

Clinical and Systemic Implications of Periodontal Disease Susceptibility: The Importance of IL-6 Polymorphism

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Abstract

The importance of the genetic influence on disease susceptibility has been well-established. The genetic regulation of the immune response is a subject of considerable ongoing research in terms of periodontal inflammation and its sequelae. The development of commercially available DNA – PCR salivary testing represents an important translational development in our understanding and management of periodontitis. This paper will discuss the importance of interleukin polymorphism, especially IL-6 and its role in the determination of disease susceptibility in the periodontal patient. The clinical significance of salivary diagnostics is emphasized as an important part of the decision-making process. This type of testing and the rapidly developing innovations can literally change the way we manage patients.

Clinical significance: By providing us with knowledge of the patient's predisposition to a hyper inflammatory reaction we can intervene at an earlier stage of disease development with considerably better long-term outcome.

Keywords: IL-6 polymorphism; Periodontal disease; Genetic regulation

Introduction

There is considerable literature regarding the inflammatory nature of the periodontal diseases, and the relationship between these opportunistic infections and systemic inflammation with increasingly numerous references in the literature with regard to the genetic predisposition of the host, and how it responds to infection. The host immune response, both innate and adaptive, is the key factor in the genesis of the immune response to the offending pathogenic microorganisms. The production of proinflammatory cytokines is modified by the patient's genetic [1,2] makeup, and environmental factors. The dissemination of inflammatory mediators, pathogenic bacteria, and adaptive immune responses (metastasis), has been addressed in the literature [3,4]. This paper will attempt to address these issues within the context of inflammatory periodontitis and interleukin polymorphisms, especially the increasing awareness of the importance of interleukin-6.

Phenotypes and Inflammatory Mediators

Periodontitis, either chronic or aggressive, is a classical inflammatory disease of opportunistic periodontopathic origins. The bulk of these pathogens form part of the plaque biofilm on the root surfaces, as well as some few planktonic forms in the gingival sulcus or periodontal pocket. Although pathogenic bacteria in the tooth related sulcular biofilm are the principal initiators of the inflammatory response, the clinical and biologic phenotypes result from a complex interaction of the systemic immune response, genetic factors, and environmental influences [5-8]. The role of genetic variation e.g. interleukin polymorphisms modifying the immune response is of considerable interest, with regard to the pathogenesis of the disease [9]. Gaining knowledge of the nature of the patient's bacterial load, and any genetic predisposition to an exaggerated inflammatory response (interleukin polymorphism) can be a valuable asset in determining treatment outcome, and prognosis for long-term success.

Following the initiation of the immune response, instigated by bacterial pathogens, a number of different inflammatory mediators or biomarkers are produced by various cellular elements. These pro-inflammatory mediators are commonly known as cytokines. When working together to modulate cellular functions they are known as cytokine networks and are part of the innate immune system. Although

not conclusive, there is evidence that cytokines such as interleukin-1 β , tumor necrosis factor, and interleukin-6, among others. Modify t-cell phenotypes and disease expression (clinical phenotype) [10].

The clinical phenotype is the expression of periodontitis as seen by the clinician. Clinical phenotypes vary from patient to patient even with the same level of disease (Figures 1 and 2).



Clinical Phenotype

Figure 1: Showing two distinctly different expressions of disease in two cases of moderate to severe periodontitis.



Another clinical phenotype

Figure 2: Showing two distinctly different expressions of disease in two cases of moderate to severe periodontitis.

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Interleukin Polymorphisms

For our purposes, a genetic variation may be known as a single nucleotide polymorphism when its influence on the expression of various inflammatory intermediary components differs from normal. In other words, an over-productive or enhanced hyper-inflammatory reaction. The importance of interleukin 1-β and its association with inflammatory periodontal disease has been evaluated since 1997 in the work by Kornman et al. [11]. He and others have shown an increased production of the gingival crevicular fluid transudate, and salivary il-1β predisposes the patient to a more severe form of chronic periodontitis due to the overproduction of inflammatory stimuli by the immune system. It was shown also, that individuals genotype il-1 β positive have a salivary flora consisting of much higher levels of the more pathogenic microbial species, than normal controls [12]. The presence of a single nucleotide polymorphism can be today detected by a simple salivary sample. This helps the clinician by giving some insight into the susceptibility of a patient to inflammatory stimuli, and is especially useful in patients with co-morbid conditions such as diabetes and heart disease.

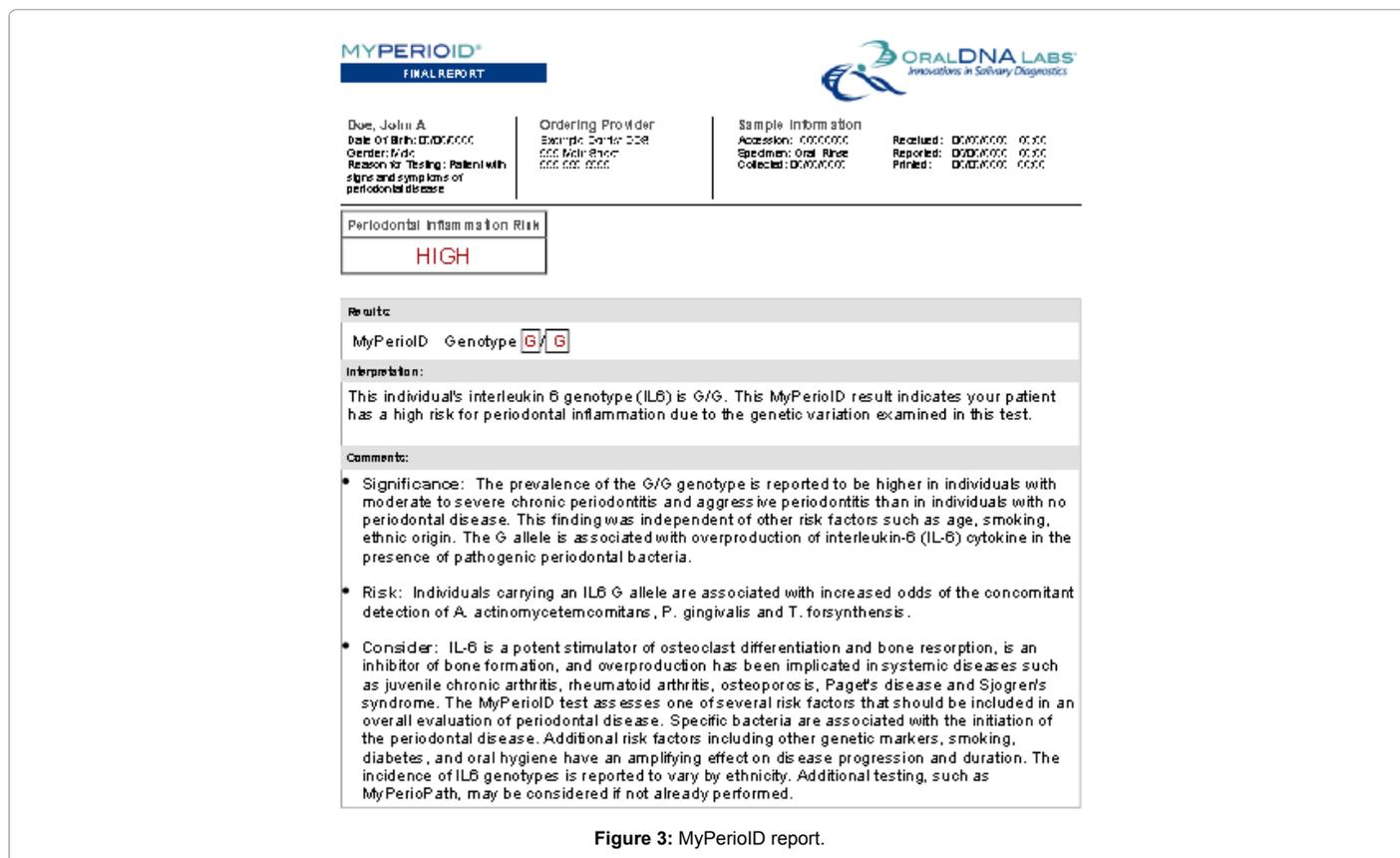
Continued research as to the role of the most commonly cited cytokines, interleukin-1, interleukin-6 and tumor necrosis factor (tNFα) continues to support the pro-inflammatory role of interleukin-6. There is considerable evidence in the literature using quantitative polymerase chain reaction (DNA/PCR) techniques for salivary analysis [13-15].

Interleukin-6-174 g/g has been described as one of the more important mediators of the aggressive inflammatory periodontal (ap) response [2], rather than simple chronic periodontitis (CP). The relationship of interleukin-6 -174 polymorphism with the presence of

aa (Aggregatibacter actinomycetemcomitans), and Pg (Porphyromonas gingivalis) in aggressive periodontitis has been demonstrated [8], along with association with systemic entities such as systemic onset juvenile chronic arthritis [16]. Pg as been reported as being in possible association with increased il-6 production during chronic periodontitis, showing a high-frequency of the G allele at position -174 [17].

One of the systemic entities that has been linked to inflammatory periodontitis because among other things, of their shared cofactors is coronary artery disease (CAD). In 2011 a study reported that patients with the GG genotype are at approximately 2.78 higher risk of coronary artery disease, and il-6 was higher as well, in a diabetes mellitus group of patients [18]. Other systemic relationships of il-5 polymorphism are systemic lupus erythematosus, nephritis, and COPD all commonly associated with systemic inflammation [19,20]. There is ample evidence in the literature pointing to a direct and dose dependent relationship between periodontitis severity and diabetic complications, with an increased risk in patients with severe periodontitis for diabetes onset. Added to this relationship is the cofactor of obesity [21-23]. In view of the substantial evidence as to the very important role of interleukin-6 polymorphism as a marker, and predictor of inflammatory changes in disease, a simple salivary test has been developed and is currently being used in private practice. The My PeriID® by Oral DN Labs is a simple salivary laboratory test that provides useful and important information on the patient's predisposition to a hyper reaction to inflammation induced by pathogenic bacteria. The salivary sample is subjected to DNAS-PCR analysis for the presence of thirteen principal periodontopathogens. It is both qualitative and quantitative with sensitivity to within 100 organisms.

As seen in Figure 3, The report shows a patient demonstrating



a genetic predisposition to inflammation, due to an interleukin-6 polymorphism, producing an overabundance of the cytokine, and being associated with three high risk pathogens, Aggregatibacter actinomycetemcomitans (Aa), Tanerella forsythia (Tf), Porphyromonas gingivalis (Pg), and less invasive, but very opportunistic members of the “orange cluster” such as Campylobacter rectus, and Eubacterium nodatum. This increased risk of association with these periodontal pathogens is well documented [2,24-26]. And this information gives the clinician the ability to share risk assessment for future inflammatory attachment loss, and in the case of the patient with co-morbid conditions such as diabetes and CVD useful information to help reduce the risk of exacerbation. Previous studies have shown that the increased inflammatory response of -174 gg patients promote the colonization of pathogens that grow very well in the presence of inflammation, which include Aa, Pg and Tf [27]. The concept of “infectogenomics” was created to suggest that genetic factors in the host may play a role in deciding which pathogens and commensal organisms infect the host [28].

Conclusion

As stated by Woo P, and Humphries SE “this polymorphism has been used as a functional variant to further clarify the role of elevated il-6 levels in various disease states, and therefore further confirming the important role of IL-6, as a causative factor in human health and disease” [29]. Now, with the simple My PerioID® salivary test we can easily test for this genetic factor, and use the knowledge gained to help manage the patient, and predict the danger of future inflammatory changes.

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