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Dental Plaque And Its Role In The Cause Of Plaque-Associated Diseases

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Abstract:
Background*: The human oral cavity harbors diverse communities of microbes that live as biofilms: highly ordered, surface-associated assemblages of microbes embedded in an extracellular matrix. Oral microbial communities contribute to human health by fine-tuning immune responses and reducing dietary nitrate. Dental caries and periodontal disease are together the most prevalent microbially mediated human diseases, worldwide.*
Materials and Methods*: Both of these oral diseases are known to be caused not by the introduction of exogenous pathogens to the oral environment, but rather by a homeostasis breakdown that leads to changes in the structure of the microbial communities present in states of health. Both dental caries and periodontal disease are mediated by synergistic interactions within communities and both diseases are further driven by specific host inputs: diet and behavior in the case of dental caries and immune system interactions in the case of periodontal disease.*
Results*: Changes in community structure (taxonomic identity and abundance) are well documented during the transition from health to disease. In this review, changes in biofilm physical structure during the transition from oral health to disease and the concomitant relationship between structure and community function will be emphasized.*
Conclusion: *Dental caries and periodontal disease are the most prevalent microbially mediated diseases in humans. Dental plaque has a highly ordered structure mediated by intercellular interactions, the environment, and the host. Periodontal disease is associated with changes in microbial community structure, i.e., taxonomic membership and abundance. Periodontal disease is thought to be mediated by synergistic interactions between subgingival microbial communities and the host.*
Key Word: *microbes, dental caries, periodontal disease.*

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I. Introduction

Numerous molecular-level sequencing studies have shown that approximately 700 species or types of microorganisms constitute the oral biofilm, and that each individual carries between 50 and 200 species 1,2 . The human oral cavity is an excellent habitat for microorganisms, including the oral mucosa, dorsum of the tongue, and hard surfaces of teeth. Site-specific DNA sequencing studies of these different habitats have revealed that these parts of the oral cavity support distinct microbial communities mediated by the characteristics of the surfaces available for attachment, oxygen availability, and exposure to host products such as saliva, supragingival surfaces, and gingival fluid, as well as subgingival surfaces. Dental caries is a lesion on the tooth surface that develops as a consequence of microbial growth and carbohydrate metabolism dependent on diet, leading to localized acidity and disruption of tooth mineralization homeostasis 4. Periodontitis is a chronic, progressive disease characterized by the expansion of the microbial biofilm on the marginal gingiva with the formation of an inflammatory infiltrate that contributes to the destruction of the connective tissue attachment to the tooth surface, resorption of the alveolar bone and can result in eventual tooth loss 5,6. Periodontal disease is correlated with certain systemic diseases, including cardiovascular disease, rheumatoid arthritis, adverse pregnancy outcomes, and malignant diseases, through cellular and molecular mechanisms that are still not well understood 7.

Dental caries and periodontal disease are mediated by the oral biofilm and their interactions with the host's entry points: diet in the case of caries and the immune system in the case of periodontal disease 4.

Transitions from health to dental caries or to periodontal disease are thought to be caused not by the introduction of exogenous pathogens, but by changes in the structure of the microbial community, i.e., taxonomic composition and relative abundance, that transform communities into pathogenic states 8. In fact, periodontal disease is correlated with an increase in the diversity of the microbial community, unlike most diseases known to be mediated by the human microflora 5. The transition from oral health to oral disease is recognized as multifactorial, interdependent between the host and other factors 4.

Approaches based on molecular sequencing, genetic and biochemical manipulation of single organisms, and controlled laboratory conditions have enabled the identification of many of the molecular and cellular processes that underlie community function 9. Early studies based on electron and light microscopy enabled the development of two hypotheses for dental plaque formation and its role in mediating disease, namely that highly ordered communities result from ecological succession and that no single pathogenic organism is responsible for periodontal disease 10,11. This review summarizes the current state of knowledge regarding dental plaque structure and in particular discusses the importance of the transition from dental health to caries and periodontal disease. The species composition and relative abundance of the microflora is often referred to in the literature as community structure 3 . This type of structural information, generated by sample homogenization and subsequent molecular identification by DNA sequencing, should not be confused with information about the physical structure of the biofilm 12 . Special emphasis will be given to the communities of supragingival and subgingival plaques because these communities are extraordinarily complex, having a highly non-random spatial structure, presumably due in part to the nature of the tooth support apparatus 4 . The oral microflora of healthy individuals is dominated by members of the following phyla: Firmicutes, Proteobacteria, Actinobacteria and Bacteroidetes, as well as Fusobacteria and Spirochaetes 13 . A recent meta-analysis of the Human Microflora Project in supragingival and subgingival dental plaques revealed that 13 genera are very highly represented and have a high prevalence in the population: Streptococcus, Corynebacterium, Capnocytophaga, Haemophilus/Aggregatibacter, Fuptovosobacter, Futvosobacter, Veillonella, Neisseria, Rothia, Actinomyces, Lautropia and Porphyromonas 14. At the genus level, the taxonomic composition of both supra and subgingival communities in healthy individuals is similar, with marked differences in relative abundance, e.g., the genus Prevotella is increased in subgingival communities, reflecting the different environmental conditions experienced by the two microbial communities.

Along with bacteria, fungi also make up the healthy oral microflora. Although the fungal burden in healthy individuals is estimated to be lower than the bacterial burden, the size and morphology of fungal colonies and their synergistic interactions with bacteria suggest an important role for these organisms in structuring dental plaque 15. Assessment of fungal diversity is also hampered by the incompleteness of fungal sequence databases, which is itself due in part to the inability to culture many species, which necessitates database construction, and the lack of standard protocols for eliminating fungal DNA caused by the extreme heterogeneity in fungal cell wall composition 16. However, recent next-generation sequencing studies of oral fungal 18S rRNA internal transcribed sequences (ITS) have identified numerous genera with high abundance and prevalence in saliva and include Candida, Cryptococcus, Fusarium, Aspergillus/Emericella/Eurotium and others 17,18.

II. Material And Methods

Emerging evidence suggests that the human microbiota performs a variety of functions that are beneficial to the host 19. The beneficial effects of the human microbiota have primarily been observed in the gut; however, recent work has identified key beneficial functions of the oral microbiota 20. It is hypothesized that the primary function of resident microbes is to act as a physical and biochemical barrier to prevent colonization or infection by exogenous organisms. Indeed, the mouth is in direct contact with the external environment and receives a myriad of airborne and droplet-associated microbes through breathing, as well as food- and water-associated microbes through eating and drinking. By physically and chemically limiting access to the host epithelium through direct occlusion, by sequestering nutrients, and by secreting antimicrobial agents, the commensal oral microbiota may play an important role in directing foreign microbes to saliva and mucus to be ingested, ingested, and brought to an extremely low pH 21.

A second hypothesized function of the commensal microflora is to promote the maturation of both the innate and adaptive host immune systems, particularly to achieve an appropriate balance between pro- and anti-inflammatory processes in the absence and during infection 22. In the mouth, studies of patients with underlying primary immunodeficiency have revealed a complex interplay between the subgingival microbial community and the host immune system, including the importance of proper neutrophil recruitment to prevent potentially compensatory inflammatory responses to the oral microflora. In addition, the key involvement of TH17 cells in mediating microflora-induced periodontal disease further supports the central involvement of neutrophils in periodontal disease 23. In the context of beneficial microbes, oral streptococcal species have been shown to play an immunomodulatory role and reduce pro-inflammatory responses to beneficial oral microbes.

III. Result

Early studies using light and electron microscopy of intact dental plaque demonstrated that these communities are highly structured, with non-random distributions of morphologically and phenotypically distinct cells. The results of extensive in vitro analyses using cultured bacterial isolates have allowed the generation of a hypothetical model for the spatial structure of dental plaque. According to this model, a subset of microbes, namely species of the genera Streptococcus and Actinomyces, are able to bind directly to the glycoprotein-rich dental pellicle that coats the tooth, through recognition of bacterial surface receptors 29,30. A process of ecological succession then takes place in which these founder organisms and other early colonizers, including species of the genus Veillonella, serve as substrates for the subsequent attachment of later colonizing organisms, culminating in a climax community rich in diversity that includes organisms that are abundant as well as those enriched in periodontal disease, bacteria of the genus Treponema etc. According to this model, Fusobacterium nucleatum and to some extent Porphyromonas gingivalis are important bridging microorganisms that physically unite early colonizers with late colonizers, as these two species have shown the ability to specifically co-aggregate with both types of colonizers.

Community structure in the context of dental caries

Mutans streptococci, especially S. mutans, as well as lactobacilli are strongly correlated with caries. S. mutans readily ferment sucrose and other sugars to produce ATP and lactic acid as the end product. Thus, the accumulation of lactate is responsible for the local acidification of the caries environment 32,33. Species of the acidophilic, i.e. acid-tolerant genus Veillonella use lactate as a carbon source and are thus involved in syntrophic carbohydrate metabolism with S. mutans. Molecular sequencing analyses have identified other acidogenic and acidogenic organisms that are strongly correlated with different stages of caries progression in vivo, including Bifidobacterium spp. Scardovia spp., Actinomyces spp., and other non-acidogenic genera, Corynebacterium, Granulicatella, and Propionibacterium, have also been found in increased numbers in the supragingival region associated with caries. Thus, the development of dental caries is accompanied by a shift in the composition of the supragingival community from one that promotes health to one that mediates disease. This breakdown of homeostasis in the composition of the microbial community, or dysbiosis, is a common phenomenon in microbiota-mediated diseases 35.

Although a systems-level spatial analysis of caries-associated dental plaque biofilms with taxonomic resolution, as described above for health-associated biofilms, has yet to be achieved, accumulating evidence from various studies suggests a substantial contribution of spatial structure to caries development. In the absence of abundant fermentable carbohydrates, mutans streptococci attach to salivary-coated teeth, grow more rapidly, and antagonize competitors by locally secreting hydrogen peroxide 36 . Acidogenic and acidic oral microbes are necessary, but not sufficient, for caries development, and frequent consumption of dietary sugars by the host is also required. During frequent exposure to fermentable carbohydrates, localized low pH sites generated by lactate producers further select for acidic organisms, resulting in a positive feedback loop that ultimately leads to highly localized demineralization 37,38 . Dietary sucrose is particularly cariogenic because its component 6-carbon sugars, glucose and fructose, are used for the synthesis of extracellular polymeric substances in the form of glucans and fructans 39. The extracellular biofilm matrix, composed of extracellular polymeric substances, glycoproteins and extracellular DNA, provides binding sites for embedded microbes, protects against biofilm removal during normal oral hygiene procedures and contributes to the generation of highly localized regions of low pH by inhibiting the exchange of saliva, which has a natural buffering capacity. Thus, nutrition and synergistic interactions shape the microbial community in both its taxonomic structure and physical structure, allowing the formation of highly localized acidic microenvironments.

These microenvironments in turn further shape the local structure of the biofilm which can lead to highly localized acidity and tissue demineralization.

Community structure in the context of periodontal disease

As with caries, no single organism is implicated in the transition from health to periodontal disease, but rather the subgingival microbial community present in states of periodontal health transitions into a state of dysbiosis in which the community structure, i.e. the composition and abundance of species, changes. towards a pathogenic state. Early approaches identified Gram-negative organisms, in the subgingival zones of patients with periodontal disease, consisting of Prophyromonas gingivalis, Treponema denticola and Tannerella forsythia. Many other periodontal pathogens have recently been discovered including the Gram-positive Filifacter alocis and other anaerobes including cells of the genera Parvimonas, Fusobacterium and Prevotella. According to the ecological plaque hypothesis, changes in environmental conditions, i.e., nutrient availability, oxygen concentration, pH, and host inflammatory mediators, drive community change by selecting for and enriching periodontal pathogens. Consistent with this hypothesis, molecular sequencing-based approaches have confirmed that periodontal pathogens are present in health-related subgingival zones at low abundance and that as ecological

changes occur, these organisms expand within communities beyond the threshold that initiates and enhances periodontal disease pathology. The newly described hypothesis of polymicrobial synergy and dysbiosis builds on this ecological concept to include dynamic and synergistic interactions between organisms and the host as a mechanism for shaping and stabilizing dysbiotic communities in their ecological context. Inflammation-related destruction of gingival tissue is thought to contribute to dysbiosis by releasing nutrients, including degraded collagen and other peptides. P. gingivalis has been shown to manipulate the host immune response in a manner that abrogates tissue destruction during inflammation, through manipulation of the complement pathway mediated by gingipain exoenzymes that act on the inactive complement precursor protein C5 to generate C5a. P. gingivalis further promotes crosstalk between complement C5a receptor 1 and Toll-like receptor 2 (TLR2) while bypassing the downstream effector Myd88 to elicit a proinflammatory, antiphagocytic response in phagocytic cells. Even further, P. gingivalis has been shown to downregulate epithelial cell expression of interleukin-8 (IL-8), a chemokine that recruits phagocytic neutrophils and Th1 cells to the gingiva, as well as T-cell interferon (IFN) γ production 47,48. Thus, P. gingivalis, present in low abundance in both health and disease-associated communities, acts as a keystone species in the developing dysbiotic community to create a proinflammatory, antiphagocytic environment that favors the growth and spread of pathobionts. The molecular crosstalk that occurs between the subgingival microflora and the host immune system does not occur in an unstructured environment, but in a highly ordered one. The structure of biological systems, including the involved host tissues and the subgingival microbial community, correlates with their function, and increasing evidence points to the importance of biofilm structure in the transition through dysbiosis.

The close arrangement of cells in polymicrobial biofilms allows for biochemical interactions, signaling, and genetic exchange between cells. Facultative aerobes in dental plaque biofilms can scavenge oxygen and form anaerobic junctions. This process may be important during the transition to dysbiosis because many periodontal pathogens are strict anaerobes. During the progression of periodontal disease, the gingival pocket increases in volume, which may lead to a greater bacterial load in this junction. The total bacterial load is increased in patients with periodontal disease because new dominant community members emerge and accumulate, rather than displacing previous colonizers, suggesting a dynamic physical interaction between biofilms and host tissue to create this new space. How these newly dominant species are distributed in expanding biofilms is being investigated. Actinomyces spp. were located primarily in the basal layer of the biofilm, i.e. closest to the tooth surface. Fusobacterium was identified in the middle layers of the biofilms along with Tannerella while Prevotella and Porphyromonas were localized to both the apical and middle layers. Cells from the Cytophaga Flavobacterium Bacteroides cluster were observed in the apical layers, while Treponema was loosely distributed superior to the densely packed biofilm.

IV. Conclusion

Dental caries and periodontal disease are highly prevalent in the human population. Both diseases are polymicrobial in their etiology and result when supragingival and subgingival microbial communities associated with health conditions experience a breakdown in homeostasis and become dysbiosis. The etiologies of these diseases are multifactorial and depend on synergistic activities, both chemical and physical, within microbial communities and between the host immune system, as well as other factors. As described here, descriptive studies of dental plaque structure in health conditions and diseases are beginning to achieve a systemic level of taxonomic resolution. The development of mature dental plaque biofilms is a dynamic process that results from ecological succession. Understanding the driving force of dysbiosis in dental plaque communities requires collaboration between scientists with diverse expertise, including microbiology, biochemistry, immunology, ecology, imaging, and genomics, as well as collaborative efforts among researchers to synthesize new knowledge. Dental caries and periodontal disease are the most prevalent microbially mediated diseases in humans. Dental plaque has a highly ordered structure mediated by intercellular interactions, the environment, and the host. Periodontal disease is associated with changes in microbial community structure, i.e., taxonomic membership and abundance. Periodontal disease is thought to be mediated by synergistic interactions between subgingival microbial communities and the host. The spatial structure of intact supragingival and subgingival biofilms is as important as taxonomic composition for understanding microbiome changes in health and disease.

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