Commentary

Host Genome, Epigenome, and Oral Microbiome Interactions: Toward Personalized Periodontal Therapy

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Periodontal diseases are multidimensional and complex. Bacterial content is the initiator, but disease progression depends on genetic and environmental parameters related to the host. Although bone loss magnitude is the common resulting outcome, the biologic process likely represents a unique inflammatory response characteristic to every individual. Therefore, it is obvious that practitioners must take into account the influence of these parameters and tailor a treatment accordingly. New, emerging deoxyribonucleotide-based technologies allow integration of the biologic impact of the environment, and periodontists should be prepared to incorporate these technologies into their practice to advance personalized medicine. This commentary provides updated insights on the distinctiveness of inflammation per individual in terms of microbiome and genome specificity and cites some educational resources helpful for implementing individualized therapy. J Periodontol 2013;84:1266-1271.

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Inflammatory reaction in periodontal diseases is a multifactorial and complex response of the host to foreign intruders. Its intensity and duration depend on the nature of the existing oral microbiome and the impact of environmental and genetic factors characteristic to every host.\textsuperscript{1-3} There is an increasing recognition that interindividual variability in such response develops as a consequence of host–environment–microbial interactions that give rise to a specific clinical phenotype. Thus, this phenomenon represents a biologic reaction unique to each individual.

Although the causality between the existence of pathogenic microbes and the initiation of periodontal diseases is well established, disease progression is multidimensional and poorly understood. Unconventional clinical cases repeatedly arise because of the complexity of such processes. For example, patients with a high content of microbial plaque and calculus may show no bone loss at all, whereas patients with unremarkable irritants may present with severe bone loss. From that perspective, our role as clinicians is no longer limited to be merely caretakers; we must try to understand the biologic characteristics of our patients and tailor a treatment accordingly. Huge progress in the field of medicine, especially in genetics, has been made, identifying most of the biomarkers implicated in the disease process and allowing practitioners to customize treatment appropriately.\textsuperscript{4,5}

Similarly, drug therapy also has different clinical outcomes based on patients’ genetics and ability to metabolize the drugs. Pharmacogenomics uncovers these genes and their variation and allows proper adjustment of the drug prescription.\textsuperscript{6,7} Some individuals are poor metabolizers, whereas others metabolize drugs rapidly. For example, customized dosage of blood clotting and pain medications (e.g., warfarin, clopidogrel, aspirin, codeine) has clinical relevance in periodontal treatment.\textsuperscript{8-10} Therefore, patients’ genetic profiles are of great interest to predict the efficiency of drug therapy and minimize its side effects.

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This commentary provides updated evidence on the distinctiveness of inflammation per individual in terms of microbiome and genome specificity and highlights the interest of genomic pharmacology in the advancement of personalized periodontal therapy.

ORAL MICROBIOME

Oral microbiota represent a complex community containing mainly bacteria and viruses that interact together and with the host, greatly impacting periodontal health. Current metagenomic studies have established the wide interindividual and intraindividual variability in bacterial community composition, although there is a minimum shared core of functionalities in the microbiome. Such variability might explain, in part, the occurrence of periodontal disease in one particular individual and not in others and the recurrent episodes in specific sites within an individual. Metagenomic techniques based on bacterial genome sequencing make it possible to determine the composition of the oral microbiome and compare the content between health and disease conditions.

It is well established that the presence of pathogenic bacteria alone does not result in periodontal damage in most cases. Although they are essential for initiation of periodontitis, the amount of plaque and the bacterial species do not often correlate with disease severity. Therefore, the nature of the oral microbiome largely depends on its interaction with the host to generate an inflammatory response. Indeed, host genetics play an important role in the establishment and shaping of the microbiota because it has been demonstrated that the composition of the bacterial community is influenced by specific host genomic loci. Also, recent data showed that each person has an individual dose-dependent response to the bacterial challenge that determines their susceptibility to diseases, including periodontitis. Taken altogether, the continuous host–microbial communication significantly affects the content of the oral microbiome, which can change with time.

Valuable learning resources have been established by research institutions to help disseminate evidence on the oral microbiome in health and disease status. For example, the National Institutes of Health (NIH) created the Human Microbiome Project (HMP) to characterize microbial communities found at multiple human body sites, including the oral cavity. In addition, the Integrated Microbial Genomes/HMP, a joint component of the Department of Energy Joint Genome Institute and HMP, allows a comparative analysis of bacterial genomes, including those of the oral cavity. A National Institute of Dental and Craniofacial Research–funded source is the Human Oral Microbiome Database, which generates a genetic catalog of oral microbiota and highlights the functional role of genomic species. As such, analyzing metagenomic content is critical to understanding the pathogenesis of periodontal disease and advancing the applicability of personalized periodontal medicine.

HOST EPIGENOME AND ENVIRONMENTAL FACTORS

Epigenome refers to the record of molecular alterations of deoxyribonucleotide (DNA) that change gene expression without changing DNA sequence, typically through changes in chromatin proteins that alter DNA accessibility for transcription, allowing some genes to be activated and others to be silenced. It includes mainly modifications to DNA and histones (e.g., DNA methylation, histone acetylation/deacetylation) and non-coding ribonucleic acid (RNA). Unlike the host genome, which is largely static within an individual, the epigenome can be dynamically altered by environmental factors (e.g., age, sex, ethnicity, lifestyle, social status, stress, diet, alcohol, smoking, diabetes, obesity) specific to each individual. Thus, these inherited changes mediate gene–environment interaction, leading notably to a unique phenotype characteristic to that individual.

It has been shown that the human epigenome is fundamentally involved in many pathologic events, including inflammation and cancer. Emerging evidence has also highlighted its role in periodontal diseases. In fact, DNA methylation, histone acetylation, and micro-RNAs have been shown to modulate the production of inflammatory mediators by switching their gene expression on and off. Moreover, recent data demonstrated that DNA methylation affects bone resorption–related genes and OPG (osteoprotegerin), thus influencing bone remodeling. These findings may explain the interindividual variability in the manifestation of periodontal diseases, in which the expression of cytokines considerably depends on the contribution of epigenomic events.

Recently, the NIH initiated the NIH Roadmap Epigenomics Mapping Consortium to identify and catalog these modifications and compare them to their counterparts in human diseases.

HOST GENOME

Periodontal inflammation involves various stages characterizing the innate immune response, starting
with initiation and followed by progression, disease manifestation, and damage. This process is controlled by multiple key genes or disease-modifying genes encoding proteins of different nature (e.g., enzymes, cytokines, cellular adhesion molecules). Due to genetic variations (e.g., gene polymorphisms), the innate immunity can be more or less severe, resulting in unpredictable bone loss. Moreover, the number and types of disease-modifying genes for the same condition may not be similar for different forms of periodontitis and different ethnic populations. Also, it has been shown that inflammatory mediators are not expressed at the same intensity in all individuals. Personal parameter values may reveal genetic predisposition to produce specific inflammatory cytokines at either pathologic or physiologic concentrations that fluctuate among individuals and occasionally within an individual. Thus, the diversity in genetic profiling among the population could explain individual differences in the ability of the immune system to respond to tissue injury and the range of the clinical presentation of inflammation.

Genetic variations are mainly single-nucleotide polymorphisms (SNPs) and copy number variants. The International HapMap Project and 1,000 Genomes project have provided a large amount of information on human genetic variation and diseases from different ethnic groups. Technologic breakthroughs in genetics (e.g., genome-wide association studies) can assess the expression of thousands of genes from different tissues and their association with common and complex diseases, including periodontal diseases. To date, genetic studies of disease association have estimated that there are hundreds of human periodontitis-associated genes. All these resources have facilitated the understanding of inflammation in an effort to stratify patients according to the risk of a disease and have become necessary to implement individualized periodontal medicine.

PERSONALIZED PERIODONTAL THERAPY

Personalized medicine can be envisioned as tailored therapy based on the interactions among genetic, clinical, and environmental factors affecting an individual. Information on personalized medicine-based initiatives can be found on the Personalized Medicine Coalition website. The advent of high-throughput technologies (e.g., SNP genotyping, NextGen sequencing, Omics techniques, HOMIM [human oral microbe identification arrays]) to determine the genetic, protein, and bacterial profiling of the individual has proven to be extremely useful for personalized therapy. Also, these technologies can be used to search for polymorphisms associated with susceptibility to periodontal diseases. Some pharmaceutical companies provide customized platforms for SNP genotyping; some of these platforms screen for thousands of SNPs. Such methodology permits a broad spectrum of patient genetic records compared to other diagnostic screening tests looking for one or two SNPs. For instance, DNA extracted from a biologic sample can be tested for SNP genotyping of many genes for proinflammatory cytokines (e.g., tumor necrosis factor-α, interleukin [IL]-1, IL-4, IL-6, IL-10), receptors (e.g., Toll-like receptor 4, Fcγ receptor), and others (e.g., vitamin D receptor, human leukocyte antigen) that have been shown to be associated with a greater susceptibility of the individual to periodontal diseases. Also, it can be analyzed for SNPs of genes that influence the bone remodeling process such as RANKL and OPG, which can provide insights on the rate of bone remodeling. Another clinical application is the use of proteomics technology to detect protein signatures in periodontitis that can be used for early diagnosis and prevention of disease progression.

DNA information combined with clinical information, especially medical records, becomes a necessity for highly customized periodontal treatment (Fig. 1). From that perspective, medical institutions have started establishing biobanks of DNA to accelerate the realization of the personalized approach to oral health care. To our knowledge, statewide and national population-based biobanks in the United States do not currently exist. Although many privately owned biobanks exist across the United States, legislatively mandated public biobanks are more appropriate for population-based repositories and are currently in the formative stages of development. The legislation was introduced in the US Senate in 2006. In Europe, biobanks exist but they are lacking strict regulatory guidelines. Recently, a group of experts from the European Commission issued a report entitled, "Biobanks for Europe, a Challenge for Governance." It deals with ethical, confidentiality, and regulatory challenges of international biobank research and provides recommendations.

Another way to implement an individualized approach in periodontal therapy is the use of systems biology. This comprehensive technique relies on the use of computational methods (e.g., mathematical modeling, simulation technologies) often combined with high-dimensional datasets to span the multiple scales of organization that characterize biologic systems. It can be applied for complex diseases, including inflammation. Also, it allows for a rational modulation at the individual level.
by analyzing all the biologic components involved in the process.

Personalized periodontal medicine is also relevant in pharmacogenomics, a domain describing how human genetic variants influence drug-response phenotypes. Pharmacogenomics has the potential to identify the particular drug and dose that is most likely to be effective and safe for each patient. Such an approach has become a common practice in clinical drug testing, with the purpose of selecting drugs that have greater efficacy with fewer side effects.

Genetic variations of drug metabolism–related genes (e.g., members 6, 9, and 19 of cytochrome P450, family 2, subfamily C, [CYP2C6, CYP2C9, and CYP2C19]) have a significant effect on drug clearance. Some individuals are poor metabolizers, whereas others metabolize drugs rapidly.6 For example, some blood clotting and pain medications relevant for periodontal therapy, such as warfarin, clopidogrel, and codeine, have a narrow therapeutic index.8-10 Therefore, genotyping patients has a huge benefit to minimize side effects.59

Two major NIH-funded resources, Pharmacogenomic Research Network and Pharmacogenomic Knowledge Base, are extremely useful for clinicians.60,61 They provide information on genetics-related drug dosage. Also, the US Food and Drug Administration has released the draft guide, “Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies,”62 which is intended to assist the pharmaceutical industry and other investigators engaged in new drug development in evaluating how variations in the human genome could affect the clinical pharmacology and clinical responses of drugs. The guide also provides recommendations on when genomic information should be considered to address questions arising during early drug development.

CONCLUSIONS

It is important to know the biology behind the procedures so that the clinical outcome can be predicted. Periodontal diseases are multifactorial: genetics and environmental factors interact with each other to determine the susceptibility of the host to inflammation. Therefore, host–microbial–environmental interactions are major determinants for the development of periodontal diseases and, thus, for the relationship between genotype and phenotype. Referring to evidence-based clinical trials and meta-analyses to guide therapeutic procedures will become less practical in the near future because the new techniques incorporate the influence of genetic and environmental parameters that nowadays are considered confounding factors when comparing different groups in clinical studies.

Finally, our approach to periodontal disease should no longer be limited to treating diseases; we should understand the biologic principles dictating the progression of the disease to efficiently target it and subsequently better manage our patients. Individualized periodontal therapy is the upcoming concept of medical treatment for an enhanced clinical outcome.

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