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The Association Between Proinflammatory Gene Polymorphisms and Level of Gingival Tissue Degradation in Chronic Periodontitis

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Chronic periodontitis (CP) is a common complex infectious disease resulting in inflammation within tissues supporting teeth, which leads to progressive attachment loss, bone loss and eventually tooth loss (1). It is characterized by degradation of extracellular matrix (ECM) components associated with an infiltration of several inflammatory cell populations into the gingival epithelium and connective tissue (2, 3). The first etiologic factor of CP is the accumulation of bacteria in gingival groove. Dental plaque bacteria and calculus have direct and indirect roles in destruction of periodontal tissues. The direct impact is due totoxins, enzymes, and metabolites of bacteria present in dental plaque, which play a key role in the initiation of immune response and induces tissue destruction indirectly by activating host defense cells, which in turns produce and release inflammatory mediators. It stimulates effectors of connective tissue breakdown. Bacteria-derived pathogenic factors such as lipopolysaccharides can activate junctional epithelial cells to release potent cytokines and proteases, leading to inflammation and connective tissue breakdown and bone resorption (4, 5). Fibroblasts, macrophages, osteoblasts, keratinocytes, and endothelial cells are activated in response to stimulus, contributing with the synthesis of cytokines and MMPs (6). Epidemiological studies revealed that differences in periodontitis among individuals could not be explained by differences in oral hygiene alone and that not everybody is equally susceptible (7). The pathogenesis of periodontitis depends on the interactions between host and microorganism and may be complicated by genetic and environmental risk factors (8). There is local infiltration of inflammatory cells and degradation of ECM macromolecules in gingival connective tissue of patients with CP. Among matrix macromolecules, collagen fibers constitute the major compartment of the gingival lamina propria and have an important role in its normal histological architecture. Loss of Collagenous compartment may reflect the severity of periodontitis (8). During the progression of periodontal inflammation, periodontal ligament and gingival fibroblasts secrete high levels of cytokines and chemokines (9). Proinflammatory cytokines play crucial roles in microbe-induced destructive inflammation (8). These molecules contribute to the breakdown of type I collagen and also promote bone resorption by stimulating proliferation, differentiation, and activation of osteoclasts (10, 11). Tissue destruction seems to be regulated by four major pathways of plasminogen-dependent, phagocytic, osteoclastic and matrix metalloproteinase (MMP) ones. It seems that the MMPs pathway is the most relevant in periodontitis. MMPs are a family of metal ions-dependent endopeptidases capable of degrading all matrix macromolecules, including collagen fibers and basement membrane constituents (12). Four major subgroups of MMPs directly related to degradation of periodontal tissues include: collagenases, gelatinases, stromelysins and membrane-type MMPs (MT-MMP). Collagenases due to their helicase activity are capable of degradation of type I collagen. Then degradation of the collagen fibrils is done by gelatinases, or lysosomal proteinases (phagocytic pathway). MMP-2 degrades fibrillar type I collagen (10, 11). Stromelysins (MMP-3) and MT-MMPs play a pivotal role during activation of other MMPs (13). Studies have reported that some cytokines are encoded by polymorphic genes, showing genotypes associated with inflammatory diseases that may confer susceptibility to periodontal disease (9). Therefore, most genetic researches in periodontitis have focused on gene polymorphisms playing role in immune system, tissue destructive processes, or metabolic mechanisms (7, 14). Gene polymorphisms are mechanisms through which individuals may exhibit variations within the range of what is considered biologically normal (7). Polymorphisms represent natural sequence variants (alleles), which may occur with more

than one form, having a frequency greater than 1% in a human population (6). Genetic variance is a major determinant of differential risk for several diseases. While microbial and other environmental factors initiate and modulate periodontitis, individuals are known to react contrastingly to common environmental challenges, and this differential reaction is influenced by the individual genetic profile. Genes obviously play a crucial role in predisposition to CP, and progression and severity of chronic periodontitis (15). The association between proinflammatory gene polymorphisms and level of tissue degradation and periodontal disease progression is not clear. We recently performed some stereological studies on gingival tissues of patients with CP with known cytokine gene polymorphisms. In a study quantitative parameters of interdental papilla was investigated in patients with CP and TGF-b1 29C/T gene polymorphisms (8). Our study showed that there was a strong association between TGF-b1 29C/T gene polymorphisms and quantitative parameters of interdental papilla in patients with CP. One the other hand, our previous study on TGF-β1 showed that TGF-β1 29 C/T polymorphism may contribute to CP development, but genotype and allele frequencies of the TGF-β1 polymorphisms at positions −509 C/T and 788 C/T were not significantly different between CP cases and controls in a sample of Iranian population (7).

In another study, we investigated quantitative parameters of interdental gingiva in patients with CP having different TNF-α (-308 G/A) gene polymorphisms. Results of our study showed that there was no association between these gene polymorphisms and stereological parameters of interdental gingiva in patients with CP (14). The evidence that individual characteristics play an important role in physiological and pathological processes led to investigate genetic polymorphisms in clinical setting. In this context, studies on inflammatory and degenerative diseases rely upon the mediators that act on degradation of ECM (13). To clarify the contribution of genetic polymorphisms to the development and progression of disease, it is important to analyze such genotype distributions and allele frequencies between different races. Conflicting results concerning gene polymorphism between different studies may be due to population heterogeneity. Many diseases differ in frequency between different geographic populations and various racial and ethnic groups, and allele frequencies can vary widely in different human populations (16). It seems that those geographically and racially remote populations tend to differ more. Therefore, a different allele of a single nucleotide polymorphism may be a genetic risk factor for disease susceptibility in one population and may not be in another one. For any certain phenotype, differences among individuals may be due to variation in environmental conditions or the result of differences in the genes coding for that phenotype. This variability is due to gene-environment interactions affecting gene expression patterns (16). Overall, discovery of genetic markers related to pathologies is clinically invaluable for identifying susceptible individuals. Further studies of gene polymorphisms would provide additional insight into the biology of periodontitis, and would aid in a better understanding of molecular influence of polymorphisms. It is hoped that identification of specific genes predisposing periodontal disease would have diagnostic and therapeutic values.

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