

INTERLEUKIN-10 – A POTENTIAL MARKER FOR PERIODONTITIS RISK

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Summary

Periodontitis is a multifactorial disease with a significant impact worldwide. In its clinical manifestation, the destructive process causes damage to tooth-supporting tissues and has the potential for tooth loss or loss of dentition. Considered as a complex disease, periodontitis shares similar pathogenetic mechanisms with other systemic diseases such as metabolic syndrome, obesity, rheumatoid arthritis, diabetes mellitus, bronchial asthma, etc. In recent decades, the discussion of the importance of single nucleotide polymorphisms of many cytokines, including Interleukin-10, both in terms of the occurrence and in relation to the clinical manifestation of many diseases, incl. periodontitis, leads to elucidation of the role of single nucleotide polymorphisms in these complex, still incompletely elucidated processes.

Key words: periodontitis, Interleukin-10, risk marker

Periodontitis is considered as an inflammatory disease that is initiated by the presence of specific periodontopathogens or groups of such and leads to progressive destruction of tooth supporting tissues, destruction of periodontal ligament and alveolar bone. Severe periodontitis is associated with subjective feelings on the part of the patient of discomfort, pain and, left untreated, often leads to tooth loss. Periodontitis is a serious health problem, and this disease is known to be one of the causes of tooth loss in patients from developed and developing countries. Although the presence of the specific microorganisms is a key point that initiates the pathological process, the body's response provokes the secretion of proinflammatory mediators, which leads to the degradation of the extracellular matrix and bone resorption. The overexpression of such mediators is strongly influenced by the presence of anti-inflammatory cytokines such as IL-10 (1). There is scientific evidence that in certain populations a certain percentage of individuals (between 5 and 15%) are characterized by an increased susceptibility to a given disease (2,3,4). Currently, clinical interest is focused on the identification of individuals susceptible to the development of periodontitis.

The interest in genetic factors related to oral diseases and periodontitis is aimed at searching for gene polymorphisms (often of pro- and anti-inflammatory

cytokines) that play a role in the immune response, tissue damage processes or metabolic processes. Many data indicate that allelic variations in genes encoding cytokines, as well as factors regulating their expression, can influence susceptibility to periodontal disease, its clinical course, its progression and severity. Gene polymorphisms exhibit a protective or destructive effect with respect to a disease, and dysregulation in their gene expression is often responsible for repeated cycles of tissue inflammation (5). It is hypothesized that the analysis of single nucleotide polymorphisms (SNPs) will facilitate the discovery of multiple periodontitis-associated genes as genetic markers.

Interleukin - 10 (IL-10) is an anti-inflammatory interleukin, the levels of which are often decreased in patients with severe periodontitis, at the expense of increased levels of pro-inflammatory mediators such as some pro-inflammatory cytokines - IL-2, IL-6, IL-8, interferons, TNF- α etc. The interest in this cytokine is associated with its role in the development of other chronic diseases sharing a similar pathogenetic pathway with periodontitis. Single gene polymorphism of IL-10 at different positions is associated with diseases such as aggressive lymphoma, cardiovascular diseases, chronic alcoholic liver disease, endometriosis, severe periodontitis, etc. diseases, but also with longevity (6). IL-10 is a cytokine that is produced by Th2 cells and inhibits the production of some cytokines by activated Th1 cells. IL-10 modulates the expression of bone marrow-derived cytokines. The role of IL-10 as an anti-inflammatory and immunosuppressive factor has been demonstrated in various experimental models (7).

Scientific evidence elucidates the role of certain cytokines and their single nucleotide polymorphisms in the pathogenesis of periodontal disease. Regarding IL-10 SNPs, three positional polymorphisms are of interest at position -1082, -819 and -592. Research has been conducted on the three promoter regions in an attempt to link a particular polymorphism to susceptibility to periodontitis and to an association of the polymorphism with more severe periodontal disease. At the same time, the fact that gene polymorphisms have different expression and influence in different populations is discussed. The distribution of IL-10 single nucleotide polymorphisms in the different geographic latitudes is characterized by specific variations in the genotypes isolated in the studied individuals. The effect of these polymorphisms on the severity of periodontitis remains debated and warrants detailed studies.

Analyses looking for an association between periodontitis and SNPs and IL-10 have been performed in different populations. Both patients with periodontitis and healthy individuals as a control group were subjected to analysis. In most studies, certain genotypes or haplotypes are associated with severe periodontitis. The significance of gene polymorphisms of single nucleotide polymorphisms (SNPs) in the promoter region of Interleukin - 10 (IL-10) at sites - 1082, -819 and -592 probably consists in maintaining the oral dysbiosis characteristic of periodontitis (8,9).

When interpreting data from meta-analyses for non-Asian study groups with respect to IL-10 SNPs, three polymorphisms were investigated: -1082, -819, -592. Regarding the IL-10 (-819) SNP, no statistically significant associations were found between polymorphism carrier and periodontal disease. This is also confirmed by modern data, some of which were obtained from a population on the Balkan Peninsula. Studies conducted in a Macedonian population for IL-10 polymorphism at position (-819) showed a predominance of the C-allele over the T-allele, however, no statistically significant association with the severity of periodontitis was found (10). Similar results

were obtained in an Iranian representative sample studied (11). Cited data from meta-analyses are based on a total of 14 studies aimed at investigating a putative association between IL-10 gene polymorphism and periodontitis. Seven of them focused on the role of the IL-10 SNP at position (-819), with the data suggesting no association between the presence of the polymorphism of the sought cytokine and periodontal disease. When analysing the ratio of TT genotype to CC+CT in European and Asian populations, a lack of statistically significant interactions is indicated (12,13).

Regarding the IL-10 SNP at position (-1082), conflicting data have been obtained. Moreira investigated the presence of a gene polymorphism of IL-10 (-1082G/A) in a Brazilian population, justifying his study with facts that genetic mechanisms influence the expression of important mediators of inflammation, modulating the body's immunological response - a process characteristic of periodontitis. In the studied population, an allelic distribution was found - 44% (AG genotype), 36% (GG genotype), 20% (AA genotype) - in patients with periodontitis. In the control group, the allelic distribution is also in favor of the A/G genotype - 43%, 40% (GG genotype), and the lowest prevalence of AA genotype 17%. A similar theoretical formulation, again in a Brazilian population, but led by Scarel et al. found that regarding the studied polymorphism, mostly women are exposed to a higher risk of developing periodontitis (14,15). An IL-10 polymorphism study was performed (-1082) in a population from Saudi Arabia, found that the AA genotype was associated with moderate and severe periodontitis in the individuals included in the study. When examining the G/A genotype in the control group of people from the same study, a predominance of the GG genotype was found (16).

Despite the existence of conflicting data on the significance of interleukin-10 single nucleotide polymorphisms at positions (-1082) and (-819), findings from meta-analyses summarize that the A-allele and AA genotype for position (-592) was significantly associated with an increased risk of periodontitis, and the A-allele was significant and had an effect for European race. It found that the CC genotype was associated with resistance to periodontitis in a European population. and that in the same population smoking increases the risk of periodontitis. Confirmatory data have been obtained regarding the presence of homozygosity for the A-allele as a risk factor, and regarding the CC-genotype - a protective role regarding the development of periodontitis. The research team concluded that the data obtained were associated with geographic differences (17,18).

In studies on IL-10 polymorphism at the (-597) site in severe periodontitis with risk of rapid progression, data in a Turkish population on the significance of IL-10 polymorphism are conflicting. Polymorphism at site (-597) is associated with susceptibility to generalized severe periodontitis with risk of rapid progression - AA genotype is associated with seven times higher risk of developing generalized severe periodontitis with risk of rapid progression compared to AC/CC genotype (OR: 7) (19,20). An IL-10 gene polymorphism study in a Chinese population found that the A-allele (OR=2.32) and the AA-genotype (OR=4.23) at the SNP at position (-592) significantly increased the risk of periodontitis, and elevated levels of A. actinomycetemcomitans were found in carriers of the specified genotype (17). These data are also confirmed in a study of patients with periodontitis and healthy controls in an Italian population. Scapoli et al. discussed in their study that the A-allele and the

AA-genotype can be discussed as a risk factor regarding the development of periodontitis (21).

Discussion

The study and analysis of gene polymorphisms is gaining wide popularity both in the field of general medicine and in particular in dental medicine. Modern data lead to the understanding that certain genes represent a risk factor for the development of certain diseases and their knowledge makes it possible to use them as indicators in diagnostics. A potential marker associated with periodontitis is IL-10, whose polymorphisms are likely to be associated with an increased risk of developing periodontitis.

Conclusion

Periodontal disease is result of long-term inflammation sustained by a local level of periodontopathogens and an unbalanced immune response, which can unlock the action of genes involved in immune, regenerative and metabolic responses. These events are considered to be major epigenetic factors determining the clinical manifestation of gene polymorphisms. The association of multiple factors, including gene polymorphisms, in the pathogenesis of several inflammatory diseases such as periodontitis determines the continuing interest in identifying and confirming the role of different cytokines with a pro/anti-inflammatory profile that influence susceptibility to periodontitis. IL-10 is known to be an anti-inflammatory cytokine with pleiotropic action. Its involvement in the complex mechanisms of initiation and clinical expression of periodontal disease gives conflicting data in different populations around the world. The lack of data on the presence of single nucleotide polymorphisms of IL-10 in our country provoked the scientific interest of the author's team in conducting a study in the Bulgarian population, whose data are yet to be analysed and published.

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