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

Sleiman Razzouk DDS, MS, PhD*, Omid Termatchi DDS*

*Faculty, Department of Periodontology and Implant Dentistry, New York University College of Dentistry, New York.

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 biological 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 DNA-based technologies allow the integration of the biological impact of the environment and periodontists should be prepared to incorporate them into their practice to advance personalized medicine. In this miniview paper, we provide updated insights on the distinctiveness of inflammation per individual in terms of microbiome and genome specificity and cite few educational resources helpful for implementing individualized therapy.

KEY WORDS:

genome, metagenome, periodontal diseases, individualized medicine.

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. There is an increasing recognition that an 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 biological reaction unique to each individual.

Although the causality between the existence of pathogenic microbes and the initiation of periodontal diseases is well established, yet disease progression is dimensional and poorly understood. Also, unconventional clinical cases repeatedly arise due to the complexity of such process. For example, patients with high content of microbial plaque and calculus may show no bone loss at all while patients with unremarkable irritants may present with severe bone loss. From that perspective, our goal as clinicians is no longer limited to a caretaker but most importantly try to understand the biological characteristics of our patients and tailor a treatment accordingly. Huge progress in the field of medicine especially in genetics started to emerge identifying most of the biomarkers implicated in the disease process, hence, allowing practitioners to customize their treatment appropriately.

Similarly, drug therapy has also different clinical outcomes based on patients’ genetics to metabolize the drugs. Pharmacogenomics uncovers these genes and their variation and allows adjustment of the drug prescription properly. Some individuals are poor metabolizers while others metabolize the drugs rapidly. For example, customized dosage of blood clotting and pain medications (e.g. warfarin, clopidogrel, aspirin, codeine) has its clinical relevance in periodontal treatment. Therefore, revealing
patients’ genetic profiling is of great interest to predict the efficiency of drug therapy and minimize its side effects.

In this miniview paper, we provide updated evidences on the distinctiveness of inflammation per individual in terms of microbiome and genome specificity and we highlight the interest of genomic pharmacology in the advance of personalized periodontal therapy.

ORAL MICROBIOME

Oral microbiota represents a complex community containing mainly bacteria and viruses that interact together and with the host, hence, 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 diseases in one particular individual and not in others, and their recurrent episodes in specific sites within the individual. Metagenomic techniques based on bacterial genome sequencing allow to determining the composition of the oral microbiome and comparing 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 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, as 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 his/her susceptibility to diseases including periodontitis. Taken all together, the continuous host-microbial communication significantly affects the content of the oral microbiome which can change over time.

Valuable learning resources have been established by research institutions to help disseminating evidence on the oral microbiome in health and disease status. For example, the NIH created the Human Microbiome Project 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. Another NIDCR-funded source is the Human Oral Microbiome Database, which generates a genetic catalogue of the oral microbiota and highlights the functional role of its genomic species. As such, analyzing metagenomic content is critical to understanding the pathogenesis of periodontal disease and advancing applicability of personalized periodontal medicine.
HOST EPIGENOME AND ENVIRONMENTAL FACTORS

Epigenome refers to the record of molecular alterations of 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 RNA. Unlike the host genome which is largely static within an individual, the epigenome can be dynamically altered by environmental factors (e.g. age, gender, ethnicity, lifestyle, social status, stress, diet, alcohol, smoking, diabetes, obesity) specific to each individual. Thus, these inherited changes mediated gene-environment interaction leading notably to a unique phenotype characteristic to that individual.

It has been shown that human epigenome is fundamentally involved in many pathological events including inflammation and cancer. Emerging evidences have also highlighted its role in periodontal diseases. In fact, DNA methylation, histone acetylation and microRNAs have been shown to modulate the production of inflammatory mediators by switching on and off their gene expression. Moreover, recent data demonstrated that DNA methylation affects bone resorption-related genes RANKL and OPG, 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 catalogue these modifications and compare them with their counterparts in human diseases.

HOST GENOME

Periodontal inflammation involves various stages characterizing the innate immune response, starting with initiation followed by a 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 polymorphism), 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 pathological or physiological levels at concentrations that fluctuate between individuals and occasionally within the same 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 the SNPs and Copy Number Variants. The International HapMap Project and 1000 Genomes project have provided a large amount of information on human genetic variation and diseases from different ethnic groups. Technological
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.\textsuperscript{1} To date, genetic studies of disease association have estimated that there are approximately few 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 became necessary to implement individualized periodontal medicine.

**PERSONALIZED PERIODONTAL THERAPY**

Personalized medicine can be envisioned as a tailored therapy based on the interactions between genetic, clinical and environmental factors affecting that individual.\textsuperscript{5} Information on personalized medicine-based initiatives can be found at the Personalized Medicine Coalition website.\textsuperscript{50}

The advent of high-throughput technologies (e.g. SNP genotyping, NextGen sequencing, Omics techniques, HOMIM arrays) to determine the genetic, protein and bacterial profiling of the individual has proven to be extremely useful for personalized therapy. Also, they can be used to search for polymorphisms associated with the susceptibility to periodontal diseases. Some pharmaceuticals companies provide customized platforms for SNP genotyping. For example, Human Omni1-Quad BeadChip SNP\textsuperscript{4} and GeneChip SNP\textsuperscript{8} screen for thousands of SNPs. Such methodology permits a broad spectrum of patient’s genetic record compared to other diagnostic screening tests looking for one or two SNPs since periodontal diseases are complex. For instance, DNA extracted from a biological sample can be tested for SNP genotyping of many proinflammatory cytokines genes (e.g. TNF\textsubscript{α}, IL-1, IL-4, IL-6, IL-10), receptors genes (e.g. TLR4, Fc\gammaR) and others genes (e.g. VDR, HLA) that have been shown to be associated with a greater susceptibility of the individual to periodontal diseases.\textsuperscript{2} 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.\textsuperscript{51} Another clinical application is the use of proteomics technology to detect protein signatures in periodontitis that can be utilized for early diagnosis and prevention of disease progression.\textsuperscript{52,53}

DNA information combined with clinical and especially medical records becomes a necessity for highly customized periodontal treatment (Figure 1). From that perspective, medical institutions start of establishing biobanks of DNA to accelerate the realization of the personalized approach to oral health care.\textsuperscript{54} To our knowledge, statewide and national population-based biobanks in the U.S. do not currently exist. Although many privately owned biobanks exist across the U.S., 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 under the act “Genomics and Personalized Medicine Act, S. 3822”.\textsuperscript{55} In Europe, the biobanks exist but they are lacking strict regulatory guidelines. Recently, a group of experts from the European Commission has issued a report entitled “Biobanks for Europe a Challenge for Governance” and published by the Publications Office of the European Union.\textsuperscript{56} It deals with ethical, confidentiality and regulatory challenges of international biobank research and provides recommendations.
Another way to implement 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 biological systems. It can be applied for complex diseases including inflammation.\(^{57,58}\) Also, it allows for a rational modulation at the individual level by analyzing all the biological components involved in the process.

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

Genetic variations of drug metabolism-related genes (e.g. CYP2C6, CYP2C9, CYP2C19) have a significant effect on drug clearance. Some individuals are poor metabolizers while others metabolize the 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 have a huge benefit to minimize their 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 FDA has released the draft guidance, Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies 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 guidance also provides recommendations on when genomic information should be considered in order to address questions arising during early drug development.

**CONCLUSION**

It is important to know the biology behind the procedures so that the clinical outcome can be predicted.

Periodontal diseases are multifactorial where 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-analysis studies to guide our therapeutic procedures will become less practical in the near future since the new techniques incorporate the influence of genetic and environmental parameters considered nowadays as confounding factors when comparing different groups in clinical studies.

Finally, our approach to periodontal disease should no longer be limited to treating diseases but to understand the biological principles dictating the progression of the disease in order 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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Correspondence: Sleiman Razzouk
154 Mason Street, Staten Island, NY, 10304, Phone: 347/466-5156, Email: razzos01@nyu.edu

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Figure 1:
Sample of a complete patient’s record includes information gathered from genomic and bacterial profiling, clinical data and environmental parameters for personalized periodontal medicine.

¶ Illumina Inc., San Diego, CA
§ Affymetrix, Santa Clara CA