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Review

Presence of IL-8 Gene Polymorphism and IL-8 Serum Levels in Patients with Chronic Periodontitis - Literature Review

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Abstract

Multifactorial nature of chronic periodontitis is well known. The data indicate that the bacteria of subgingival biofilm (with their presence at high levels, too), as well as the immune response of the organism, genetic components and environmental factors play a significant role in the development of periodontal destructive disease. On the one hand the strong relationship between microorganisms from the "red complex" has been proved. On the other hand the initiation and progression of chronic periodontitis has been verified, as well. The presence of bacterial metabolic products and other substances (lipopolysaccharides, enzymes and toxins) results in increased expression of proinflammatory cytokines and release of active agents leading to the development of a local tissue lesion. Thus, the negative (destructive) side of the immune response is expressed and associated with the immunopathological nature of periodontitis. Literary data testify the importance of interleukin-8 (IL-8) in regulating the inflammatory response to bacterial infection and suggest its association with susceptibility to periodontitis.

Keywords

chronic periodontitis, cytokines, interleukin-8, gene polymorphism.

INTRODUCTION

Periodontal diseases are a widespread infection of the oral cavity, with chronic periodontitis being the most common form of the disease. It is estimated to affect between 5% and 79.6% of the human population worldwide.[1-3] The clinical manifestation of periodontitis is associated with the loss of adjacent tooth tissues and consequent loss of teeth especially among the adult population.

Periodontal diseases are initiated by a small number of specific microorganisms which have the ability to activate a local and a systemic response with a cascade of inflammatory and immunological processes associated with periodontal destructive effects. There is evidence in the literature that cytokines play a crucial role both in the maintenance of tissue homeostasis and in the pathogenesis of destructive periodontal diseases. The impaired balance and enhanced expression, as well as the on-going release of biological mediators of inflammation in tissues, are considered to account for the local tissue destruction and progression of periodontitis.[4-6]

Many authors seek evidence of determinants of chronic periodontitis in the environment (smoking, stress, systemic diseases) as well as genetic factors (including the family of proinflammatory cytokines, such as IL-1 and TNF-α, IL-8 chemokines, IL-6 adipokines, RANKL, bone destruction factors, such as PGE2, etc.) as a basis for determining and maturing individual sensitivity of individuals to periodontitis.[7-11] There is evidence that individual reactivity to the environment and different expressions of immune response in periodontitis are related to genetic factors. According to Michalowicz et al., in 50% of cases chronic periodontitis is

associated with heredity.[2]

While reviewing the mechanisms of initiation and progression of chronic periodontitis most authors make analogy with other inflammatory diseases and conditions, such as rheumatoid arthritis, coronary heart disease, ulcerative colitis and Crohn's disease, cellular oral carcinoma, known to exhibit a great number of variations in the clinical course.[12-14] An explanation for this could be precisely the influence of various gene polymorphisms on the onset of the disease process. According to some researchers, subgroups of patients in the population could have a certain genetic profile with different genetic variations, and this would determine the so-called "susceptibility" to the clinical expression of the respective disease.[13,15] Like other complex diseases, it may be expected that certain gene polymorphisms are also involved in the pathological process of chronic periodontitis.

However, there is evidence that genetic variations affect the response of the organism by means of receptor expression and secretion of proinflammatory cytokines and chemokines quantified in the crevicular fluid, such as IL-1β, IL-8, IL-10 and RANTES (regulator of the activity of normal T-cell expression and secretion) that are associated with a certain periodontal status. There is data that genetic factors are likely to be important determinants of the risk of periodontal diseases by suggesting that these diseases are polygenic rather than monogenic.[11,16-18] The role of bacterial infection for the development of periodontitis is known, but the presence of environmental factors as well as genetic factors are also suggested to be involved in the susceptibility of the organism to the development of periodontal disease.[19,20]

Studies have been published to attempt to identify genetic factors in relation to predisposition to periodontitis. Special attention is paid to proinflammatory cytokines (IL-1, IL-6), TNF-α, as well as IL-8, a known chemokine responsible for inducing chemotaxis and migration of polymorphonuclear leukocytes (PMNs) to the inflammation site.[8,10,21]

Interleukin-8 is recognized as a significant factor in the regulation of the body's inflammatory response.[22] It is related to the attraction and activation of neutrophils into the area of inflammation, which is an expression of the first line of defense against periodontal pathogens, migrating from the peripheral blood to gingiva.[20,23]

Interleukin-8 is usually released from multiple cells, such as lymphocytes, monocytes, macrophages, fibroblasts and epithelial cells. It has a significant effect on the regulation of polymorphonuclear leukocyte function, not only by inducing the adhesion of neutrophils to endothelial cells but also by stimulating exocytosis of granules of neutrophils associated with the release of lysosomal enzymes. The production of proinflammatory chemokine-8 is important for regulating the inflammatory response of an organism. Interleukin-8 is known to be expressed in gingival epithelial cells due to stimulation by the parodontopathogenes Porphyromonas gingivalis and Tannerella forsythia as well as the levels of other proinflammatory cytokines - IL-1 and TNF-α at the site of inflammation.[20,24,25] Interleukin-8 is unique in since it is produced at the earliest compared to other inflammatory cytokines and persists for a long period of time - from a few days to a week.[26,27]

The IL-8 gene is located in chromosome 4q13-q21 containing two single nucleotide polymorphisms (SNPs) at position -251A / T (rs4073) and -845T / C (rs2227532).[28] Interleukin-8 (IL-8) production is controlled by the nuclear factor (NF)-kB that regulates the expression of several genes accounting for the inflammatory response of the organism, cellular response to stress, plays a role in osteoclasts formation and turns out to be a significant factor in the pathogenesis of periodontitis.[29,30]

An analysis of the presence of SNP polymorphism in locus -251A / T indicates that the availability of allele A leads to increased levels of IL-8 after stimulation with lipopolysaccharides (LPS) from the cell walls of parodontopathogenic microorganisms. Therefore, the relationship between 251A / T polymorphism and periodontitis is an object of interest.[32] The relationship between the presence of single nucleotide gene polymorphism (SNP) in the reference sequence (rs4073) and chronic periodontitis has been well studied by setting the levels of IL-8 mRNA in gingival tissue and serum from diseased and healthy individuals with corresponding genotypes.[28,31,33]

There are studies in the literature investigating the relationship between SNP (rs4073) and diseases, such as stomach cancer, breast cancer, oral squamous cell carcinoma, prostate carcinoma, etc. It has been shown that the availability of A allele or genotype AA is associated with an increased risk of such diseases in the respective individuals.[12-14]

The significance of IL-8 chemokine in the pathogenesis of periodontitis has also been investigated. The first study on the relationship between IL-8 gene polymorphism and periodontitis was carried out by Kim et al. The authors found out that the presence of -251A / T SNP in IL-8 gene was not associated with a risk of developing periodontitis in Brazilian populations.[35] However, in a subsequent study by Andia et al. it is assumed that polymorphisms in the IL-8 gene rather have a protective role in the development of periodontitis again in Brazilian populations.[28] Hull et al. proved that white blood cells (PMNs) in individuals carrying A allele, produced higher levels of IL-8 as well as of pro-inflammatory cytokines, such as IL-1 and TNF-α in response to stimulation of parodontopathogenic microorganisms by LPS.[12,31] Linhartova et al.[38] studied the linkage of four polymorphisms in the IL-8 gene with the progression of chronic (CP) and aggressive periodontitis (AgP). These polymorphisms were localized in a chromosome at the following positions rs2227532 (-845 T / C), rs4073 (-251 T / A), rs2227307 (+ 396T / G) and rs2227306 (+781 C / T), respectively. Various allelic combinations between IL-8 genes can determine susceptibility to developing chronic or aggressive periodontitis - for example, finding (-251T / A) heterozygosity and (+ 396T / T) homozygosity

in genotype has been associated with increased susceptibility of individuals to the development of chronic periodontitis.[29,34,36,37,39,40] The conducted clinical trials have shown that patients with chronic periodontitis have higher serum levels and gingival exudate of IL-8 compared to patients with healthy periodontium.[4,6,17,23,41]

From the conducted studies and data available related to the detection of IL-8 gene polymorphism and its serum levels in patients with chronic periodontitis, it has not yet been fully elucidated whether the presence of this cytokine is related to the severity of periodontal disease. It is known that periodontitis is regarded as a multifactorial condition that manifests as a consequence of the interaction between the external, microbial and genetic factors.

CONCLUSION

For the last years, much attention has been devoted to the significance of genetic factors in etiology and pathogenesis of periodontal diseases and their importance in determining the risk of periodontal disease progression. Performing genetic tests can help to determine more accurately the degree of susceptibility of individual to the development of periodontitis and the likelihood of tooth loss due to periodontal disease. Determining available genetic factors and specific inflammatory biomarkers, related to them, may help the clinician choose the right approach to prevention and control of periodontal disease in patients with proven susceptibility. It is assumed that dynamic interactions between cytokines and their derivatives, as well as their amount can be a factor in control of inducing reduction of cytokines, typical for periodontal disease. Knowing these facts will determine the future need for further studies on the presence of IL-8 gene polymorphism and IL-8 levels in order to obtain reliable data on the significance of interleukin-8 and its role in the development of chronic or aggressive periodontitis.

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Наличие полиморфизма гена IL-8 и уровней сывороточного IL-8 у пациентов с хроническим периодонтитом - обзор литературы

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Абстракт

Многофакторная природа хронического периодонтита хорошо известна. Данные показывают, что бактерии из сублингвальной биоплёнки (с высоким уровнем), а также иммунный ответ организма, генетические компоненты и факторы окружающей среды играют важную роль в развитии деструктивного заболевания пародонта. С одной стороны, была доказана тесная связь между микроорганизмами «красного комплекса». С другой стороны, начало и развитие хронического периодонтита также были установлены. Присутствие продуктов метаболизма бактерий и других веществ (липополисахаридов, ферментов и токсинов) приводит к повышенной экспрессии провоспалительных цитокинов и высвобождению активных веществ, что приводит к образованию локального поражения ткани. Таким образом, отрицательная (деструктивная) сторона иммунного ответа выражена и связана с иммунопатологической природой периодонтита. Литература подтверждает важность интерлейкина-8 (IL-8) в регуляции воспалительного ответа на бактериальную инфекцию и предполагает его связь с предрасположенностью к пародонтиту.

Ключевые слова

хронический периодонтит, цитокины, интерлейкин-8, полиморфизм генов