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REVIEWS

PERIODONTAL DISEASE ETIOLOGY. A REVIEW

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ABSTRACT

Periodontitis is a chronic inflammatory disease that is characterized by destruction of the tooth-supporting tissues, periodontal pocket formation, and ultimately, loss of teeth. The primary cause of periodontitis is bacteria in the dental biofilm. The development of effective treatment strategies is challenging due to the complex pathogenesis of the disease, which is best explained by a polymicrobial synergy and dysbiosis model.

Keywords: *periodontal disease etiology, Porphyromonas gingivalis, Treponema denticola, Tannerela forsythia, Aggregatibacter actinomycetemcomitans*

INTRODUCTION

Periodontal disease is a general term that refers to various conditions affecting the tissues surrounding the teeth. The most common types of disease triggered by the buildup of dental plaque biofilm are gingivitis and periodontitis (1). If left untreated, gingivitis can progress to periodontitis. While gingivitis is reversible and remains confined solely to the gingiva, periodontitis involves the destruction of the underlying bone and periodontal fibers (1).

In the 1970s, several studies showed that the bacterial composition of dental plaque varies between individuals, as well as between diseased and healthy sites in the same individual (2–6). This has prompted scientists to search for bacterial species or combinations of species whose presence in the dental biofilm is more strongly represented in cases of periodontal destruction.

At the World Workshop on Periodontology in 1996, three bacterial species were accepted as probable periodontopathogens: *Aggregatibacter actinomycetemcomitans (A.a.)*, *Porphyromonas gingivalis (P.g.)*, and *Tannerella forsythia (T.f.)* (7).

The introduction of molecular methods for bacterial identification (PCR, DNA hybridization, ELISA, etc.) greatly enhanced the potential for associative studies, as limitations related to culturing microorganisms were overcome (8).

The fundamental work of Socransky et al. in 1998 (9) led to the grouping of bacterial species from the dental biofilm into microbial complexes, which are color-coded according to their virulence and time of attachment. The red-complex bacteria (*Tannerella forsythia*, *Porphyromonas gingivalis* and *Treponema denticola*) were associated with increased clinical indicators for periodontitis, particularly pocket depth, and bleeding on probing. The study showed that microorganisms in dental plaque are not merely an accumulated mass of bacteria but they are highly organized with specific interactions between species.

Despite the association of Socransky's Red Complex with disease presence, it cannot be definitively determined whether this association is caus-

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al or correlative. The red complex constitutes a small portion of the total microorganisms in the oral cavity, and its presence is also found in individuals without periodontitis (10). This inconsistency is explained with the keystone-pathogen hypothesis (11) and polymicrobial synergy and dysbiosis (PSD) model (12), which encompass the current notion of periodontal disease etiology.

The keystone-pathogen hypothesis is a concept in microbiology and immunology that suggests that certain microbial pathogens, despite being present in relatively low abundance within a microbial community, can disproportionately influence the composition and behavior of the entire community, leading to disease (11,12).

Although bacteria in the tooth-associated biofilm play an essential role in initiating periodontitis, it is the host's inflammatory response to these bacteria, rather than the direct microbial action, that leads to periodontal tissue breakdown (13–17). Systemic host factors and behavioral factors, as well as genetics, can modify the host response and aggravate periodontal destruction, disease severity, and disease progression (18).

AIM

The current review aims to summarize the available data for the etiology of periodontitis.

MATERIALS AND METHODS

A search for publications between 1970 and June 2024 in the online database of Medline/PubMed and Google Scholar was conducted. After eliminating duplicates, 147 articles remained and were used as a basis for the present review.

RESULTS AND DISCUSSION

Chronic periodontitis is a polymicrobial disease that results from the overgrowth of a limited number of bacterial species that are normal members of the oral microbiota (19). It is widely accepted that *T. denticola*, *P. gingivalis*, and *T. forsythia* form a bacterial consortium, often referred to as the Red Complex, which is strongly associated with the clinical progression of chronic periodontitis (9,20,21). The levels of *P. gingivalis* and *T. denticola* in subgingival plaque have been shown to allow for prediction of periodontal breakdown in a longitudinal clinical trial (22). *A. actinomycetemcomitans* is strongly associated with the rapidly progressing forms of periodontitis (23–25).

While no single species has been implicated as the primary pathogen and the available evidence is consistent with a polymicrobial disease etiology, the red-complex bacteria consisting of *P. gingivalis*, *T. denticola,* and *T. forsythia* have been strongly implicated in the onset of periodontitis (9,15,26).

Red-Complex Bacteria

Porphyromonas gingivalis

Partly because *P. gingivalis* was the easiest of the red-complex bacteria to grow and genetically manipulate, it became the most widely studied periodontal bacterium (12).

Porphyromonas gingivalis is a non-motile, black-pigmented, asaccharolytic, Gram-negative microorganism that grows in anaerobic conditions in the presence of heme or hemin and vitamin K (27). It derives its necessary energy by metabolizing amino acids; an ability crucial for its survival in deep periodontal pockets, where carbohydrates are extremely scarce (27). The black pigmentation of *P. gingivalis* colonies on blood agar is due to the aggregation of heme on the bacterial surface (28, 29). There is a link between the presence of heme in the nutrient environment and the expression of virulence factors by *P. gingivalis*; in the absence of heme, its virulence decreases (30).

P. gingivalis actively invades gingival cells, where it maintains its vitality and ability to replicate (31, 32). It can also invade macrophages, but its replication is less active in them (33). Once *P. gingivalis* becomes intracellular, there are no signs of necrosis or apoptosis in the invaded cell (34). It is suggested that this is due to an ATP-hydrolyzing enzyme synthesized by *P. gingivalis*, which suppresses ATP-dependent apoptosis (35). Subsequently, *P. gingivalis* can spread from cell to cell via the actin cytoskeleton without causing cell death (36), simultaneously avoiding immune defense mechanisms (27).

To date, it has been established that *P. gingivalis* is not an aggressor regarding the inflammatory response but rather an opportunist that circumvents and undermines the host's defense mechanisms (27). A recent study found that *P. gingivalis* not only does

not stimulate an immune response but also has the ability to suppress immune reactions against other microorganisms, allowing for their (and its own) survival and replication (37).

P. gingivalis possesses several virulence factors that define its opportunistic nature and establish its role as a major periodontal pathogen (27). Some of these virulence factors are associated with changes in the systemic immune response, suggesting that *P. gingivalis* may be involved in various systemic diseases. This virulence factors include bacterial lypopolysacharide (LPS), capsule (CPS, also known as K-antigen), fimbriae, outer-membrane vesicles and bacterial enzymes (27). The latter include the gingipains and *Porphyromonas gingivalis* peptidylarginine deiminase (PPAD). The production of PPAD is a unique ability of *P. gingivalis* and a possible link between periodontitis and rheumatoid arthritis (RA) (38).

Unlike the endotoxin of other Gram-negative bacteria, lipid A from *P. gingivalis* LPS has a heterogeneous acylation pattern that varies with microenvironmental conditions and thus facilitates bacterial cell survival (39). Structural changes are hemin-dependent (39). Penta-acylated lipid A activates toll-like receptor 4 (TLR4), while tetra-acylated lipid A acts as an antagonist for TLR4 and thus modulates the immune response (40). *P. gingivalis* LPS exhibits controversial characteristics with respect to the induction of an inflammatory response by the macroorganism (27). It is a weaker cytokine activator compared to LPS of enteropathogenic origin (41). It may also act as an antagonist to cytokine stimulation by other putative pathogens (42, 43). The LPS of *P. gingivalis* induces the so-called chemokine paralysis; it blocks the secretion of the chemokine interleukin-8 (IL-8) from the gingival epithelial cells, which inhibits the activation of neutrophils, eosinophils, and basophils (44).

The presence of a capsule is associated with increased resistance to phagocytosis (44). On the other hand, encapsulated *P. gingivalis* strains are less efficient in terms of cell invasion than non-encapsulated ones (45). The K-antigen of *P. gingivalis* has the ability to modulate the immune response of the macroorganism to bacteria, reducing the synthesis of cytokines, in particular IL-1, IL-6, and IL-8, by fibroblasts (46).

P. gingivalis expresses two types of fimbriae on its cell surface – major and minor fimbriae (44). Major fimbriae play a leading role in colonization of the host and invasion of its cells (27). Minor fimbriae have pronounced proinflammatory properties (27). Both types of fimbriae have an activating effect on the production of cytokines (IL-1, IL-6, IL-8, TNF-α) and matrix metalloproteinases (MMPs), especially MMP-9 (27). *P. gingivalis* fimbriae have been suggested to play a role in the progression of atherosclerosis by influencing the activity of regulatory T-lymphocytes (Tregs) and triggering an autoimmune response (47). *P. gingivalis* fimbriae activate both TLR2 and TLR4 (27).

Outer membrane vesicles (OMVs) produced by *P. gingivalis* transport bacterial nucleic acids and signaling molecules to distant host organs (48). *P. gingivalis* OMVs can aggregate a wide range of microorganisms around them: *Streptococcus spp.*, *Fusobacterium nucleatum*, *T. denticola*, *Lachnoanaerobaculum saburreum*, *Actinomyces naeslundii,* and *Actinomyces viscosus* (48 – 50). They can also protect other bacterial species against complement actions, aiding the pathogenetic processes in periodontitis (48).

Gingipains are cysteine proteinases produced by *P. gingivalis* (27). They account for about 85% of the proteolytic activity of *P. gingivalis* (51). Gingipains cleave polypeptide chains at the C-terminal region after a lysine or arginine residue (44). Accordingly, they are divided into lysine-specific (Lys-X) and arginine-specific (Arg-X) (27). Arg-X gingipains are of two types – RgpA and RgpB (27). Lys-X gingipain is only one type and is designated as Kgp (27). Arg-X degrade extracellular matrix components (integrins, fibronectin), cytokines, immunoglobulins, and factors of the complement system (44). Both types of gingipains favor the growth of other periodontal pathogens such as *T. forsythi*a and *A. actinomycetemcomitans* (52,53).

Gingipains cleave the T-cell receptors CD2, CD4, and CD8, which impairs the cell-mediated immune response, and degrade anti-bacterial peptidases such as α-defensins and complement factors (C3 and C4) (52, 54). They stimulate the production of IL-6 by oral epithelial cells and IL-8 by gingival fibroblasts, which enhances the inflammatory response (27). At the same time, they can inactivate

both anti-inflammatory (IL-4, IL-5) and pro-inflammatory (IL-12, INF-γ) cytokines (27). Gingipains degrade fibrinogen and heme-containing proteins, which inhibits blood clotting, increases bleeding, and thus provides the hemin required for bacterial growth (44).

Tannerella forsythia

Tannerella forsythia was first isolated from advanced periodontal lesions in human oral cavities by Tanner et al. at the Forsyth Dental Center in Boston, MA, USA (55). *T. forsythia* is a Gram-negative nonmotile bacterium with filamentous cell morphology when grown with external supply of the essential cell wall sugar N-acetylmuramic acid (MurNAc) (56). Based on their metabolic activity, eight human-derived *T. forsythia* strains can be identified (57). The genome sequences of seven *T. forsythia* strains are available in public databases (55). Interestingly, a *Tannerella* species associated with periodontal health was described, and it is the closest phylogenetic relative of *T. forsythia* (58,59). *T. forsythia* is associated more frequently and/or in higher levels with disease, including gingivitis and periodontitis, than with health (15). Several studies have also implicated *T. forsythia* in the progression of clinical attachment loss associated with periodontitis (60–62).

Tannerella forsythia is a Gram-negative, asachrolytic rod (15). It exhibits a typical Gram-negative cell-membrane structure consisting of a cytoplasmic membrane, a periplasm and an outer membrane that contains lipopolysaccharide (63). The outer membrane of the bacterium is completely covered by a unique surface-layer (S-layer) (64).

Several virulence factors that likely contribute to the pathogenicity of *T. forsythia* have been identified (15). Among them: the bacterium S-layer (65,66), the outer membrane glycoprotein BspA (67,68), envelope lipoproteins (69), PrtH protease (70), glycosidases (15), lipopolysaccharide (26,63), and OMVs (71).

S-layers protect the bacterial cell and play a role in the maintenance of bacterial integrity, display of bacterial components and interaction with the host cells (72–74). Compared to other S-layer-carrying bacteria, *T. forsythia* is unique since it is the only Gram-negative bacterium that is known to possess a glycosylated S-layer comprising two glycosylated proteins instead of just one (64,75). The S-layer glycoproteins are the most abundant glycoproteins of *T. forsythia* (55).

It has been demonstrated that surface lipoproteins of *T. forsythia* activate host cells, prompting them to release proinflammatory cytokines and triggering cellular apoptosis (69). Additionally, it was found that lipoprotein fractions from *T. forsythia*, which contain ester-bound fatty acids, stimulate human gingival fibroblasts and monocytic cells to secrete IL-6 and tumor necrosis factor alpha (TNF-α) (69).

T. forsythia produces a cysteine proteinase (PrtH), initially identified as a forsythia detachment factor (FDF), because of its ability to detach cells from the substratum (15). PrtH also increases mitochondrial oxidative membrane potential, leading to IL-8 production from detached cells (15). It is implicated in the disintegration of gingival epithelium and IL-8 induction, potentially contributing to periodontal disease (15). Clinical studies have shown that the prtH genotype is associated with higher levels of *T. forsythia* and an increased risk of periodontitis, with baseline levels of prtH being lower in individuals without attachment loss compared to those who experienced attachment loss (70).

Despite its asaccharolytic nature, *T. forsythia* has been shown to express a variety of glycosidases (15). These glycosidases can hydrolyze terminal glycosidic linkages in complex oligosaccharides and proteoglycans abundantly found in saliva, gingival crevicular fluid and periodontal tissue (15). The degradation of host oligosaccharides and proteoglycans would affect the functional integrity of periodontium and may promote disease progression. It can also provide nutrients for other bacteria in the biofilm community (15).

T. forsythia OMVs contain a number of virulence factors and glycoproteins, and showed a concentration-dependent inflammatory response that was significantly higher than that caused by whole bacterial cells (71).

Stimulation of human macrophages with *T. forsythia* LPS resulted in the production of the proinflammatory cytokines IL-1, IL-6, and TNF-α in a dose-dependent manner (63). The response to *T. forsythia* LPS was observed only upon stimulation in the presence of fetal calf serum (FCS), whereas no

cytokine production was observed in the absence of FCS (63). This finding suggests that the presence of certain additional cofactors is necessary for the immune response induced by *T. forsythia* LPS.

Treponema denticola

Spirochetes comprise up to 50% of the polymicrobial population in subgingival plaque in periodontitis, and less than 1% in health (76). Only members of the genus *Treponema* have been found in the oral cavity (77). Among them *Treponema denticola* is the most commonly isolated and cultivable species (76). It is part of Socransky's red microbial complex (9).

T. denticola is a Gram-negative motile microorganism that requires essential elements such as iron, zinc and manganese for its survival (77). Its virulence factors include a chymotrypsin-like protease (dentilisin), plasmids, major sheath protein (Msp), OMVs.

T. denticola produces a chymotrypsin-like serine protease (dentilisin), which is expressed as a surface protein of the outer membrane and is able to degrade diverse substrates, including extracellular matrix proteins (ECM), immunoglobulins (IgA), α_1-antitrypsin, complement C3, bioactive peptides, cytokines (IL-1β, IL-6, and TNF-α) (78 – 82), suggesting involvement in bacterial adhesion, tissue penetration, and immune evasion. In vitro studies on *T. denticola* have revealed that its outer membrane (OM) dentilisin damages the intercellular contacts of oral epithelial cells, leading to the loss of desmosomes and a reduction in transepithelial electrical impedance and barrier function (76,83). Exposure of KB-cells to *T. denticola* results in the rapid depolymerization of cortical filamentous actin (F-actin), cell shrinkage, and the eventual detachment of portions of cells from the substratum (84). Outer membrane extracts of *T. denticola* contain dentilisin activity and cause depolymerization of F-actin in host cells (85). *T. denticola* is able to bind and degrade gingival epithelial proteoglycans and matrix proteins like laminin and fibronectin in cultures of human gingival fibroblasts (HGFs) (86, 87). Through its capacity to cause these unique cytopathic effects, the chymotrypsin-like proteinase of *T. denticola* has the potential to contribute to the initiation of periodontal disease (83).

T. denticola harbours plasmids, like pTSI, and is able to transfer DNA between itself and other *Treponema* species (88). It had also been found that genetic transfer is possible between *T. denticola* and members of other genus like the mitis group streptococci and *S. gordonii* in particular (89). This probably allows *T. denticola*, like other spirochetes, to adapt to the host environment and evade host immune responses through intragenomic recombination (77).

The Msp is the most abundant protein in the *T. denticola* outer membrane (19). It is one of the immunodominant *T. denticola* antigens recognized by human serum antibodies (90). It mediates colonization of host tissues and has cytopathic pore-forming activity against cultured epithelial cells (91). Interaction of host cells with *T. denticola* Msp causes actin remodeling and reorganization, which leads to impaired neutrophil chemotaxis and phagocytic activity (92–96).

T. denticola OMVs have been proposed as a long-range virulence factor that can penetrate tissues more readily than the bacterium itself (97–99).

Cell-surface components, especially proteins, act as the sensors and effectors of interactions with the host and other bacteria and are largely the targets of the host adaptive immune response. One of the unifying features of the red-complex bacteria, which are responsible for chronic periodontitis progression, is their high levels of extracellular proteolytic activity that is mediated by cell-surface-located proteases (19).

Aggregatibacter actinomycetemcomitans

Aggregatibacter actinomycetemcomitans (formerly known as *Actinobacillus actinomycetemcomitans*) has been associated for decades with the rapidly progressing forms of periodontitis (23, 25). It is also implicated in some severe non-oral infections (25, 100). *A.a.* is part of the HACEK group (*Haemophilus* and *Aggregatibacter spp.*, *A. actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens,* and *Kingella kingae*), and is associated with systemic diseases, especially endocarditis (100–102).

A. actinomycetemcomitans is a facultative anaerobic Gram-negative coccobacillus (103). It forms two types of colonies, depending on the presence or absence of fimbriae: colonies with star-shaped interior (star-positive) for the fimbriated strains and star-

negative for the non-fimbriated strains, respectively (103). *A.a.* has seven serotypes (a, b, c, d, e, f, and g), depending on its LPS O-antigen structural characteristics (23,25,103). The virulence potential of *A.a.* varies among strains (25,104). Serotypes a, b, and c are the most commonly found in the oral cavity (105). A specific clone of serotype b, the JP2 clone, known for its high leukotoxic activity (104), is primarily linked to cases of localized rapidly progressing forms of periodontitis (24, 106–108). In contrast, serotype c is frequently detected in healthy individuals (105). *A.a.* can be transmitted from one individual to another (108). It possesses an array of virulence factors, including: leukotoxin (LtxA), cytolethal distending toxin (CDT), LPS, and OMVs (109).

A. actinomycetemcomitans can invade epithelial cells and increase the production of pro-inflammatory cytokines TNF-α, IL-1β, IL-6, and IL-8, as well as cell apoptosis (110, 111).

The *A.a.* leukotoxin is considered a primary virulence factor in some forms of periodontitis (previously known as localized juvenile periodontitis) (107). The LtxA triggers neutrophil degranulation, leading to the massive release of lysosomal enzymes, net-like structures, and MMPs; and also induces apoptosis in lymphocytes (112–114).

The CDT family comprises a number of bacterial protein exotoxins that is expressed by several Gram-negative species (109). *A. actinomycetemcomitans* is the only oral species to date known for expressing CDT. Approximately 66% to 86% of its strains produce CDT, which is associated with periodontal disease (115). The pathogenic effects of *A.a.* CDT are likely linked to its ability to induce DNA damage, cell cycle arrest, and apoptosis in affected cells (115). These effects have been observed in structural cells such as gingival fibroblasts and periodontal ligament cells (116,117), gingival epithelial cells (111,118–120), and gingival tissue explants (119).

Dental plaque bacteria exist as part of a complex, structured multispecies biofilm in the relatively protected region of the gingival crevice or periodontal pocket, which is largely protected from the shear forces associated with salivary flow and the effects of mastication (19). The red-complex bacteria tend to inhabit the deeper periodontal pockets and are late colonizers of the subgingival plaque (121). Treponemes, including *T. denticola*, are located on the surface of the dense subgingival bacterial biofilm, at the interface of the biofilm and the gingival epithelium (122–124). *T. denticola* has been shown to bind specifically to both *P. gingivalis* and *T. forsythia* with similar avidity, which may explain the close association of the species (19).

T. denticola and *P. gingivalis* display symbiosis in protein degradation, nutrient utilization, and growth promotion (123,125–127). When grown together in continuous culture, *P.g.* and *T.d.* bind to each other and develop a stable cell ratio of 6:1, respectively, as determined by real-time PCR (19). This indicates that they do not directly compete under specific growth conditions. It has been shown that *T.d.* and *P.g.* synergistically hydrolyze fibrinogen, thereby promoting vascular disruption, bleeding, and inflammation and retarding tissue repair (128).

P. gingivalis can bind specifically to *S. Gordonii*. This interaction is mediated by the minor fimbriae which bind with discrete domains on the streptococcal surface proteins (12–131). The *P. gingivalis-S.gordonii* communities exhibit mutualistic growth (132). In mice co-aggregates of *P.g.* and *S.g.* induce greater alveolar bone loss compared with either species alone, while interference with *P. gingivalis-S. gordonii* binding abrogates bone loss (133). This underlines the importance of coadhesion and subsequent signaling in the development of a pathogenic community.

It has been demonstrated that co-culture of *A.a.* with *S. gordonii* enhances the pathogenicity of *A.a.* in a mouse abscess model (134).

Although traditionally seen as commensals, some studies have shown a higher proportion of *S. gordonii* in the subgingival biofilm of periodontitis subjects compared with healthy individuals (135). Organisms such as the mitis group streptococci, whose pathogenic potential only becomes evident in the context of a heterotypic microbial community, are considered accessory pathogens (136).

A number of studies have illustrated that both eukaryotic and prokaryotic viruses within subgingival plaque and periodontal tissues affect the putative periodontopathogens and the host immune response (137–146), and suggest implication on periodontitis onset. In addition, the microbial ecology of the oral cavity is shaped by the omnipresence of

bacteriophages (147). Understanding the variety of mechanisms that bacteriophages have evolved to infect their bacterial hosts suggests that bacteriophages potentially play a role in the microbial dysbiosis and immune dysregulation that occurs in periodontitis (147).

CONCLUSION

Periodontitis is a complex disease resulting from the interplay of microbial and host-related factors. The primary etiological agents of periodontal disease are pathogenic microorganisms in dental plaque. Plaque biofilms consist of a diverse microbial community, with certain bacteria playing pivotal roles in disease progression. Additionally, factors that change the oral ecosystem or modify the host immune response can trigger disease onset or aggravate present disease. A comprehensive understanding of periodontal disease etiology and pathogenetic mechanisms is essential for developing targeted prevention and treatment strategies.

Future research should focus on elucidating the precise mechanisms, through which all contributing factors interact, and identifying potential therapeutic targets to mitigate disease progression.

REFERENCES

1. Abdulkareem AA, Al-Taweel FB, Al-Sharqi AJB, Gul SS, Sha A, Chapple ILC. Current concepts in the pathogenesis of periodontitis: from symbiosis to dysbiosis. J Oral Microbiol. 2023 Apr 2;15(1):2197779. doi: 10.1080/20002297.2023.2197779.
2. Newman MG, Socransky SS, Savitt ED, Propas DA, Crawford A. Studies of the microbiology of periodontosis. J Periodontol. 1976 Jul;47(7):373-9. doi: 10.1902/jop.1976.47.7.373.
3. Newman MG, Socransky SS. Predominant cultivable microbiota in periodontosis. J Periodontal Res. 1977 Mar;12(2):120-8. doi: 10.1111/j.1600-0765.1977.tb00114.x.
4. Slots J. The predominant cultivable organisms in juvenile periodontitis. Scand J Dent Res. 1976 Jan;84(1):1-10. doi: 10.1111/j.1600-0722.1976.tb00454.x.
5. Slots J. The predominant cultivable microflora of advanced periodontitis. Scand J Dent Res. 1977 Jan-Feb;85(2):114-21. doi: 10.1111/j.1600-0722.1977.tb00541.x.
6. Tanner AC, Haffer C, Bratthall GT, Visconti RA, Socransky SS. A study of the bacteria associated with advancing periodontitis in man. J Clin Periodontol. 1979 Oct;6(5):278-307. doi: 10.1111/j.1600-051x.1979.tb01931.x.
7. Consensus report. Periodontal diseases: pathogenesis and microbial factors. Ann Periodontol. 1996 Nov;1(1):926-32. doi: 10.1902/annals.1996.1.1.926.
8. Slots J, Bragd L, Wikström M, Dahlén G. The occurrence of Actinobacillus actinomycetemcomitans, Bacteroides gingivalis and Bacteroides intermedius in destructive periodontal disease in adults. J Clin Periodontol. 1986 Jul;13(6):570-7. doi: 10.1111/j.1600-051x.1986.tb00849.x.
9. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr. Microbial complexes in subgingival plaque. J Clin Periodontol. 1998 Feb;25(2):134-44. doi: 10.1111/j.1600-051x.1998.tb02419.x.
10. Hajishengallis G, Liang S, Payne MA, Hashim A, Jotwani R, Eskan MA, et al. Low-abundance biofilm species orchestrates inflammatory periodontal disease through the commensal microbiota and complement. Cell Host Microbe. 2011 Nov 17;10(5):497-506. doi: 10.1016/j.chom.2011.10.006.
11. Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. Nat Rev Microbiol. 2012 Oct;10(10):717-25. doi: 10.1038/nrmicro2873.
12. Hajishengallis G, Lamont RJ. Beyond the red complex and into more complexity: the polymicrobial synergy and dysbiosis (PSD) model of periodontal disease etiology. Mol Oral Microbiol. 2012 Dec;27(6):409-19. doi: 10.1111/j.2041-1014.2012.00663.x.
13. Hajishengallis G. Complement and periodontitis. Biochem Pharmacol. 2010 Dec 15;80(12):1992-2001. doi: 10.1016/j.bcp.2010.06.017.
14. Graves D. Cytokines that promote periodontal tissue destruction. J Periodontol. 2008 Aug;79(8 Suppl):1585-91. doi: 10.1902/jop.2008.080183.
15. Sharma A. Virulence mechanisms of Tannerella forsythia. Periodontol 2000. 2010 Oct;54(1):106-16. doi: 10.1111/j.1600-0757.2009.00332.x.
16. Gaffen SL, Hajishengallis G. A new inflammatory cytokine on the block: re-thinking periodontal disease and the Th1/Th2 paradigm in the context of Th17 cells and IL-17. J Dent Res. 2008 Sep;87(9):817-28. doi: 10.1177/154405910808700908.
17. Graves D. Cytokines that promote periodontal tissue destruction. J Periodontol. 2008 Aug;79(8 Suppl):1585-91. doi: 10.1902/jop.2008.080183.
18. Tonetti MS, Greenwell H, Kornman KS. Staging and grading of periodontitis: Framework and proposal of a new classification and case definition. J Clin Periodontol. 2018 Jun;45 Suppl 20:S149-S161. doi: 10.1111/jcpe.12945.
19. Dashper SG, Seers CA, Tan KH, Reynolds EC. Virulence factors of the oral spirochete Treponema denticola. J Dent Res. 2011 Jun;90(6):691-703. doi: 10.1177/0022034510385242.

20. Holt SC, Ebersole JL. Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia: the "red complex", a prototype polybacterial pathogenic consortium in periodontitis. Periodontol 2000. 2005;38:72-122. doi: 10.1111/j.1600-0757.2005.00113.x.

21. Lamont RJ, Jenkinson HF. Life below the gum line: pathogenic mechanisms of Porphyromonas gingivalis. Microbiol Mol Biol Rev. 1998 Dec;62(4):1244-63. doi: 10.1128/MMBR.62.4.1244-1263.1998.

22. Byrne SJ, Dashper SG, Darby IB, Adams GG, Hoffmann B, Reynolds EC. Progression of chronic periodontitis can be predicted by the levels of Porphyromonas gingivalis and Treponema denticola in subgingival plaque. Oral Microbiol Immunol. 2009 Dec;24(6):469-77. doi: 10.1111/j.1399-302X.2009.00544.x.

23. Haubek D, Johansson A. Pathogenicity of the highly leukotoxic JP2 clone of Aggregatibacter actinomycetemcomitans and its geographic dissemination and role in aggressive periodontitis. J Oral Microbiol. 2014 Aug 14;6. doi: 10.3402/jom.v6.23980.

24. Haubek D, Poulsen K, Westergaard J, Dahlèn G, Kilian M. Highly toxic clone of Actinobacillus actinomycetemcomitans in geographically widespread cases of juvenile periodontitis in adolescents of African origin. J Clin Microbiol. 1996 Jun;34(6):1576-8. doi: 10.1128/jcm.34.6.1576-1578.1996.

25. Åberg CH, Kelk P, Johansson A. Aggregatibacter actinomycetemcomitans: virulence of its leukotoxin and association with aggressive periodontitis. Virulence. 2015;6(3):188-95. doi: 10.4161/21505594.2014.982428.

26. Bodet C, Chandad F, Grenier D. Inflammatory responses of a macrophage/epithelial cell co-culture model to mono and mixed infections with Porphyromonas gingivalis, Treponema denticola, and Tannerella forsythia. Microbes Infect. 2006 Jan;8(1):27-35. doi: 10.1016/j.micinf.2005.05.015.

27. Bostanci N, Belibasakis GN. Porphyromonas gingivalis: an invasive and evasive opportunistic oral pathogen. FEMS Microbiol Lett. 2012 Aug;333(1):1-9. doi: 10.1111/j.1574-6968.2012.02579.x.

28. Liu X, Sroka A, Potempa J, Genco CA. Coordinate expression of the Porphyromonas gingivalis lysine-specific gingipain proteinase, Kgp, arginine-specific gingipain proteinase, RgpA, and the heme/hemoglobin receptor, HmuR. Biol Chem. 2004 Nov;385(11):1049-57. doi: 10.1515/BC.2004.136.

29. Smalley JW, Birss AJ, Szmigielski B, Potempa J. The HA2 haemagglutinin domain of the lysine-specific gingipain (Kgp) of Porphyromonas gingivalis promotes micro-oxo bishaem formation from monomeric iron(III) protoporphyrin IX. Microbiology (Reading). 2006 Jun;152(Pt 6):1839-1845. doi: 10.1099/mic.0.28835-0.

30. McKee AS, McDermid AS, Baskerville A, Dowsett AB, Ellwood DC, Marsh PD. Effect of hemin on the physiology and virulence of Bacteroides gingivalis W50. Infect Immun. 1986 May;52(2):349-55. doi: 10.1128/iai.52.2.349-355.1986.

31. Belton CM, Izutsu KT, Goodwin PC, Park Y, Lamont RJ. Fluorescence image analysis of the association between Porphyromonas gingivalis and gingival epithelial cells. Cell Microbiol. 1999 Nov;1(3):215-23. doi: 10.1046/j.1462-5822.1999.00022.x.

32. Tribble GD, Mao S, James CE, Lamont RJ. A Porphyromonas gingivalis haloacid dehalogenase family phosphatase interacts with human phosphoproteins and is important for invasion. Proc Natl Acad Sci U S A. 2006 Jul 18;103(29):11027-32. doi: 10.1073/pnas.0509813103.

33. Grenier D, Mayrand D. Functional characterization of extracellular vesicles produced by Bacteroides gingivalis. Infect Immun. 1987 Jan;55(1):111-7. doi: 10.1128/iai.55.1.111-117.1987.

34. Nakhjiri SF, Park Y, Yilmaz O, Chung WO, Watanabe K, El-Sabaeny A, et al. Inhibition of epithelial cell apoptosis by Porphyromonas gingivalis. FEMS Microbiol Lett. 2001 Jun 25;200(2):145-9. doi: 10.1111/j.1574-6968.2001.tb10706.x.

35. Yilmaz O, Yao L, Maeda K, Rose TM, Lewis EL, Duman M, et al. ATP scavenging by the intracellular pathogen Porphyromonas gingivalis inhibits P2X7-mediated host-cell apoptosis. Cell Microbiol. 2008 Apr;10(4):863-75. doi: 10.1111/j.1462-5822.2007.01089.x.

36. Yilmaz O, Verbeke P, Lamont RJ, Ojcius DM. Intercellular spreading of Porphyromonas gingivalis infection in primary gingival epithelial cells. Infect Immun. 2006 Jan;74(1):703-10. doi: 10.1128/IAI.74.1.703-710.2006.

37. Abdi K, Chen T, Klein BA, Tai AK, Coursen J, Liu X, et al. Mechanisms by which Porphyromonas gingivalis evades innate immunity. PLoS One. 2017 Aug 3;12(8):e0182164. doi: 10.1371/journal.pone.0182164..

38. Goulas T, Mizgalska D, Garcia-Ferrer I, Kantyka T, Guevara T, Szmigielski B, et al. Structure and mechanism of a bacterial host-protein citrullinating virulence factor, Porphyromonas gingivalis peptidylarginine deiminase. Sci Rep. 2015 Jul 1;5:11969. doi: 10.1038/srep11969.

39. Al-Qutub MN, Braham PH, Karimi-Naser LM, Liu X, Genco CA, Darveau RP. Hemin-dependent modulation of the lipid A structure of Porphyromonas gingivalis lipopolysaccharide. Infect Immun. 2006 Aug;74(8):4474-85. doi: 10.1128/IAI.01924-05.

40. Darveau RP, Pham TT, Lemley K, Reife RA, Bainbridge BW, Coats SR, et al. Porphyromonas gingivalis lipopolysaccharide contains multiple lipid A species that functionally interact with both toll-like receptors 2 and 4. Infect Immun. 2004 Sep;72(9):5041-51. doi: 10.1128/IAI.72.9.5041-5051.2004.

41. Liu R, Desta T, Raptis M, Darveau RP, Graves DT. P. gingivalis and E. coli lipopolysaccharides exhibit different systemic but similar local induction of inflammatory markers. J Periodontol. 2008 Jul;79(7):1241-7. doi: 10.1902/jop.2008.070575.

42. Bostanci N, Allaker RP, Belibasakis GN, Rangarajan M, Curtis MA, Hughes FJ, et al. Porphyromonas gingivalis antagonises Campylobacter rectus induced cytokine production by human monocytes. Cytokine. 2007 Aug;39(2):147-56. doi: 10.1016/j.cyto.2007.07.002.

43. Bostanci N, Allaker R, Johansson U, Rangarajan M, Curtis MA, Hughes FJ, et al. Interleukin-1alpha stimulation in monocytes by periodontal bacteria: antagonistic effects of Porphyromonas gingivalis. Oral Microbiol Immunol. 2007b Feb;22(1):52-60. doi: 10.1111/j.1399-302X.2007.00322.x.

44. How KY, Song KP, Chan KG. Porphyromonas gingivalis: An Overview of Periodontopathic Pathogen below the Gum Line. Front Microbiol. 2016 Feb 9;7:53. doi: 10.3389/fmicb.2016.00053.

45. Irshad M, van der Reijden WA, Crielaard W, Laine ML. In vitro invasion and survival of Porphyromonas gingivalis in gingival fibroblasts; role of the capsule. Arch Immunol Ther Exp (Warsz). 2012 Dec;60(6):469-76. doi: 10.1007/s00005-012-0196-8.

46. Brunner J, Scheres N, El Idrissi NB, Deng DM, Laine ML, van Winkelhoff AJ, et al. The capsule of Porphyromonas gingivalis reduces the immune response of human gingival fibroblasts. BMC Microbiol. 2010 Jan 11;10:5. doi: 10.1186/1471-2180-10-5.

47. Yang J, Wu J, Liu Y, Huang J, Lu Z, Xie L, et al. Porphyromonas gingivalis infection reduces regulatory T cells in infected atherosclerosis patients. PLoS One. 2014 Jan 23;9(1):e86599. doi: 10.1371/journal.pone.0086599.

48. Okamura H, Hirota K, Yoshida K, Weng Y, He Y, Shiotsu N, et al. Outer membrane vesicles of Porphyromonas gingivalis: Novel communication tool and strategy. Jpn Dent Sci Rev. 2021 Nov;57:138-146. doi: 10.1016/j.jdsr.2021.07.003.

49. Kamaguchi A, Nakayama K, Ichiyama S, Nakamura R, Watanabe T, Ohta M, et al. Effect of Porphyromonas gingivalis vesicles on coaggregation of Staphylococcus aureus to oral microorganisms. Curr Microbiol 2003;47:485–91.

50. Grenier D. Porphyromonas gingivalis outer membrane vesicles mediate coaggregation and piggybacking of Treponema denticola and Lachnoanaerobaculum saburreum. Int J Dent. 2013;2013:305476.

51. de Diego I, Veillard F, Sztukowska MN, Guevara T, Potempa B, Pomowski A, et al. Structure and mechanism of cysteine peptidase gingipain K (Kgp), a major virulence factor of Porphyromonas gingivalis in periodontitis. J Biol Chem. 2014 Nov 14;289(46):32291-302. doi: 10.1074/jbc.M114.602052.

52. Bao K, Belibasakis GN, Thurnheer T, Aduse-Opoku J, Curtis MA, Bostanci N. Role of Porphyromonas gingivalis gingipains in multi-species biofilm formation. BMC Microbiol. 2014 Oct 2;14:258. doi: 10.1186/s12866-014-0258-7.

53. Haraguchi A, Miura M, Fujise O, Hamachi T, Nishimura F. Porphyromonas gingivalis gingipain is involved in the detachment and aggregation of Aggregatibacter actinomycetemcomitans biofilm. Mol Oral Microbiol. 2014 Jun;29(3):131-43. doi: 10.1111/omi.12051.

54. Hajishengallis G, Abe T, Maekawa T, Hajishengallis E, Lambris JD. Role of complement in host-microbe homeostasis of the periodontium. Semin Immunol. 2013 Feb;25(1):65-72. doi: 10.1016/j.smim.2013.04.004.

55. Bloch S, Tomek MB, Friedrich V, Messner P, Schäffer C. Nonulosonic acids contribute to the pathogenicity of the oral bacterium Tannerella forsythia. Interface Focus. 2019 Apr 6;9(2):20180064. doi: 10.1098/rsfs.2018.0064.

56. Wyss C. Dependence of proliferation of Bacteroides forsythus on exogenous N-acetylmuramic acid. Infect Immun. 1989 Jun;57(6):1757-9. doi: 10.1128/iai.57.6.1757-1759.1989.

57. Braham PH, Moncla BJ. Rapid presumptive identification and further characterization of Bacteroides forsythus. J Clin Microbiol. 1992 Mar;30(3):649-54. doi: 10.1128/jcm.30.3.649-654.1992.

58. Beall CJ, Campbell AG, Dayeh DM, Griffen AL, Podar M, Leys EJ. Single cell genomics of uncultured, health-associated Tannerella BU063 (Oral Taxon 286) and comparison to the closely related pathogen Tannerella forsythia. PLoS One. 2014 Feb 14;9(2):e89398. doi: 10.1371/journal.pone.0089398.

59. Frey AM, Ansbro K, Kamble NS, Pham TK, Stafford GP. Characterisation and pure culture of putative health-associated oral bacterium BU063 (Tannerella sp. HOT-286) reveals presence of a potentially novel glycosylated S-layer. FEMS Microbiol Lett. 2018 Sep 1;365(17). doi: 10.1093/femsle/fny180.

60. Grossi SG, Zambon JJ, Ho AW, Koch G, Dunford RG, Machtei EE, et al. Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. J Periodontol. 1994 Mar;65(3):260-7. doi: 10.1902/jop.1994.65.3.260.

61. Grossi SG, Genco RJ, Machtei EE, Ho AW, Koch G, Dunford R, et al. Assessment of risk for periodontal disease. II. Risk indicators for alveolar bone loss. J Periodontol. 1995 Jan;66(1):23-9. doi: 10.1902/jop.1995.66.1.23.

62. Tanner A, Maiden MF, Macuch PJ, Murray LL, Kent RL Jr. Microbiota of health, gingivitis, and initial periodontitis. J Clin Periodontol. 1998 Feb;25(2):85-98. doi: 10.1111/j.1600-051x.1998.tb02414.x.

63. Posch G, Andrukhov O, Vinogradov E, Lindner B, Messner P, Holst O, et al. Structure and immunogenicity of the rough-type lipopolysaccharide from the periodontal pathogen Tannerella forsythia. Clin Vaccine Immunol. 2013 Jun;20(6):945-53. doi: 10.1128/CVI.00139-13.

64. Sekot G, Posch G, Oh YJ, Zayni S, Mayer HF, Pum D, et al. Analysis of the cell surface layer ultrastructure of the oral pathogen Tannerella forsythia. Arch Microbiol. 2012 Jun;194(6):525-39. doi: 10.1007/s00203-012-0792-3.

65. Sakakibara J, Nagano K, Murakami Y, Higuchi N, Nakamura H, Shimozato K, et al. Loss of adherence ability to human gingival epithelial cells in S-layer protein-deficient mutants of Tannerella forsythensis. Microbiology (Reading). 2007 Mar;153(Pt 3):866-876. doi: 10.1099/mic.0.29275-0.

66. Sekot G, Posch G, Messner P, Matejka M, Rausch-Fan X, Andrukhov O, et al. Potential of the Tannerella forsythia S-layer to delay the immune response. J Dent Res. 2011 Jan;90(1):109-14. doi: 10.1177/0022034510384622.

67. Onishi S, Honma K, Liang S, Stathopoulou P, Kinane D, Hajishengallis G, et al. Toll-like receptor 2-mediated interleukin-8 expression in gingival epithelial cells by the Tannerella forsythia leucine-rich repeat protein BspA. Infect Immun. 2008 Jan;76(1):198-205. doi: 10.1128/IAI.01139-07.

68. Sharma A, Sojar HT, Glurich I, Honma K, Kuramitsu HK, Genco RJ. Cloning, expression, and sequencing of a cell surface antigen containing a leucine-rich repeat motif from Bacteroides forsythus ATCC 43037. Infect Immun. 1998 Dec;66(12):5703-10. doi: 10.1128/IAI.66.12.5703-5710.1998.

69. Hasebe A, Yoshimura A, Into T, Kataoka H, Tanaka S, Arakawa S, et al. Biological activities of Bacteroides forsythus lipoproteins and their possible pathological roles in periodontal disease. Infect Immun. 2004 Mar;72(3):1318-25. doi: 10.1128/IAI.72.3.1318-1325.2004.

70. Hamlet SM, Ganashan N, Cullinan MP, Westerman B, Palmer JE, Seymour GJ. A 5-year longitudinal study of Tannerella forsythia prtH genotype: association with loss of attachment. J Periodontol. 2008 Jan;79(1):144-9. doi: 10.1902/jop.2008.070228.

71. Friedrich V, Gruber C, Nimeth I, Pabinger S, Sekot G, Posch G, et al. Outer membrane vesicles of Tannerella forsythia: biogenesis, composition, and virulence. Mol Oral Microbiol. 2015 Dec;30(6):451-73. doi: 10.1111/omi.12104.

72. Sára M, Sleytr UB. S-Layer proteins. J Bacteriol. 2000 Feb;182(4):859-68. doi: 10.1128/JB.182.4.859-868.2000.

73. Sleytr UB, Schuster B, Egelseer EM, Pum D. S-layers: principles and applications. FEMS Microbiol Rev. 2014 Sep;38(5):823-64. doi: 10.1111/1574-6976.12063.

74. Fagan RP, Fairweather NF. Biogenesis and functions of bacterial S-layers. Nat Rev Microbiol. 2014 Mar;12(3):211-22. doi: 10.1038/nrmicro3213.

75. Sekot G, Schuster D, Messner P, Pum D, Peterlik H, Schäffer C. Small-angle X-ray scattering for imaging of surface layers on intact bacteria in the native environment. J Bacteriol. 2013 May;195(10):2408-14. doi: 10.1128/JB.02164-12.

76. Ellen RP. Perturbation and exploitation of host cell cytoskeleton by periodontal pathogens. Microbes Infect. 1999 Jul;1(8):621-32. doi: 10.1016/s1286-4579(99)80062-8.

77. Visser MB, Ellen RP. New insights into the emerging role of oral spirochaetes in periodontal disease. Clin Microbiol Infect. 2011 Apr;17(4):502-12. doi: 10.1111/j.1469-0691.2011.03460.x.

78. Mäkinen PL, Mäkinen KK, Syed SA. Role of the chymotrypsin-like membrane-associated proteinase from Treponema denticola ATCC 35405 in inactivation of bioactive peptides. Infect Immun. 1995 Sep;63(9):3567-75. doi: 10.1128/iai.63.9.3567-3575.1995.

79. Miyamoto M, Ishihara K, Okuda K. The Treponema denticola surface protease dentilisin degrades interleukin-1 beta (IL-1 beta), IL-6, and tumor necrosis factor alpha. Infect Immun. 2006 Apr;74(4):2462-7. doi: 10.1128/IAI.74.4.2462-2467.2006.

80. Uitto VJ, Grenier D, Chan EC, McBride BC. Isolation of a chymotrypsinlike enzyme from Treponema denticola. Infect Immun. 1988 Oct;56(10):2717-22. doi: 10.1128/iai.56.10.2717-2722.1988.

81. Yamazaki T, Miyamoto M, Yamada S, Okuda K, Ishihara K. Surface protease of Treponema denticola hydrolyzes C3 and influences function of polymorphonuclear leukocytes. Microbes Infect. 2006 Jun;8(7):1758-63. doi: 10.1016/j.micinf.2006.02.013.

82. Miao D, Fenno JC, Timm JC, Joo NE, Kapila YL. The Treponema denticola chymotrypsin-like protease dentilisin induces matrix metalloproteinase-2-dependent fibronectin fragmentation in periodontal ligament cells. Infect Immun. 2011 Feb;79(2):806-11. doi: 10.1128/IAI.01001-10.

83. Uitto VJ, Pan YM, Leung WK, Larjava H, Ellen RP, Finlay BB, McBride BC. Cytopathic effects of Treponema denticola chymotrypsin-like proteinase on migrating and stratified epithelial cells. Infect Immun. 1995 Sep;63(9):3401-10. doi: 10.1128/iai.63.9.3401-3410.1995.

84. De Filippo AB, Ellen RP, McCulloch CA. Induction of cytoskeletal rearrangements and loss of volume regulation in epithelial cells by Treponema denticola. Arch Oral Biol. 1995 Mar;40(3):199-207. doi: 10.1016/0003-9969(95)98809-d.

85. Yang PF, Song M, Grove DA, Ellen RP. Filamentous actin disruption and diminished inositol phosphate response in gingival fibroblasts caused by Treponema denticola.

Infect Immun. 1998 Feb;66(2):696-702. doi: 10.1128/IAI.66.2.696-702.1998.

86. Ellen RP, Song M, McCulloch CA. Degradation of endogenous plasma membrane fibronectin concomitant with Treponema denticola 35405 adhesion to gingival fibroblasts. Infect Immun. 1994 Jul;62(7):3033-7. doi: 10.1128/iai.62.7.3033-3037.1994.

87. Grenier D, Uitto VJ, McBride BC. Cellular location of a Treponema denticola chymotrypsinlike protease and importance of the protease in migration through the basement membrane. Infect Immun. 1990 Feb;58(2):347-51. doi: 10.1128/iai.58.2.347-351.1990.

88. Chan EC, Klitorinos A, Gharbia S, Caudry SD, Rahal MD, Siboo R. Characterization of a 4.2-kb plasmid isolated from periodontopathic spirochetes. Oral Microbiol Immunol. 1996 Oct;11(5):365-8. doi: 10.1111/j.1399-302x.1996.tb00196.x.

89. Wang BY, Chi B, Kuramitsu HK. Genetic exchange between Treponema denticola and Streptococcus gordonii in biofilms. Oral Microbiol Immunol. 2002 Apr;17(2):108-12. doi: 10.1046/j.0902-0055.2001.00001.x.

90. Capone R, Wang HT, Ning Y, Sweier DG, Lopatin DE, Fenno JC. Human serum antibodies recognize Treponema denticola Msp and PrtP protease complex proteins. Oral Microbiol Immunol. 2008 Apr;23(2):165-9. doi: 10.1111/j.1399-302X.2007.00404.x.

91. Fenno JC, McBride BC. Virulence factors of oral treponemes. Anaerobe. 1998 Feb;4(1):1-17. doi: 10.1006/anae.1997.0131.

92. Batista da Silva AP, Lee W, Bajenova E, McCulloch CA, Ellen RP. The major outer sheath protein of Treponema denticola inhibits the binding step of collagen phagocytosis in fibroblasts. Cell Microbiol. 2004 May;6(5):485-98. doi: 10.1111/j.1462-5822.2004.00377.x.

93. Puthengady Thomas B, Sun CX, Bajenova E, Ellen RP, Glogauer M. Modulation of human neutrophil functions in vitro by Treponema denticola major outer sheath protein. Infect Immun. 2006 Mar;74(3):1954-7. doi: 10.1128/IAI.74.3.1954-1957.2006.

94. Amin M, Grove DA, Kapus A, Glogauer M, Ellen RP. An actin-stabilizing peptide conjugate deduced from the major outer sheath protein of the bacterium Treponema denticola. Cell Motil Cytoskeleton. 2007 Sep;64(9):662-74. doi: 10.1002/cm.20213.

95. Jobin MC, Virdee I, McCulloch CA, Ellen RP. Activation of MAPK in fibroblasts by Treponema denticola major outer sheath protein. Biochem Biophys Res Commun. 2007 Apr 27;356(1):213-8. doi: 10.1016/j.bbrc.2007.02.111.

96. Magalhães MA, Sun CX, Glogauer M, Ellen RP. The major outer sheath protein of Treponema denticola selectively inhibits Rac1 activation in murine neutrophils. Cell Microbiol. 2008 Feb;10(2):344-54. doi: 10.1111/j.1462-5822.2007.01045.x.

97. Cimasoni G, McBride BC. Adherence of Treponema denticola to modified hydroxyapatite. J Dent Res. 1987 Dec;66(12):1727-9. doi: 10.1177/00220345870660120601.

98. Kuehn MJ, Kesty NC. Bacterial outer membrane vesicles and the host-pathogen interaction. Genes Dev. 2005 Nov 15;19(22):2645-55. doi: 10.1101/gad.1299905.

99. Weinberg A, Holt SC. Chemical and biological activities of a 64-kilodalton outer sheath protein from Treponema denticola strains. J Bacteriol. 1991 Nov;173(21):6935-47. doi: 10.1128/jb.173.21.6935-6947.1991.

100. Herbert BA, Novince CM, Kirkwood KL. Aggregatibacter actinomycetemcomitans, a potent immunoregulator of the periodontal host defense system and alveolar bone homeostasis. Mol Oral Microbiol. 2016 Jun;31(3):207-27. doi: 10.1111/omi.12119.

101. Nørskov-Lauritsen N. Classification, identification, and clinical significance of Haemophilus and Aggregatibacter species with host specificity for humans. Clin Microbiol Rev. 2014 Apr;27(2):214-40. doi: 10.1128/CMR.00103-13.

102. Vega BA, Belinka BA Jr, Kachlany SC. Aggregatibacter actinomycetemcomitans Leukotoxin (LtxA; Leukothera®): Mechanisms of Action and Therapeutic Applications. Toxins (Basel). 2019 Aug 26;11(9):489. doi: 10.3390/toxins11090489.

103. Raja M, Ummer F, Dhivakar CP. Aggregatibacter actinomycetemcomitans - a tooth killer? J Clin Diagn Res. 2014 Aug;8(8):ZE13-6. doi: 10.7860/JCDR/2014/9845.4766.

104. Brogan JM, Lally ET, Poulsen K, Kilian M, Demuth DR. Regulation of Actinobacillus actinomycetemcomitans leukotoxin expression: analysis of the promoter regions of leukotoxic and minimally leukotoxic strains. Infect Immun. 1994 Feb;62(2):501-8. doi: 10.1128/iai.62.2.501-508.1994.

105. Zambon JJ, Christersson LA, Slots J. Actinobacillus actinomycetemcomitans in human periodontal disease. Prevalence in patient groups and distribution of biotypes and serotypes within families. J Periodontol. 1983 Dec;54(12):707-11. doi: 10.1902/jop.1983.54.12.707.

106. Haubek D, Dirienzo JM, Tinoco EM, Westergaard J, López NJ, Chung CP, et al. Racial tropism of a highly toxic clone of Actinobacillus actinomycetemcomitans associated with juvenile periodontitis. J Clin Microbiol. 1997 Dec;35(12):3037-42. doi: 10.1128/jcm.35.12.3037-3042.1997.

107. Bueno LC, Mayer MP, DiRienzo JM. Relationship between conversion of localized juvenile periodontitis-susceptible children from health to disease and Actinobacillus actinomycetemcomitans leukotoxin promoter structure. J Periodontol. 1998 Sep;69(9):998-1007. doi: 10.1902/jop.1998.69.9.998.

108. DiRienzo JM, Slots J, Sixou M, Sol MA, Harmon R, McKay TL. Specific genetic variants of Actinobacillus

actinomycetemcomitans correlate with disease and health in a regional population of families with localized juvenile periodontitis. Infect Immun. 1994 Aug;62(8):3058-65. doi: 10.1128/iai.62.8.3058-3065.1994.

109. Belibasakis GN, Maula T, Bao K, Lindholm M, Bostanci N, Oscarsson J, et al. Virulence and Pathogenicity Properties of Aggregatibacter actinomycetemcomitans. Pathogens. 2019 Nov 6;8(4):222. doi: 10.3390/pathogens8040222.

110. Dickinson BC, Moffatt CE, Hagerty D, Whitmore SE, Brown TA, Graves DT, et al. Interaction of oral bacteria with gingival epithelial cell multilayers. Mol Oral Microbiol. 2011 Jun;26(3):210-20. doi: 10.1111/j.2041-1014.2011.00609.x.

111. Alaoui-El-Azher M, Mans JJ, Baker HV, Chen C, Progulske-Fox A, Lamont RJ, et al. Role of the ATM-checkpoint kinase 2 pathway in CDT-mediated apoptosis of gingival epithelial cells. PLoS One. 2010 Jul 23;5(7):e11714. doi: 10.1371/journal.pone.0011714.

112. Claesson R, Johansson A, Belibasakis G, Hänström L, Kalfas S. Release and activation of matrix metalloproteinase 8 from human neutrophils triggered by the leukotoxin of Actinobacillus actinomycetemcomitans. J Periodontal Res. 2002 Oct;37(5):353-9. doi: 10.1034/j.1600-0765.2002.00365.x.

113. Johansson A, Claesson R, Hänström L, Sandström G, Kalfas S. Polymorphonuclear leukocyte degranulation induced by leukotoxin from Actinobacillus actinomycetemcomitans. J Periodontal Res. 2000 Apr;35(2):85-92. doi: 10.1034/j.1600-0765.2000.035002085.x.

114. Hirschfeld J, Roberts HM, Chapple IL, Parčina M, Jepsen S, Johansson A, et al. Effects of Aggregatibacter actinomycetemcomitans leukotoxin on neutrophil migration and extracellular trap formation. J Oral Microbiol. 2016 Nov 8;8:33070. doi: 10.3402/jom.v8.33070.

115. Faïs T, Delmas J, Serres A, Bonnet R, Dalmasso G. Impact of CDT Toxin on Human Diseases. Toxins (Basel). 2016 Jul 15;8(7):220. doi: 10.3390/toxins8070220.

116. Belibasakis G, Johansson A, Wang Y, Claesson R, Chen C, Asikainen S, et al. Inhibited proliferation of human periodontal ligament cells and gingival fibroblasts by Actinobacillus actinomycetemcomitans: involvement of the cytolethal distending toxin. Eur J Oral Sci. 2002 Oct;110(5):366-73. doi: 10.1034/j.1600-0722.2002.21350.x.

117. Belibasakis GN, Mattsson A, Wang Y, Chen C, Johansson A. Cell cycle arrest of human gingival fibroblasts and periodontal ligament cells by Actinobacillus actinomycetemcomitans: involvement of the cytolethal distending toxin. APMIS. 2004 Oct;112(10):674-85. doi: 10.1111/j.1600-0463.2004.apm1121006.x.

118. Kang P, Korostoff J, Volgina A, Grzesik W, DiRienzo JM. Differential effect of the cytolethal distending toxin of Actinobacillus actinomycetemcomitans on co-cultures of human oral cells. J Med Microbiol. 2005 Aug;54(Pt 8):785-794. doi: 10.1099/jmm.0.46077-0.

119. Damek-Poprawa M, Haris M, Volgina A, Korostoff J, DiRienzo JM. Cytolethal distending toxin damages the oral epithelium of gingival explants. J Dent Res. 2011 Jul;90(7):874-9. doi: 10.1177/0022034511403743.

120. Kanno F, Korostoff J, Volgina A, DiRienzo JM. Resistance of human periodontal ligament fibroblasts to the cytolethal distending toxin of Actinobacillus actinomycetemcomitans. J Periodontol. 2005 Jul;76(7):1189-201. doi: 10.1902/jop.2005.76.7.1189.

121. Kolenbrander PE, Andersen RN, Blehert DS, Egland PG, Foster JS, Palmer RJ Jr. Communication among oral bacteria. Microbiol Mol Biol Rev. 2002 Sep;66(3):486-505, table of contents. doi: 10.1128/MMBR.66.3.486-505.2002.

122. Zijnge V, van Leeuwen MB, Degener JE, Abbas F, Thurnheer T, Gmür R, et al. Oral biofilm architecture on natural teeth. PLoS One. 2010 Feb 24;5(2):e9321. doi: 10.1371/journal.pone.0009321.

123. Kigure T, Saito A, Seida K, Yamada S, Ishihara K, Okuda K. Distribution of Porphyromonas gingivalis and Treponema denticola in human subgingival plaque at different periodontal pocket depths examined by immunohistochemical methods. J Periodontal Res. 1995 Sep;30(5):332-41. doi: 10.1111/j.1600-0765.1995.tb01284.x.

124. Ellen RP, Galimanas VB. Spirochetes at the forefront of periodontal infections. Periodontol 2000. 2005;38:13-32. doi: 10.1111/j.1600-0757.2005.00108.x.

125. Grenier D. Nutritional interactions between two suspected periodontopathogens, Treponema denticola and Porphyromonas gingivalis. Infect Immun. 1992 Dec;60(12):5298-301. doi: 10.1128/iai.60.12.5298-5301.1992.

126. Nilius AM, Spencer SC, Simonson LG. Stimulation of in vitro growth of Treponema denticola by extracellular growth factors produced by Porphyromonas gingivalis. J Dent Res. 1993 Jun;72(6):1027-31. doi: 10.1177/00220345930720060601.

127. Yoneda M, Yoshikane T, Motooka N, Yamada K, Hisama K, Naito T, et al. Stimulation of growth of Porphyromonas gingivalis by cell extracts from Tannerella forsythia. J Periodontal Res. 2005 Apr;40(2):105-9. doi: 10.1111/j.1600-0765.2005.00774.x.

128. Bamford CV, Fenno JC, Jenkinson HF, Dymock D. The chymotrypsin-like protease complex of Treponema denticola ATCC 35405 mediates fibrinogen adherence and degradation. Infect Immun. 2007 Sep;75(9):4364-72. doi: 10.1128/IAI.00258-07.

129. Demuth DR, Irvine DC, Costerton JW, Cook GS, Lamont RJ. Discrete protein determinant directs the species-specific adherence of Porphyromonas gingivalis to oral streptococci. Infect Immun. 2001 Sep;69(9):5736-41. doi: 10.1128/IAI.69.9.5736-5741.2001.

130. Park Y, Simionato MR, Sekiya K, Murakami Y, James D, Chen W, et al. Short fimbriae of Porphyromonas gingivalis and their role in coadhesion with Streptococcus gordonii. Infect Immun. 2005 Jul;73(7):3983-9. doi: 10.1128/IAI.73.7.3983-3989.2005.

131. Daep CA, Lamont RJ, Demuth DR. Interaction of Porphyromonas gingivalis with oral streptococci requires a motif that resembles the eukaryotic nuclear receptor box protein-protein interaction domain. Infect Immun. 2008 Jul;76(7):3273-80. doi: 10.1128/IAI.00366-08.

132. Periasamy S, Kolenbrander PE. Mutualistic biofilm communities develop with Porphyromonas gingivalis and initial, early, and late colonizers of enamel. J Bacteriol. 2009 Nov;191(22):6804-11. doi: 10.1128/JB.01006-09.

133. Daep CA, Novak EA, Lamont RJ, Demuth DR. Structural dissection and in vivo effectiveness of a peptide inhibitor of Porphyromonas gingivalis adherence to Streptococcus gordonii. Infect Immun. 2011 Jan;79(1):67-74. doi: 10.1128/IAI.00361-10.

134. Ramsey MM, Rumbaugh KP, Whiteley M. Metabolite cross-feeding enhances virulence in a model polymicrobial infection. PLoS Pathog. 2011 Mar;7(3):e1002012. doi: 10.1371/journal.ppat.1002012.

135. Abiko Y, Sato T, Mayanagi G, Takahashi N. Profiling of subgingival plaque biofilm microflora from periodontally healthy subjects and from subjects with periodontitis using quantitative real-time PCR. J Periodontal Res. 2010 Jun;45(3):389-95. doi: 10.1111/j.1600-0765.2009.01250.x.

136. Whitmore SE, Lamont RJ. The pathogenic persona of community-associated oral streptococci. Mol Microbiol. 2011 Jul;81(2):305-14. doi: 10.1111/j.1365-2958.2011.07707.x.

137. Saygun I, Kubar A, Ozdemir A, Slots J. Periodontitis lesions are a source of salivary cytomegalovirus and Epstein-Barr virus. J Periodontal Res. 2005 Apr;40(2):187-91. doi: 10.1111/j.1600-0765.2005.00790.x.

138. Khosropanah H, Karandish M, Ziaeyan M, Jamalidoust M. Quantification of Epstein-Barr Virus and Human Cytomegalovirus in Chronic Periodontal Patients. Jundishapur J Microbiol. 2015 Jun 30;8(6):e18691. doi: 10.5812/jjm.8(5)2015.18691.

139. Klemenc P, Skaleric U, Artnik B, Nograsek P, Marin J. Prevalence of some herpesviruses in gingival crevicular fluid. J Clin Virol. 2005 Oct;34(2):147-52. doi: 10.1016/j.jcv.2005.03.001.

140. Shah R, Mehta DS. Prevalence of herpesviruses in gingivitis and chronic periodontitis: relationship to clinical parameters and effect of treatment. J Indian Soc Periodontol. 2016 May-Jun;20(3):279-85. doi: 10.4103/0972-124X.179896.

141. Saygun I, Kubar A, Sahin S, Sener K, Slots J. Quantitative analysis of association between herpesviruses and bacterial pathogens in periodontitis. J Periodontal Res. 2008 Jun;43(3):352-9. doi: 10.1111/j.1600-0765.2007.01043.x.

142. Slots J, Kamma JJ, Sugar C. The herpesvirus-Porphyromonas gingivalis-periodontitis axis. J Periodontal Res. 2003 Jun;38(3):318-23. doi: 10.1034/j.1600-0765.2003.00659.x.

143. Kato A, Imai K, Sato H, Ogata Y. Prevalence of Epstein-Barr virus DNA and Porphyromonas gingivalis in Japanese peri-implantitis patients. BMC Oral Health. 2017 Dec 12;17(1):148. doi: 10.1186/s12903-017-0438-6.

144. Vincent-Bugnas S, Vitale S, Mouline CC, Khaali W, Charbit Y, Mahler P, et al. EBV infection is common in gingival epithelial cells of the periodontium and worsens during chronic periodontitis. PLoS One. 2013 Dec 19;8(12):e80336. doi: 10.1371/journal.pone.0080336.

145. Kato A, Imai K, Ochiai K, Ogata Y. Prevalence and quantitative analysis of Epstein-Barr virus DNA and Porphyromonas gingivalis associated with Japanese chronic periodontitis patients. Clin Oral Investig. 2015 Sep;19(7):1605-10. doi: 10.1007/s00784-014-1387-y.

146. Kato A, Imai K, Ochiai K, Ogata Y. Higher prevalence of Epstein-Barr virus DNA in deeper periodontal pockets of chronic periodontitis in Japanese patients. PLoS One. 2013 Aug 26;8(8):e71990. doi: 10.1371/journal.pone.0071990.

147. Martínez A, Kuraji R, Kapila YL. The human oral virome: Shedding light on the dark matter. Periodontol 2000. 2021 Oct;87(1):282-298. doi: 10.1111/prd.12396.