REVIEW ARTICLE

Periodontal Infectogenomics: A Review

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ABSTRACT

The genetic memory of a person affects his susceptibility to various diseases and other oral conditions. Parallel DNA sequencing has recently suggested the presence of nearly 19000 bacterial phylotypes in a number of bacterial species in the oral cavity. Genetic variations may identify patients at risk for the development of abnormal inflammatory responses to different disease conditions. The concept of infectogenomics defines the study of the interaction between host genetic variations and colonization by pathogenic microbes. The association between several genetic and microbial factors can be evidenced using the field of infectogenomics in determining the pathways of different forms of periodontitis and might also assist in prevention and management of periodontal diseases. This can be used as a diagnostic marker for determining different stages of periodontal conditions and their management.

KEYWORDS: Periodontitis, Infectogenomics, Bacterial Species

INTRODUCTION

The genetic memory of a person affects his susceptibility to various diseases and other oral conditions. Periodontitis, a chronic inflammatory disease, caused by gram-negative microorganisms in the periodontal pockets, is no exception. Parallel DNA sequencing has recently suggested the presence of nearly 19000 bacterial phylotypes in a number of bacterial species in the oral cavity.[1] Although most of the microorganisms live in a symbiotic relationship with the host and one or more colonizing bacteria it is assumed that each individual will only have a proportion of the total numbers of bacteria found in the general populations measured. The risk of acquiring infection and / or becoming ill may be attributed to a variety of environmental and social factors.[2] While considering the setting of the host this inherent virulence of the pathogen should always be considered, however it is not possible to differentiate whether virulence of the pathogen is more virulent or the susceptibility of the host.

The concept of infectogenomics defines the study of the interaction between host genetic variations and colonization by pathogenic microbes.[3] This review basically highlights the association between host genetic and microbiological factors in patients affected by periodontitis. Often the pathogen can be regarded as a constant, thereby revealing the contribution of the host. Colonization of the specific bacteria is mainly dependent on the genetic factors of the host.

HOST VARIATION IN INFECTIOUS DISEASE

Inflammation is a complex process that is preceded by initial tissue trauma and is completed with the induction of tissue repair. The inflammatory response mainly occurs due to innate immune response. Hence, variation in the genetics that disrupt the innate immune sensing is responsible for the varied immune response. Such genetic variations may identify patients at risk for the development of abnormal inflammatory responses.

The occurrence of classical Mendelian trait has large discrete effects, suggesting that, searching the human genome will reveal polymorphism thereby affecting the susceptibility to specific infectious diseases. Single nucleotide polymorphisms known as single base variations are the most commonly used variants. With increasing interest various single nucleotide polymorphisms have been explored involving genes responsible for the control of inflammatory cascades. Various potential markers of susceptibility and severity can be identified by studying these SNPs.

HOST GENETICS OF COMMON INFECTIONS

The interplay between the fitness of the host and of the pathogen determines sickness and response to various infections.[4,5,6] Resistance, subclinical infection or overt infection occurs when a host is exposed to a pathogen.

An infectogenomic approach analogous to pharmacogenetics can be envisaged to common infections that are seldom pathogenic and thus appearance of a disease or symptom following exposure to an infectious agent can be regarded as an unusual “side effect” just like an adverse reaction to a drug. With the wrong genotype, such adverse reactions can be severe indeed.For example, 85% of the global human population

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are persistently infected with Epstein-Barr virus (EBV). Most of us become infected in infancy without diagnosed illness, although infection in adolescence causes infectious mononucleosis. Moreover, common infections with low virulence may represent the unknown environmental trigger for diseases that are not clearly infectious; such as multiple sclerosis, asthma, and acute lymphocytic leukemia - when infecting a genotype predisposed to the disease. Therefore, not only seeking microbial markers of virulence, but also more efforts should be spent to identify the human genetic factors that predispose to invasion by pathogens.

GENETIC FACTORS PREDISPOSING TO PATHOGEN INVASION

The main function of host genotype presents its function through differences in gene transcription or functional differences in proteins. The mode via which pathogens remodel the host's gene expression patterns [7] and provide a wealth of candidate genes for genetic susceptibility studies have been detected by analyzing gene expression via microarrays and proteomics.

The CCR5 gene (chromosome 3) codes for the CCR5 receptor, which binds chemokines. However, this protein is also a co-receptor for HIV, aiding its entry into target cells (T cells and macrophages). A genetic variant in this gene (CCR5-D32 – deletion of a 32 bp segment) results in a nonfunctional receptor, thus preventing HIV entry. This confers complete resistance to the majority of HIV strains which enter through this receptor in the homozygous state and partial resistance and hence slower progression in the heterozygous state.[8]

THE GENETIC FACTORS PREDISPOSING TO PATHOGEN CLEARANCE/ PROLIFERATION

The interaction between microbes and host genome is greatly affected by factors of pathogen proliferation. For instance, the b-globin gene (chromosome 11) codes for hemoglobin (Hb). A genetic variant in this gene (HbS, AAT single nucleotide mutation resulting in a glutamate Avaline substitution) causes the formation of fibrous precipitates in cellular hemoglobin, with no major consequences in the heterozygous state. However, in the case of HbS homozygosity, the presence of long-chain polymers of HbS distorts the red blood cells shape, making them fragile and susceptible to breaking within capillaries (sickle cell anemia). Plasmodium falciparum causes malaria, and it spends part of its life in red blood cells. In HbS homozygous individuals, the presence of P. falciparum causes the red blood cell to rupture, and therefore, although it can enter its target cells, it cannot proliferate. As a consequence, HbS heterozygous subjects are more resistant to malaria than subjects homozygous for the normal gene. [9] Changes in gene expression profiles can also betray the type of pathogen present with the potential of identifying the pathogen through host gene expression **(Huang et al., 2001**). Thus, gene expression patterns in the blood could serve as a window into the pathogenesis and diagnosis of infectious diseases. A transcriptional profile may also be expected to aid prognosis and response to treatment. For e.g. some HIV-infected patients on antiviral therapy do not respond to falling viral load even when the virus itself shows no markers of drug resistance and it may be that host factor determines not – responsiveness in these cases. Similarly, only a proportion of patients with hepatitis C infection respond to interferon treatment and transcriptional profiling may indicate why this is so.

PERIODONTAL INFECTOGENOMICS

Periodontitis is a bacterially driven disease.[10] However, it is still questionable whether this disease is a generic response to all plaque bacteria or is caused by a selected group of oral bacteria. These two arguments have been termed the non-specific and specific plaque hypotheses. Currently, at least three bacteria have been confirmed as periodontal pathogenic: Aggregatibacter (Actinobacillus) actinomycetemcomitans, Porphyromonas gingivalis and Tannerella forsythia (American Academy of Periodontology, 2005). Putative periodontopathogens currently comprises several other bacteria. An immunopathological reaction triggered by the presence of bacteria in the crevice between the teeth and the gums results in a pathogenic damage characteristic of periodontitis. In addition to environmental epidemiological, evidence suggests genetics as a disease-modifying effect for periodontitis. Efforts in periodontal research have recently focused on the possible effect of genetic variants on periodontal pathogenesis wherein host susceptibility has been associated with the severity of plaque- induced gingivitis [11] bacteria, similarly genetic factors have been associated with periodontitis.[12] The onset of periodontitis in the presence of subgingival plaque can be determined by the presence of a few single gene disorder, usually associated with syndromes.[13] A polygenic predisposition is seen in most of the periodontitis cases, determined by the cumulative effect of subtle gene variants.[13] Among these, cytokine [such as interleukin-1 (IL-1), IL-6] and neutrophil (such as Fcc receptor) gene polymorphisms with an effect on inflammatory responses have emerged as reasonable candidates for single nucleotide polymorphism analysis, from association studies.

The effect of the genetic factors on the subgingival microbiota and its role in colonizing specific pathogens came in light due to studies on A. actinomycetemcomitans JP2 clone. This clone has a 530 bp deletion from the promoter of the leukotoxin gene missing with the consequence that it produces more of this leukocyte-killing toxin.[14] This variant has been consistently associated with people of North African/Mediterranean origin (Rylev & Kilian, 2008) and

a recent longitudinal study of Moroccan adolescents found that individuals carrying only the JP2 clone had a considerably increased risk of developing periodontitis compared with individuals who did not harbor this clone subgingivally.[15] This shows the tropism of this bacterial clone towards people within specific ethnic groups and leads to speculation that the predominant periodontal pathogenic microbiota preferably develop in subjects with a specific genetic susceptibility.

In a study of patients with chronic periodontitis (Socransky et al., 2000), subjects positive for the composite IL-1 genotype (Kornman et al., 1997) had increased counts of 14/40 bacteria (especially red and orange complexes, such as Tannerella forsythia and Treponema denticola). The authors concluded that differences in host genotype influenced the composition of the subgingival microbiota. Nibali et al. (2007, 2008) from his studies showed an association between IL 6 gene and Fcγ receptor variants and subgingivally detection of A. actinomycetemcomitans and P. gingivalis patients.[16, 17]

GENETIC FACTORS PREDISPOSING TO PERIODONTAL PATHOGEN INVASION

Requisites for microbes to invade subgingival sites[10] ***(Socransky and Hafajee, 1991):***

1. The ability to attach to the tissue surface,
2. The ability to multiply,
3. The ability to compete against other microbial species,
4. The ability to defend against host responses.

The first 3 features are dictated by the innate bacterial characteristics, while the 4th one is dictated by the host genotype where the huge machinery of inflammation and immunity comes into play in terms of recognizing bacteria and attempting to kill and remove them.

Genetic factors coding for surface receptors of neutrophils, macrophages or monocytes [Tolllike receptors (TLRs), formyl peptide receptors, Fcc receptors] involved in recognizing and killing bacteria may affect bacterial clearance. For example, TLR4 polymorphisms have been shown to affect responsiveness to P. gingivalis from gingival epithelial cells. [18] Neutrophils can recognize Ig-opsonized bacteria through specific Fcc receptors ***(van Sorge et al., 2003).***

GENETIC FACTORS PREDISPOSING TO PATHOGEN PROLIFERATION

Proliferation and initiation of the immunopathological reactions determining tissue destruction occur as soon as the bacteria colonize the periodontal tissues in susceptible individuals. Overgrowth of particular components of the opportunistic microbiota (such as, for example, A. actinomycetemcomitans) that grow well in inflamed areas occur as a result of increased inflammatory response to plaque accumulation in subjects carrying specific gene polymorphisms. For example, IL-6 is a multifunctional cytokine crucial in the inflammatory response to infectious agents (especially Gram-negative bacteria) (Dalrymple et al., 1996). Homozygosity for the G allele at position 2174 in the promoter region of the IL-6 gene has been linked to increased promoter activity and increased serum concentrations of IL-6 (Fishman et al., 1998) and is suspected as a susceptibility factor for periodontitis .[16, 17, 19]

Nibali et al (2007, 2008) showed an association between IL-6 genetic variants and subgingival detection of periodontal-pathogenic bacteria (A. actinomycetemcomitans and P. gingivalis) in two independent periodontitis patients cohorts (Nibali et al., 2007, 2008). We concluded that IL-6 hyper producer (based on their IL-6 genotypes) might be predisposed to colonization by specific bacteria and in turn to rapidly progressive forms of periodontitis upon chronic stimulation with these bacteria. Therefore, IL-6 genetic factors may affect microbial proliferation and the transformation of bacterial subgingival colonization into a chronic inflammatory process. [16, 17]

CONCLUSION

While analyzing host- pathogen interactions, the functional genomics of the host is of crucial importance. The outcome of many pathogenic infections and the influence on the genetic makeup of human populations by several pathogens can be determined mainly by host genetic variation. The association between several genetic and microbial factors can be evidenced using the field of infectogenomics in determining the pathways of different forms of periodontitis and might also assist in prevention and management of periodontal diseases. Apart from seeking new microbial virulence markers, human genetic factors should also be identified as they can serve as an essential tool in determining pathogen invasion and proliferation (Kellam & Weiss, 2006). Newer adjunctive pharmacologic treatment can be developed as the advances in gene expression profiling may shed more light in the pathogenic processes.[20]

FUTURE DEVELOPMENTS

Infectogenomics can be harnessed to identify infectious states, to understand the host response, to predict disease outcomes, to monitor responses to anti -microbial therapies, and to indicate promising new types of treatment. Periodontal infectogenomics is complicated by the biofilm nature of subgingival bacteria [10] (Socransky & Haffajee, 1991), where bacteria – some of which are considered exogenous [21, 22] ***(Haubek et al., 1996; Kaplan et al., 2002)*** – are organized in a biofilm at least 50– 100 cells thick and may not behave independently but as part of a complex. Various genetic variants having an effect on subgingival bacterial invasion and proliferation can be identified using

genome- wide association studies and pyrosequencing analysis of the periodontal microflora.

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