POLYMICROBIAL SYNERGESIS & DYSBIOSIS CONCEPT: A REVIEW

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ABSTRACT

Periodontal research shows periodontitis is initiated by a synergistic & dysbiotic microbial community rather than selective ‘periopathogens’ like red complex bacteria. In this specific gene combinations or different members fulfill distinct roles to shape & stabilize a disease provoking microbiota. In Polymicrobial Synergy & Dysbiosis concept, there is an increase in the ability of bacteria to colonize or elevate disease symptoms in presence of other bacteria. PSD concept states that there is a formation of biofilm orchestrating in a medley of show with the host response throwing its weight to the more plausible. Oral dysbiosis, a shift from the beneficial symbiotic bacteria to the pathogenic bacteria, is at least partially responsible for development of periodontitis. An in depth understanding of periodontal pathogenesis on the basis of PSD model offer new targets for therapeutic intervention.

INTRODUCTION

Periodontitis is characterised by loss of connective tissue attachment that begins at, or just apical to, the cementoenamel junction and extends apically along the root surface. The traditional clinical diagnosis is made by measuring either the loss of connective tissue attachment to the root surface (clinical attachment loss) or the loss of alveolar bone (radiographic bone loss). Disease evaluation, as performed at one point of time, attempts to identify and quantify current clinical signs of inflammation as historic evidence of damage, with its extent and severity. However, evaluation cannot reliably identify sites with ongoing periodontal destruction and does not provide any information on the cause of the condition, on the patient’s susceptibility to disease, whether the response to therapy will be positive or negative.

Synergism is the interaction or cooperation of two or more organizations, substances, or other agents to produce a combined effect greater than the sum of their separate effects. In polymicrobial synergy, different members or specific gene combinations, within the community, fulfill distinct roles, that converge to shape & stabilize a disease provoking microbiota. Dysbiosis (Dysbacteriosis) is a term for a microbial imbalance or maladaptation on or inside the body, Dysbiosis, as the term implies, is a symbiosis that has gone awry. Keystone pathogens along with accessory pathogens elevate the virulence of entire microbial community eliciting a non-resolving & tissue destructive periodontal response.2

With the plethora of the organism and their dubious role, Hajishengallis and Lamont in a recent review introduced the spirit of polymicrobial synergy and dysbiosis model of periodontal disease. The model revolves around certain species, termed “keystone pathogens,” to modulate host response in ways that impair immune surveillance and tip the balance from homeostasis to dysbiosis.3

The current view of the natural destructive periodontal disease is that disease susceptibility and host mechanism are generalized. However, the disease process itself is considered to be site specific and has a multifactorial origin in which periodontal pathogens, host response and genetic, systemic and behavioral risk factor interplay to develop the disease process. Hence, this review article aims to throw light on the interrelationship between the healthy microbial load and diseased microbial community existing in synergism in human oral cavity.

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**Polymicrobial Synergesis & Dysbiosis (PSD) Concept**

The Polymicrobial Synergy & Dysbiosis (PSD) Model states that periodontal disease ensues from the action of a polymicrobial community in which pathogenicity is defined by interactions among functionally specialized organisms. Pathogenic communities then induce dysbiotic host responses, which fail to control the microbial challenge & contribute to tissue destruction. The concept that not one single organism, but several organisms contained in the biofilm orchestrating in a medley of the show appears to be more plausible.4

About 20 years ago Socransky aptly summed up the microbial etiology of periodontal disease with a disarming statement “specific bacteria of right clonal type with essential genetic elements in numbers for that host with appropriate additional species in the right environment.”

We next come to the issue that single microorganism may not be the culprit, but an orchestrated group of more than one might be the main offenders. In a classic paper in 1998 Socransky et al. used cluster analysis and community ordination methodologies. This elaborate and highly technological research on the subgingival microbiota resulted in organizing the organisms into several complexes indicated by various colors.5

**The Healthy Microbiome**

The oral cavity is highly populated with numerous polymicrobial communities, each occupying highly specific niches that differ in both anatomic location and nutrient availability.6 Oral host colonization is a reflection of the proficiency of bacteria to adapt to a variety of different niches through high rates of genetic recombination. One consequence of robust colonization with commensal bacteria is to prevent colonization with pathogenic bacteria through a process termed colonization resistance.

Colonization resistance has long been recognized as an important function of commensal bacteria, and the detrimental effects of depletion of commensal bacteria by the application of broad spectrum antibiotics have been documented.7,8

However, more recently, studies examining host–bacteria interactions have revealed that commensal bacteria not only protect the host simply by niche occupation but that interactions of bacteria with host tissue also promote the development of proper tissue structure and function. These data indicate that our host-associated polymicrobial communities, such as those found in the oral cavity, co-evolved with us and have become an integral part of who we are.9

The most significant and clear studies with respect to the ability of polymicrobial commensal communities to direct proper tissue structure and function are found in the intestine.10,11 The human oral cavity is similar to the intestinal system in that both contain highly evolved polymicrobial communities and both have a state of ‘controlled’ inflammation.12,13 In order for causation to be established, Hill’s criteria require that most of the following conditions are fulfilled: Biological plausibility, dose response, strength of association, specificity of association, consistency, and temporality.14

It appears that the etiology of periodontitis might be more readily established, if current research combines the pathogenic microbial community concept with Hill’s criteria of causality. However, significantly less is understood concerning the contribution of the oral polymicrobial community on the structure and function of oral tissue.

**Dysbiosis: Change in Composition and Numbers of Oral Microbiome; The Unhealthy Microbiome**

Periodontitis is a dysbiotic disease.15 This is not a new concept; rather, it is a better name to describe what was previously described as a shift from mostly gram-positive bacteria found in healthy sites to mostly gram-negative bacteria found in clinically diseased sites.8 Dysbiosis, as the term implies, is a symbiosis that has gone awry. It is the concept that some diseases are caused by a decrease in the number of beneficial symbionts and/or an increase in the number of pathogens.15 Instead of contributing to healthy tissue function, as described above, the oral polymicrobial community interferes with normal periodontal tissue function. This is the definition of disease, when normal tissue function is disturbed.

There are numerous cases of dysbiotic diseases, including inflammatory bowel disease, otitis media and bacterial vaginosis.16 A key contribution of describing periodontitis as a dysbiotic disease is its emphasis on bacterial community and the ramifications thereof in understanding periodontitis etiology. For example, one ramification of bacterial community thinking is that not all bacteria in the community need to have the same function. This notion was recently demonstrated by showing that Porphyromonas gingivalis, a designated periodontopathogen16 required other members of the oral microbial community to elicit periodontitis in a mouse model of disease.17

Based upon these data, P. gingivalis was proposed to be a keystone species in the oral polymicrobial community and provided another scientific rationale for its high association with disease. Interference with numerous different host component protection mechanisms are likely to alter the homeostatic balance produced by evolution for proper functioning periodontal tissue.18

This study lends support to the notion that indeed there are specific periopathogens, and that creating dysbiotic situations, facilitates their outgrowth and subsequent detrimental effects on periodontal function. Local factors in the oral cavity, such as heavy calculus, restoration overhangs, areas of food impaction or even active caries, might produce similar dysbiotic effects in humans.

This in turn reinforces our need to understand the dysbiotic community and suggests that novel therapeutic intervention strategies may arise from learning more about bacteria–bacteria interactions in the context of host responses.

**Early Concepts of the Pathogenesis of Periodontal Disease**

The modern era of the pathogenesis, prevention, and treatment of periodontal diseases began in the mid- 1960s with human and animal experimental evidence demonstrating the critical role of bacteria in the initiation of gingivitis and periodontitis.19,20 This led to a clear concept of pathogenesis, i.e., bacteria cause periodontal disease (Fig. 1A). This model implicated bacterial plaque deposits as the primary, direct factor in the development of periodontitis and resulted in the
abandonment of former concepts that involved non-bacterial factors, such as trauma from occlusion, systemic conditions, and diet. This tenet of the critical role of bacteria dramatically changed the prevention and treatment of periodontitis.

The extensive research through the mid-1980s led to critical refinements in the pathogenesis concept, many of which were not broadly appreciated outside of the research community (Fig. 1B). In most of the models of the late 1980s, specific bacteria initiated the disease process by activating host responses, which were protective and destructive.

The basic conceptual model of periodontitis was revised in 1997 (Fig. 1C) in great part to acknowledge that various risk factors operated by modifying host responses led to changes in disease expression. In this model, host immune-inflammatory mechanisms are activated by bacterial products. Such activation of the host response induces the expression of antibodies as well as activating PMNs in an attempt to control the microbial challenge in the gingival sulcus. In addition, cytokines and prostaglandins, as well as matrix metalloproteinases activated through the host response, may stimulate damage to connective tissue and bone and shape the clinical presentation of disease.

To add further complexity to the earlier conceptual models, there was a growing appreciation during this period of the importance of genetic variations in determining the development and severity of periodontal disease, with genetic influences accounting for as much as 30% to 60% of the variability in the clinical severity of periodontitis.21,22


**Future Prospects & Treatment Modalities**

Even though many of the concepts presented in the 1997 non-linear model of periodontal disease remains relevant till day, there have been advances in knowledge about periodontal disease that may alter the models of pathogenesis of periodontitis. First, it was demonstrated that microbial periodontal pathogens are found in ecologic complexes, and an ecologic shift can lead to emergence of a specific set of microbial pathogens.23,24

Second, a number of studies have confirmed that a small group of disease modifiers, including diabetes, genotype, and smoking, contribute strongly to individual patient differences in the susceptibility to periodontitis.25,26

Third, many studies described associations between periodontitis and other diseases, such as cardiovascular disease, and potentially explained such associations through bacterial seeding, common inflammatory mechanisms, and/or common modifying factors.27,28

Fourth, there was an extension of knowledge about specific bacterial mechanisms and immune-inflammatory mechanisms in periodontitis.29

We know multiple etiologies are involved in development of periodontitis (Fig. 2), choosing appropriate treatment options can be quite difficult. Despite these complications, recent advances show tremendous potential to help patients suffering from periodontitis. Host modulation therapy, photodynamic therapy, gene therapy, stem cell therapy and probiotic therapy may provide advantages that are not observed when antibiotics or antiseptics are used.

Host modulation therapy means modifying or modulating destructive or damaging aspects of the inflammatory host response that develops in the periodontal tissues as result of the chronic challenge presented by the subgingival bacterial plaque.

Gene therapy is transfer of genetic information to the target cells, which enables them to synthesize a protein of interest to treat periodontal disease. The primary aim of gene therapy is to treat disease states through gene insertion strategies to correct genetic defects in somatic cells. The technology can be used to treat disorders that result from single point mutations or to increase protein production. It can be viewed as using DNA as a drug, either to correct a defect, enhance a response or mark a foreign cell for subsequent eradication.

Photodynamic therapy (PDT) has emerged in recent years as a non-invasive therapeutic modality for the treatment of various infections by bacteria, fungi and viruses. It involves the use of low power lasers with appropriate wavelength to kill microorganisms treated with a photosensitizer drug. PDT could be a useful adjunct to mechanical, as well as antibiotics, in eliminating periopathogenic bacteria. This therapy is defined as an oxygen-dependent photochemical reaction that occurs upon light-mediated activation of a photosensitizing compound leading to the generation of cytotoxic reactive oxygen species; predominantly singlet oxygen.

Tissue engineering more than anything else on the horizon promises of rewriting rules of regeneration. The surgical limits of what clinicians can and cannot do are primarily based on available blood supply, but in future it is likely that surgeons will have materials capable of enhancing blood supply to the defect so that the limits of repair and regeneration will be redefined. The implantation of cells in the defects adds on an entirely new dimension to treatment, although near term ability...
to gain regulatory approval for projects of this type may be challenging. The advantage of cell based therapies is that cells communicate with each other and with the native cells of the defect thus ensuring the delivery of metabolically active molecules exactly where needed and in the exact amounts required.

Over the past 50 years, a number of conceptual models describing the pathogenesis of periodontal disease have been presented based on existing knowledge at the time. The more recently explored biologic systems approach to modeling holds promise for revolutionizing conceptual models of the past by providing a comprehensive view of the disease process as a complex regulatory network.

Within this framework, discrete modules of genetic, environmental, and other modifying factors would define a specific expression pattern that represents the shift from health to disease.

Genomic, proteomic, and metabolomic data related to periodontal diseases are being collected. When these data are combined with knowledge of even a limited set of environmental and genetic factors contributing to periodontitis, we should be able to build more robust models of the pathogenesis of periodontal diseases.

In humans, periodontitis risk factors also can be categorized as environmental or genetic, although less is known about how these may create dysbiotic communities. Environmental factors include smoking and obesity, and both have been shown to be associated with dysbiotic subgingival and intestinal communities, respectively. In fact, it has recently been found that smoking creates a subgingival microbiome in healthy sites that more closely resembles that of diseased sites, suggesting that smoking creates ‘an at-risk-for-harm environment’ to create periodontitis. Diabetes is also associated with periodontitis and it has been postulated that a more complete analysis of the periodontal microbiome is necessary to determine if this disease is associated with a dysbiotic periodontal community. Human genetic risk factors have been, and remain, the subject of numerous studies, which have been reviewed elsewhere. It will be interesting to see, in the future, if any of the putative periopathogenic single nucleotide polymorphisms in host-response and other genes are associated with dysbiotic oral communities.

However, much research still needs to be performed on these new alternatives. Most importantly, well-designed and large-scale randomized clinical trials are required to compare the “gold standard” of scaling and root planing to the new therapies used alone or adjunctively with scaling and root planing.

**Significance of PSD Concept**

PSD drive periodontitis in a susceptible host. Dysbiosis involves specialized accessory & keystone pathogens. The dysbiotic microbiota sustains itself by feast on the ‘inflammatory spoils’. Disruption of symbiotic community creates a dysbiosis, either by overgrowth of specific or nonspecific microorganisms or by changes in the local host response where the community then supports a disease state. Keystone pathogens, even at low abundance, elevate community virulence, & the resulting dysbiotic community provides the link between systemic changes (diabetes) & exogenous risk factors, (smoking), & the dysbiotic community drives periodontal tissue destruction.

Other risk factors associated with periodontal disease, such as stress, aging and genetics, also affect the microbial community. More research is needed, utilizing sophisticated bacterial taxonomic techniques, to elucidate more clearly the effects on the microbiome & to develop strategies to target the dysbiotic mechanisms & improve periodontal health.

New therapeutic regimens, involving selective bacterial killing & probiotic and prebiotic approaches, require a more intimate knowledge of the polymicrobial dependencies for survival in the oral biofilm. This review emphasizes polymicrobial interactions with the host in both health & disease.

**CONCLUSION**

The literature as it currently stands appears to indicate that oral dysbiosis, or a shift from beneficial symbiotic bacteria to pathogenic bacteria, is at least partially responsible for the development of periodontitis. Thus, while a microbial shift is known to play a significant role in the development of periodontitis, genetic, immunological, and environmental factors must also be investigated in order for clinicians and researchers to fully understand disease progression. Because of the various risk factors that contribute to periodontitis, it is possible that there will be no “magic bullet” treatment. Indeed, the complexity of periodontitis emphasizes the necessity of a treatment that is highly tailored to the specific needs of the patient.

Overall, the goal for both researchers and clinicians is to find the best treatment. From a biological perspective, the most successful treatments need to attack the integrity of the periodontal biofilm and suppress the destructive host inflammatory response. From a clinical perspective, the best treatments are those that are simple, affordable, and able and able to confer a clinically relevant benefit to the patient. It is hoped that by gaining a better understanding of bacterial communities, more accurate, useful diagnostic & therapeutic interventions can be elucidated.

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