Gene polymorphisms in periodontitis. Overview

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Today, it is known that pathogenic bacteria are the key factors for the initiation of periodontal disease, but the host response and the severity of clinical expression are largely determined by genetic susceptibility and environmental factors. There is evidence that the individual response to the environment and variations in the immune response in periodontitis are associated with genetic factors. Of particular interest are the polymorphisms of interleukin-1 beta (IL-1b), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-a) genes and the factors that determine the production of these cytokines, since they play an important role in the pathophysiology of inflammation and in particular, in periodontal diseases. The identification of a specific IL-1 family genotype which correlates with the severity of periodontitis, demonstrates that it is genetic mechanisms that determine the intensity of immunoinflammatory response in different individuals (and hence, the severity of periodontal disease) due to the presence and persistence of bacterial plaque. This mini-review focuses on the current state of knowledge of genetic polymorphisms in patients with chronic periodontitis. Extensive studies on genetic factors in chronic periodontitis raise hopes for the identification of determinants related to disease susceptibility and improved diagnosis and treatment of chronic periodontitis, as well as prediction of disease progression.

Keywords: chronic periodontitis; gene polymorphisms; interleukin-1 beta; interleukin-6; tumour necrosis factor-alpha; immunoinflammatory response

Introduction

The present-day concept of the initiation and progression of periodontal diseases is centred on the etiological significance of bacterial biofilm and the features of the host response against pathogenic bacteria. The current state of knowledge of the pathogenesis of chronic periodontitis suggests a similarity with other inflammatory diseases and conditions, which also exhibit large variations in the clinical course and are related to genetic factors.

There is abundant evidence about the importance of plaque-induced gingival inflammation in the development of chronic periodontitis. Nevertheless, the ‘susceptibility’ to periodontal disease and the characteristics of the host’s response are still not fully understood.[1–3] One line of research attempts to seek evidence for determinants of chronic periodontitis associated with the host. This approach is based on the hypothesis that there are underlying genetic factors that determine and modulate the individual susceptibility to periodontitis. There is evidence that the individual response to the environment and variations in the immune response in periodontitis are associated with genetic factors. According to Michalowicz et al.,[4] chronic periodontitis is associated with heredity in 50% of cases. Other authors suppose that persistent gingival inflammation is a major risk factor for the loss of clinical attachment and subsequent loss of teeth.[5–7]

There is often considered to be an association between susceptibility to gingivitis and that to periodontitis.[8,9] According to some reports, the clinical expression, susceptibility and development of periodontal disease can be affected by different alleles of cytokine genes and factors determining their expression.[10–12] Thus, the inability to regulate the expression of these cytokine genes may be the cause of ongoing inflammation of the tissues, such as that characteristic of periodontal diseases.[13]

Interleukin-1 beta (IL-1b)

The 1990s witnessed a boom in research on the role of gene polymorphisms in periodontitis and the concept has continued to develop since. For example, the genetic variations in the production of IL-1 family cytokines could offer an explanation of the differences in the degrees of severity of periodontal disease.[14] Moreover, it is considered that some of the identified polymorphisms may contribute to the detection of individual variations in cytokine production proportional to the severity of periodontal disease.[15] In other words, the genetic basis of periodontitis, like of many diseases with multifactorial pathogenesis, may be influenced by small phenotypic differences caused by common alleles of several disease-related mutant genes.[16]
The mechanisms of initiation and progression of chronic periodontitis appear to bear some similarity with other inflammatory diseases and conditions, which are known to show large variations in the clinical course. One possible explanation could be that various gene polymorphisms may influence the disease process. It has been suggested that, in the population, there may be subgroups of individuals with a specific genetic profile (with different gene variations), which defines the so-called ‘susceptibility’ to the clinical expression of the disease. It could be expected that certain major genes may be implicated in the pathology of chronic periodontitis, similar to other complex diseases.[17]

There are some reports that attempt to identify genetic factors associated with periodontitis.[4,16] These include primarily polymorphisms of interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) genes. It is not surprising that there should be such interest in the factors that determine the production of these cytokines, since they are known to play a role in the pathophysiology of inflammation as a whole[18] and in particular, in periodontal diseases.[19–24] With respect to chronic periodontitis, efforts have focused on detecting the presence of polymorphisms of the interleukin-1β gene and the relationship with periodontal destruction. A growing pool of data show significant associations of interleukin-1β gene polymorphisms with destructive periodontal disease and the severity of attachment loss and bone loss in chronic periodontitis.[21,25]

There are three IL-1 genes in human chromosome 2q13.[26] Two of the IL-1 family genes, IL-1A and IL-1B, encode the proinflammatory proteins IL-1α and IL-1β, respectively, while the third gene, IL-1RN, encodes a protein that binds to IL-1 receptors but acts as a receptor antagonist (IL-1ra), and has the only known function to prevent the activation of target cells.[27] The overall sum of IL-1α and IL-1β, and the IL-1/IL-1ra ratio has been shown to correlate with bone loss in periodontitis.[28] In their study, Kornman et al.[10] concluded that the genotype comprising the carriage of common 2 allele (‘2) at IL-1A and IL-1B, can be used as a genetic marker for the severity of disease in patients with chronic periodontitis. It has been shown that the IL-1 genotype is a marker for certain biological changes that can lead to the development of severe periodontitis, without regard for the level of pathogenic bacteria (bacterial load).

The role that a positive IL-1 genotype might play in a primarily Caucasian population was described by Socraisky et al.[29] They found that the mean counts of specific microbial species were higher when IL-1 positive genotypes were presented compared to negative subjects. These periodontal pathogens in high levels were also frequently related with periodontal inflammation and an association between positive genotype and severe chronic periodontitis was observed only in older individuals and in patients with deep pockets.

The positive genotype should, therefore, be viewed as a ‘severity factor’. It is noteworthy that the positive genotype (allele 2) was detected in only 8% of the examined Afro-Americans[30] and in only 2.3% of the examined Chinese patients[31] but in every third Caucasian. Positive genotype becomes critically important only in combination with additional risk co-factors. Additional important risks for periodontitis, alone or combined, are well known: smoking and poor oral hygiene, and also systemic conditions (diabetes, HIV), stress, age.[32]

The specificity of periodontitis associated with the IL-1 genotype appears to be rooted in the presence of allele 2 in IL-1B (+3953), which determines an increased production of IL-1β.[33] For example, there is evidence that two alleles, −889T and 3953/4T allele of the IL-1B gene, may be related to the development of the severe form of periodontitis.[34] The meta-analysis made by Nikolopoulos et al.[34] indicates that IL-1A C[−889]T and IL-1B C[3953/4]T (+3954 previously described as +3953) are risk factors for chronic periodontitis. On the other hand, allele 2 in IL-1RN is associated with an increased production of IL-1ra, both in vitro and in vivo.[35,36] This is of particular significance, as the production of IL-1ra has been shown to be directly related to periodontitis. Several studies have investigated genetic polymorphisms for some cytokines as potential genetic markers for periodontitis. There is also evidence for a relationship between the severity of periodontitis and elevated levels of IL-1β and lower levels of IL-1ra in gingival crevicular fluid.[28] Ishihara et al.[28] reported that the IL-1 genotype (IL-1α + IL-1β) and IL-1ra are associated with the severity of periodontitis. There is accumulating evidence that IL-1A and IL-1B polymorphisms are associated with a higher severity of periodontitis as well as with disease prediction.[10,11,17,37,38,40–42] For example, López et al.[42] reported that the frequency of the heterozygous state of IL-1B+3954 was significantly higher in cases than in controls and was associated with periodontitis. The prevalence of positive genotype (at least one allele 2 present at each locus) was also significantly higher in cases with chronic periodontitis than in controls and was significantly associated with periodontitis.[42]

Similarly, other authors have also attempted to determine the distribution of IL-1 gene polymorphisms (IL-1A+4845 and IL-1B+3954) and their association with periodontal disease severity. The results of Agrawal et al.[41] support the understanding that the IL-1 genotype could be considered as a risk factor for severe chronic periodontitis. In their study, positivity for the composite genotype (IL-1A allele2+IL-1B allele2) was found to be significantly associated with severe chronic periodontitis.
It has been suggested that other genetic factors, like chemokine ligand 5, may also predispose individuals to periodontal diseases.[38] For example, Shih et al. [38] have reported a significant association between the type of periodontitis and the presence of allele A or G in the −403 single nucleotide polymorphism (SNP) of chemokine ligand 5 (CCL5-403).

However, as highlighted in another recent review, that of Kornman and Polverini,[39] IL-1 genes may have not been identified in chronic periodontitis genome-wide association studies due to limited search by SNP, specific gene—non-gene (environmental factors) interactions and other factors. Thus, the specific genetic markers that are associated with an increased production of IL-1β remain important suspect indicators as regards to the severity of periodontitis. The fact that a specific IL-1 family genotype has been found to correlate with the severity of periodontitis demonstrates that it is genetic mechanisms that determine the intensity of immunoinflammatory response in different individuals (and hence, the severity of periodontal disease) due to the presence and persistence of bacterial plaque.[37–44]

This understanding has evolved into the development of gene tests. For instance, several specialized laboratories currently propose interleukin-1 gene tests that measure the SNPs for the IL-1A at locus +4845 or −889 (identical), and for IL-1B at locus +3954. These are all based on the DNA analysis by using polymerase chain reaction.[32]

**Tumour necrosis factor-alpha (TNF-α)**

Similarly to interleukin-1β, TNF-α is also considered to be a key cytokine in the development of the inflammatory response in periodontitis and could be assumed to be important for the efficiency of the immune response, and the degree of clinical outcomes during the anti-inflammatory therapy of the disease.[45,46] *In vitro* studies have shown differences in the individual production of TNF-α in various inflammatory stimuli.[47] There is evidence for the significance of the TNF-α polymorphism (namely transition from guanine–guanine (G) to adenine–adenine (A) of the TNF-α-308 allele) and an increased risk for diseases, such as ulcerative colitis and Crohn’s disease.[48] pediatric-onset inflammatory bowel disease [49] and periodontitis.[50,51] On the other hand, carriage of allele LT-α-252 (Lymphotoxin-alpha, formerly known as TNF-β), has been found to be related to an increased production of TNF-α both in *vivo* [52] and in *vivo*.[53,54]

Kornman and Di Giovine [55] reported an increased TNF-α-308n2 allele frequency in Caucasian patients with chronic periodontitis compared with periodontally healthy subjects. A correlation was also established with the severity of periodontal disease.[55] Moreover, Galbraith et al. [51,56] found that the TNF-α-308n2 allele is a risk factor related to the severity of chronic periodontitis.

According to Scapoli et al., [57] Lin et al. also demonstrated an increased frequency of TNF-α-308n2 allele in Chinese patients with chronic periodontitis. Conversely, Fassmann et al. [50] did not show the TNF-α (−308G/A)-polymorphism to be associated with chronic periodontitis in a cohort of Czech patients.

**Interleukin-6 (IL-6)**

Another gene which has been investigated in relation to periodontal disease is the gene encoding interleukin-6 (IL-6), and more specifically its polymorphisms (−174)G/C, (−190)C/T and (−597)G/A.[2,49] IL-6 is a proinflammatory cytokine associated with destructive periodontal tissue changes and has been proposed as a ‘biomarker’ in the progression of periodontitis.[58] IL-6 is produced by different cells: monocytes, macrophages, activated T-cells, mast cells, endothelial cells, fibroblasts. It is considered to be a regulator of the immune response, haemopoiesis, and the transition between acute and chronic inflammation.[59,60] IL-6 is also related to increased bone resorption through increased osteoclast formation.[61,62] Increased production of IL-6 in an inflamed tissue is often associated with an increased production of other cytokines, such as IL-1β and TNF-α.[63,64] The local production of IL-6 in the inflamed periodontal tissues has been found to correlate with the probing depth of periodontal pockets [20,58,65–68] and the loss of attachment.[66,68] The serum level of IL-6 tends to increase immediately after subgingival instrumentation.[69–71] Furthermore, it has been suggested that the resolution of periodontal inflammation can be followed by a reduction in serum levels of IL-6 after the initial periodontal therapy.[22,72]

Certain polymorphisms affecting the cytokine gene sequences appear to be associated with the transcriptional activity.[29,73–75] Another investigated polymorphism in the gene encoding IL-6 is the IL-6-174 GG genotype, which is associated with the prevalence of periodontal disease in patients with moderate and severe periodontitis.[76] Interestingly, this IL-6-174 genotype and the prevalence of moderate and severe periodontitis appear to correlate with serum concentrations of IL-6.[77] The substitution of G to C at position −174 of the promoter of IL-6 is located directly opposite of the common element located at position −173 to −151, which is considered also responsible for the initial transcription.[78] This C allele leads to the alteration of IL-6 gene transcription and corresponding responses to irritants, such as lipopolysaccharides and IL-1.[79] This allele has also been suggested to be related to genetic susceptibility to inflammatory diseases. Moreover, a similar structural and functional disorder is related to the substitution of a G at position −308. [80,81]
Periodontal inflammation is generally considered in two aspects. On one hand, the inflammatory response has a protective role in eliminating microorganisms from affected tissues. On the other hand, the persistence of chronic inflammation is responsible for the expression of inflammatory mediators and can lead to tissue destruction and tissue changes in periodontitis (loss of epithelial attachment, connective tissue attachment, periodontal ligament, alveolar bone). Progression of periodontitis may be regarded as a result of a specific combination of environmental factors and factors of the macroorganism (including genetic ones), the presence of pathogenic microorganisms, high tissue levels of inflammatory cytokines, production of destructive enzymes (matrix metalloproteinases) and prostaglandins.[82]

Conclusions
As a result of extensive research on the involvement of genetic factors in the pathological process of periodontal diseases, certain genetic factors have become relevant to the diagnosis, clinical course, treatment and control in patients with periodontitis. In the presence of numerous bacteria, including periodontal pathogens, the immune response in conjunction with tissue destruction have been shown to play an important role in the chronic inflammatory process in periodontium. It has been suggested that cytokines are probably significant factors in the maintenance of tissue homeostasis and ensure the delicate balance between different factors internal and external to the host. In this regard, a number of mediator molecules have been observed to be elevated in cases with chronic periodontitis (prostaglandin E₂, interleukin-1 alpha, interleukin-1 beta, interleukin-8, interleukin-6, interleukin-10, TNF-alpha). Hence, the large body of investigations on the key role of these specific biomolecules in both disease development and disease progression. Moreover, attempts have been made to outline and describe how these parameters influence the disease course and treatment results. Current evidence points to the impact of genetic factors in the pathogenesis of periodontitis, e.g. some gene polymorphisms of interleukin-1 beta (IL-1β +3954), TNF-alpha (TNF-α -308) and interleukin-6 (IL-6 -174, IL-6 -597), which appear to correlate with disease severity. Thus, a commercially available test has been developed to determine the ‘susceptibility’ of patients to periodontitis based on the discovered gene polymorphism of IL-1β. However, despite the continuously accumulating body of experimental data there is still no sufficient clarity about the importance and mechanisms by which the presence of a particular polymorphism of inflammatory cytokines influences the expression of chronic periodontitis. In addition, genetic factors are not the only explanation for the development of chronic periodontitis. At present, the inconclusive reports suggest that further detailed studies are needed on the genetic polymorphisms of the major cytokines that are known to be involved in the protective—destructive immune response in periodontal diseases.

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