors alter the course of inflammatory reactions, the functions of fibroblasts, osteoblasts, and immune cells, and the production of other virulence factors.

Lipids and the Mechanisms of Periodontogenic Bacteria to Invade Cells

When discussing the role of lipids in the pathogenesis of periodontal diseases, the mechanism of the interaction between periodontogenic bacteria and microorganism cells should be addressed. Thus, it is known that *P. gingivalis* being a key periodontogenic pathogen closely contacts and adheres to the epithelial cells of the periodontal pocket while *P. gingivalis* co-culturing with epithelial cells results in the ultrastructural thickening of fused membranes as *P. gingivalis* internalizes [60]. This contact allows for delivering bacterial lipids directly to the cellular membranes of host epithelial cells. Another mechanism of the invasion of bacterial lipids into cells can be seen under *P. gingivalis* interaction with fibroblasts: co-cultured bacterial lipids form lipid films which are ingested by human gingival fibroblasts [61]. *P. gingivalis* lipids are likely transported in gingival tissue cells either after a close contact with these bacteria or by chemical diffusion of contaminated lipids across the affected tooth surface. Any of these processes can result in the deposition of bacterial lipids in eukaryotic cell membranes thereby exposing cells (including their lipid rafts) to bacterial sphingolipids and serine dipeptide lipids [62].

Cross-contact between host cells and pathogens initiates

microbial interactions with signal transduction machinery of infected cells. The major interface of this machinery is lipid rafts [63] and their associated receptors. Lipid rafts are membrane microdomains enriched with cholesterol, sphingolipids, and glycosyl-phosphatidylinositol-anchoring proteins which separate the receptors for different intracellular signaling and transporting processes [64]. Lipid raft formation is related to the ability of sphingolipids and cholesterol to interact mainly with each other that results in their spontaneous separation from other phospholipids of cell membranes. In addition, cholesterol is believed to stabilize lipid rafts by filling the gaps between rather large glycosphingolipids [65].

Cholesterol-enriched membrane microdomains are involved in the induction of both innate and adaptive immunity [66,67]. Lipid rafts are the add-ons to host-pathogen interactions by functioning as the sites for the action of some periodontogenic bacterial toxins [68,69] and the entry of some intracellular pathogens [70]. Lipid rafts act as platforms for protein sorting and signal transduction [64].

P. gingivalis [63,70] and *A. actinomycetemcomitans* [71] are now recognized to penetrate the lipid rafts of the epithelial cells of periodontal tissues. Bacterial penetration through the lipid rafts has at least two advantages, i.e., the avoidance of intracellular degradation pathway (which results in bacterial degradation) and the induction of intracellular signaling (which results in reduced membrane density and cytoskeletal rearrangement required for bacterial penetration) [70]. Some authors report that internalized lipid rafts cannot easily fuse with lysosomes [72] while cholesterol exhaustion leads to increased *P. gingivalis* localization in association with lysosomes and further pathogen degradation [73].

The penetration of periodontogenic bacteria into epithelial cells through the lipid rafts not only affects the survival of these pathogens but also modulates the functions of epithelial cells. Lipid rafts orchestrate a number of epithelial cell functions, e.g., epithelial barrier function and fighting against bacterial invasion [72]. As demonstrated by the example of *A. actinomycetemcomitans*, human gingival epithelial cells exposed to the infection with this pathogen contribute to the increase in the levels of proinflammatory cytokines (IL-6 and IL-8) *in vitro* while TLR4 integration into lipid rafts is a trigger for this process [73].

The results of functional and visualized studies highlight the importance of macrophagic lipid rafts as engulfing and signaling platforms for *P. gingivalis* to facilitate its survival [74]. Recent data demonstrate that pathogenic microorganisms entering the macrophages through the lipid rafts are generally localized in autophagosomes [75]. However, these autophagosomes do not acquire cathepsins

required for their generation. As a result, *P. gingivalis* is able to reproduce in autophagosomes containing non-degraded material [76].

The ability to survive within the macrophages mainly accounts for the systemic effects of periodontogenic bacteria. The presence of alive *P. gingivalis* within the macrophages may be sufficient to allow this microbe for using the migratory potential of macrophages by providing their transfer to other tissues and the infection of other cells that are less resistant to invasion (e.g., endothelial cells). The hypothesis on macrophages as Trojan Horses for the systemic dissemination of *P. gingivalis* is important and should be further developed. Moreover, it was demonstrated that *P. gingivalis* can leave primarily infected host cells and enter new epithelial and endothelial cells to reproduce in them [77].

Therefore, a number of periodontogenic bacteria are intracellular parasites. This property helps penetrate epithelial barrier and migrate to distant organs and tissues by entering macrophages thus providing systemic effects. Periodontogenic bacteria penetrate into host cells through the lipid rafts. This process is largely mediated by sphingolipids produced by these bacteria. This lipid-dependent pathway of intracellular invasion largely promotes the survival of periodontogenic bacteria within the cells.

Lipid Components of Human Biological Media in Infectious Inflammatory Periodontal Diseases

Lipids are important molecules of the innate immunity in barrier tissues [78]. Thus, saliva contains many lipids including cholesterol, fatty acids, triglycerides, wax esters, cholesterol esters, and squalene. These lipids contribute to various cellular and immune processes including the transport of fat-soluble antioxidants to the mucosal surface and back, mucosal anti-inflammatory and antimicrobial properties [79,80].

Epithelial sphingolipids and short-chain fatty acids are contained in the saliva, corneum stratum of gingival and hard palate epithelium, and mucosal epithelium. These substances demonstrate antimicrobial activity against gram-positive and gram-negative bacteria. These lipids are thought to be the obligatory factors of the innate immune defense against the bacterial infections of barrier tissues [81].

Four potential mechanisms of the realization of the antimicrobial activity of fatty lipids and sphingolipids against bacteria are recognized: (1) membrane destruction mediated by detergent activity; (2) the inclusion of lipids

in a bacterial cytoplasmic membrane; (3) the transport of lipids across the bacterial membrane into cytosol; and (4) specific interactions between the lipids and proteins of the bacterial membrane. Fatty acids ultimately result in pore formation in bacterial cytoplasmic membranes, the changes in the structure and functions of cell membrane, cell lysis, and the alterations of various cellular processes either by the interference of the spatial arrangement of molecules or by direct binding with proteins [82]. Thus, bacterial cytoplasmic membranes are the key sites of the realization of lipid activity against *P. gingivalis* that is provided by the incorporation of antimicrobial lipids into these membranes [83].

It was demonstrated that lipid profile of periodontal tissues (as a fatty acid level) determines local inflammatory reactions in infectious inflammatory periodontal diseases [84]. It was shown experimentally that saturated fatty acids (e.g., palmitic acid), in contrast to unsaturated fatty acids, induce inflammatory reactions by stimulating the secretion of proinflammatory cytokines (IL-6 and IL-8) by gingival fibroblasts through the upregulation of surface CD36 as well as the resorption of the alveolar bone in obese mice infected with *P. gingivalis* or exposed to the LPS of *A. actinomycetemcomitans* [84-86].

Polyunsaturated (omega-3 and omega-6) fatty acids are the basis for the generation of one of the important classes of molecules regulating inflammation (lipid mediators, or eicosanoids) [87]. Arachidonic acid, eicosapentaenoic acid, and docosahexaenoic acid are the precursors for the biosynthesis of various lipid mediators [88]. These acids are either taken with meals [89] or generated from the phospholipids of cell membranes [90]. There are two pathways of lipid mediator synthesis, i.e., cyclooxygenase-mediated and lipoxygenase-mediated ones. These pathways were described 40 years ago and even then were studied with regard to oral disorders [91,92]. More recently, it was hypothesized that some lipid mediators related to oral disorders are the perspective markers of the risk factors of other systemic conditions [93].

The most clinically significant lipid mediators are leukotrienes, prostaglandins, lipoxins, and resolvins [94]. The elevated level of leukotriene B₄ in the gingival crevicular fluid clearly correlates with gingival inflammation, the indices of periodontal diseases, and the clinical signs of the loss of tooth attachment to the alveolar bone [95] as demonstrated by experimental studies [96].

Among prostaglandins, the relation with periodontal diseases was demonstrated primarily for prostaglandin E₂. Thus, prostaglandin E₂ produced by gingival fibroblasts [97] is associated with periodontal diseases and bone tissue loss. As a result, its inhibitors were recommended for

periodontitis treatment [98,99].

Lipoxin A4 was recognized as an immunomodulatory agent in periodontal diseases due to its ability to suppress leukocyte involvement in the inflammatory process caused by *Porphyromonas gingivalis* [100]. Recently, it was demonstrated that lipoxin A4 activates bone tissue regeneration in a pig model of periodontitis [101] and induces the proliferation and migration of human periodontal stem cells [102].

Resolvins are of particular interest. Resolvins are the metabolites of omega-3 polyunsaturated fatty acids which are produced in the course of the inflammatory response being predominant lipid mediators when inflammation resolves [103,104] by limiting the infiltration with leukocytes and the involvement of monocytes in inflammation [105,106]. These natural mediators of the resolution of inflammation actively contribute to tissue regeneration and bacterial clearance and enhance (but not inhibit) host defense mechanisms [107].

The analysis of phagocytic cells after resolvin D2 administration demonstrated the increase in circulating neutrophil number, however, neither migration nor accumulation in gingival tissues were observed [108]. This is in line with the observations implying that resolvins prevent the transmigration of these cells along the epithelium [109,110]. In contrast, monocyte count reduces while the levels in periodontal tissues increase. However, the phenotype of these macrophages was M2 (resident macrophages) that contributed to the resolution of inflammation [111]. Rapid termination of the local innate immune response and the ability of resolvin D2 to alter dendritic cell maturation via the downregulation of the expression of major histocompatibility complex (MHC) class II molecules account for the reduced efficacy of antigen presentation to CD4⁺ T cells under the effect of these lipid mediators [112]. This resolvin decreases the production of TNF- α and IFN- γ by stimulated human helper T cells (CD4⁺) and cytotoxic T cells (CD8⁺). It was also demonstrated that D-series resolvins play a crucial role in T cell differentiation by preventing the generation of activated Th1 and Th17 which induce inflammation and by boosting the differentiation of regulatory T cells which exhibit suppressor activity [113].

Experiments with small animals have demonstrated that the control of inflammation and adaptive immune response using resolvins contribute to the prevention and treatment of experimental periodontitis [114-116].

Therefore, periodontal lipids exhibit antimicrobial properties, prevent inflammation and bone resorption, and affect the immune status. Moreover, protective properties of some lipid mediators account for the strong efforts of their

potential use in the prevention and treatment for periodontal diseases.

Conclusion

The role of lipids as components of major periodontogenic bacteria, in the course of the interaction of periodontogenic bacteria with periodontal tissue cells, and as components of human biological media in infectious inflammatory periodontal diseases is clear being highly relevant in terms of pathogenicity. The structure of lipid A (endotoxin) and the ability of periodontogenic bacteria to synthesize sphingolipids with various geometry largely account for the severity of the proinflammatory action of these bacteria, their effects on bone resorption, the ability to produce other virulence factors and to determine infection chronicity.

Sphingolipids of periodontogenic bacteria largely determine how these microbes enter host cells (i.e., epithelial cells, fibroblasts, macrophages etc.) and the ability to migrate to distant organs and tissues. Intracellular invasion is mediated by sphingolipid integration into cell lipid rafts followed by pathogen survival within the endosomes that do not destroy bacteria. Host lipid metabolism largely determines the resistance to microbial invasion, the severity of inflammation, the type of immune reactions, and the ability of periodontal tissues to counteract their dysfunctions.

In conclusion, lipid metabolism in periodontogenic bacteria and host organism (both local and systemic ones) is important for the development and progression of periodontal diseases. More research in this area holds promise for the advances in clinical periodontology and the design of innovative preventive and therapeutic modalities for these common conditions that have systemic effects.

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