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Pathobionts in Periodontitis-Reshaping Disease Progression and New Treatment Avenues

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Abstract: ***The increase in knowledge about alterations in microbial communities that reside within the host has made a strong impact on our understanding of several diseases. Periodontitis is a multi-factorial polymicrobial disease associated with dysbiosis. Dysbiosis is largely dependent on cooperative and competitive interactions among oral microbes. Recent studies elucidate the roles of individual oral bacteria, including a new type of pathobionts that possess strong immuno-stimulatory activity, which is critical for alveolar bone loss. Better understanding of the roles of oral pathobionts is expected to lead to a better understanding of periodontitis disease and to the development of novel preventive and therapeutic approaches for the disease.***

Keywords: Commensal bacteria; Alveolar bone resorption; Microbe; Plaque hypothesis.

1. Introduction

An emerging concept is the relationship between dysbiosis (microbiota imbalance) and disease. Past studies on infectious diseases have focused vastly on pathogenic microbes that directly damage tissues in the host. However, evidence is gathering that another set of microbes can also induce disease or aid critically to disease progress. These microbes live as normal residents on the skin and internal cavities and are called commensals [1]. Among them, a particular group of commensals can cause or promote disease and these commensals are often called pathobionts. The concept "pathobiont" includes some opportunistic pathogens that live as commensals in healthy hosts but can cause disease in susceptible hosts (e.g., immunodeficient individuals). The overgrowth of pathobionts is often triggered by immunodeficiency, pathogen infection and treatment with antibiotics and host-damaging drugs [1].

Periodontitis is one of the most well-characterized human diseases associated with dysbiosis [2]. "Red complex" bacteria that include *Porphyromonas gingivalis* (Pg), *Tannerella forsythia,* and *Treponema denticola* are already associated with the disease [3] Non-culture-based studies further identified *Filifactor alocis,* unnamed Treponema, Prevotella, Selenomonas, Peptostreptococcus, Anaeroglobus and Desulfobulbus spp., unclassified Lachnospiraceae, Synergistetes and TM7 species as the dominant bacterial species associated with periodontitis development [4].

Red complex bacteria possess high levels of protein-degrading activity that is largely mediated by proteases including gingipains (from Pg), PrtH (*T. forsythia*) and dentilisin (*T. denticola*) and these bacterial proteases appear to be important for virulence [5]. Accumulation of red complex bacteria is supported by other oral commensals that physically and metabolically interact with red complex bacteria. These include streptococci, the pioneer colonizers on the surfaces of host epithelium and tooth, and Fusobacteria, which interact with red complex and other bacteria to facilitate the formation of a more complex microbial community at anaerobic periodontal pockets [6].

Colonization of Pg also contributes to dysbiosis by interfering with the complement-mediated immune system [7] which led to the hypothesis that keystone bacteria such as Pg trigger dysbiosis and the alteration of host immune responses and that other bacteria orchestrate inflammatory disease [8]. *Aggregatibacter actinomycetemcomitans* (Aa) is another bacterium which is tightly, but not completely associated with a particular form of periodontitis called aggressive periodontitis [9]. Aa JP2 strains secrete high levels of leukotoxin, an RTX-type toxin that damages host cells [10]. Therefore, both chronic and aggressive periodontitis are associated with bacteria that damage host soft tissues that is critical for the development of alveolar bone loss.

Dysbiosis in periodontitis development is dependent on metabolic and physical interactions and competitive toxicity among oral bacteria. For example, red complex bacteria are obligate anaerobes and many in the periodontitis-associated non-red complex are obligate anaerobes or microaerobes. Therefore, anaerobic growth conditions are required for the accumulation of red complex bacteria. The genomes of Pg (W83, ATCC 33277, and TDC60; GenBank accession NC_002950, NC_015571 and NC_010729, respectively) and T. forsythia ATCC 43037 (GenBank accession NC_016610) lack several orthologues of E. coli heme biosynthesis genes [11]. Therefore, growth of these bacteria requires exogenous heme. Potential sources of heme are other bacteria that synthesize heme and this might be one of the reasons why Pg and T. forsythia are dependent on other oral bacteria for growth. However, Pg also possesses the ability to sense and recover heme from host tissues, suggesting that another source of heme in vivo is potentially the host [12]. Metabolomic analysis showed that there are increased amounts of amino acids and other digested macromolecules in oral fluid from periodontitis patients [13] suggesting that bacteria can commonly share energy sources produced by red complex and other bacteria. Conversely, these common nutritional sources are competitively used by several bacteria for their growth.

Red complex bacteria possess several proteins which interact with other bacteria. For example, biofilm-forming *Streptococcus gordonii* produce SspB to bind the minor fimbrial Mfa1 protein of Pg in addition to the interaction

between the major fimbrial FimA protein of Pg and S. Gordonii GAPDH, which facilitates Pg colonization and Pg-induced alveolar bone loss [14]. Furthermore, hemagglutinin A (HagA) and gingipains mediate the interaction of Pg with T. denticola [15]. Importantly, intra-bacterial interactions can modify bacteria/host interactions. For example, in vitro studies showed that *S. gordonii* provides H_2O_2 to enhance the expression of ApiA in Aa [16]. *F. nucleatum* possesses FadA, which can mediate its interaction with host epithelial cells and facilitates the penetration of non-invasive bacteria into endothelial cell layers in vitro [17] suggesting that intra-bacterial interactions are potentially important for immuno-stimulation by non-invasive oral bacteria.

In an effort to identify probiotics, bacteriocins produced by oral resident and non-resident bacteria, including *Lactobacillus paracasei* HL32 and *Bacillus amyloliquefacien*s, were found to inhibit Pg growth [18]. These studies suggest a potential mechanism of dysbiosis through the production of bacteriocins. Notably, bacteriocins from *S. salivarius* are effective in the treatment of the oral bacterial species involved in halitosis [19]. Bacteriocin from *Prevotella nigrescens* is bactericidal against *P. gingivalis*, but bacteriocin from *P. intermedia* is not [20]. Further analysis is required for the role of bacteriocins in the regulation of intra-species interactions and dysbiosis in the oral cavity to be understood.

A proposed model for the role of immuno-stimulatory pathobionts in periodontitis

Accumulating evidence is mounting suggesting that host immune responses to oral bacteria mediate alveolar bone loss in periodontitis. Complement, phagocytosis, iNOS-mediated immune responses and production of antigen-specific immunoglobulin (IGs) protect hosts from translocated harmful bacteria. Meanwhile, alveolar bone resorption by increased osteoclast differentiation and activation is triggered by two types of pathobionts. Many pathobionts, including red complex bacteria subvert the host immune system and/or are immunosuppressive. Red complex pathobionts damage the epithelial tissue through the production of high protease activity which allows for the translocation of immuno-stimulatory bacterial molecules into tissues. *P. gingivalis* gingipain proteases also inactivate the complement system by cleaving C3 and C5. NOD1 ligands produced by specific pathobionts are released from bacteria and function as immuno-stimulants away from bacteria to cause alveolar bone loss at damaged gingival sites. NOD1 ligands possess the ability to recruit neutrophils which secrete inflammatory cytokines such as TNF and IL-1 to alter the RANKL/osteoprotegerin (OPG) expression balance in activated T- (actT), B-cells and osteoblasts. Neutrophils and other phagocytic cells also express innate immune receptors such as Toll-like receptor 2 (TLR2) and complement C3a and C5a receptors (C3aR and C5aR) at high levels. C3aR and C5aR also mediate recruitment of the phagocytic cells. The increased level of RANKL and the decreased level of OPG increase osteoclast differentiation, which results in alveolar bone loss.

2. Conclusion

Accumulating evidence supports the "keystone-pathogen hypothesis" in which colonization of keystone bacteria such as Pg triggers dysbiosis and alteration of host immune responses, and other bacteria orchestrate inflammatory disease leading to bone loss [8]. The finding that NOD1-stimulatory pathobionts can induce alveolar bone loss further refines the "keystone-pathogen hypothesis" by suggesting that individual oral pathobionts that accumulate during dysbiosis play a critical and specific role in periodontitis development.

References

[1] Chow J, Tang H, Mazmanian SK. Pathobionts of the gastrointestinal microbiota and inflammatory disease. Curr Opin Immunol 2011; 23: 473-480.
[2] Jenkinson HF, Lamont RJ. Oral microbial communities in sickness and in health. Trends Microbiol 2005; 13: 589-595.
[3] Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL., Jr. Microbial complexes in subgingival plaque. J Clin Periodontol 2005; 25: 134-144.
[4] Griffen AL, Beall CJ, Campbell JH, Firestone ND, Kumar PS, Yang ZK, et al. Distinct and complex bacterial profiles in human periodontitis and health revealed by 16S pyrosequencing. ISME J 2012; 6: 1176-1185.
[5] 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; 75: 4364-4372.
[6] Kolenbrander PE, Andersen RN, Blehert DS, Egland PG, Foster JS, Palmer RJ., Jr Communication among oral bacteria. Microbiol Mol Biol Rev 66:486-505
[7] 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; 10: 497-506.
[8] Hajishengallis G, Darveau RP, Curtis MA. The keystone-pathogen hypothesis. Nat Rev Microbiol 2012; 10: 717-725.
[9] Fine DH, Markowitz K, Fairlie K, Tischio-Bereski D, Ferrendiz J, Furgang D, et al. A consortium of Aggregatibacter actinomycetemcomitans, Streptococcus parasanguinis, and Filifactor alocis is present in sites prior to bone loss in a longitudinal study of localized aggressive periodontitis. J Clin Microbiol 2013; 51: 2850-2861.
[10] Henderson B, Ward JM, Ready D. Aggregatibacter (Actinobacillus) actinomycetemcomitans: a triple A* periodontopathogen? Periodontol 2000 2010; 54: 78-105.
[11] Schobert M, Jahn D. Regulation of heme biosynthesis in nonphototrophic bacteria. J Mol Microbiol Biotechnol 2002; 4: 287-294.
[12] Scott JC, Klein BA, Duran-Pinedo A, Hu L, Duncan MJ. A two-component system regulates hemin acquisition in Porphyromonas gingivalis. PLoS One 2013; 8: e73351.
[13] Barnes VM, Ciancio SG, Shibly O, Xu T, Devizio W, Trivedi HM, et al. Metabolomics reveals elevated macromolecular degradation in periodontal disease. J Dent Res 2011; 90: 1293-1297.
[14] 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; 79: 67-74.
[15] Ito R, Ishihara K, Shoji M, Nakayama K, Okuda K. Hemagglutinin/adhesin domains of Porphyromonas gingivalis play key roles in coaggregation with Treponema denticola. FEMS Immunol Med Microbiol 2010; 60: 251-260.
[16] Ramsey MM, Whiteley M. Polymicrobial interactions stimulate resistance to host innate immunity through metabolite perception. Proc Natl Acad Sci USA 2009; 106: 1578-1583.
[17] Fardini Y, Wang X, Témoin S, Nithianantham S, Lee D, Shoham M, et al. Fusobacterium nucleatum adhesin FadA binds vascular endothelial cadherin and alters endothelial integrity. Mol Microbiol 2011; 82:1468-1480.
[18] Hammami R, Fernandez B, Lacroix C, Fliss I. Anti-infective properties of bacteriocins: an update. Cell Mol Life Sci 2013; 70: 2947-2967.
[19] Burton JP, Chilcott CN, Moore CJ, Speiser G, Tagg JR. A preliminary study of the effect of probiotic Streptococcus salivarius K12 on oral malodour parameters. J Appl Microbiol 2006; 100: 754-764.
[20] Kaewsrichan J, Douglas CW, Nissen-Meyer J, Fimland G, Teanpaisan R. Characterization of a bacteriocin produced by Prevotella nigrescens ATCC 25261. Lett Appl Microbiol 2004; 39: 451-458.