Review paper

The genetic determinants of immunologic response in periodontitis

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Abstract

This article summarizes some experimental and clinical data about genetic aspects of immunologic response in periodontitis. Both the innate and adaptive immunological reactivity can be modified by genetic factors. Many studies have supported the hypothesis of genetic implications in the etiopathogenesis of periodontitis. Genetic polymorphism being emphasized as a distinctively important phenomenon. The particular genotype determines the susceptibility or resistance to periodontal disease. The HLA molecules play a significant role in the progress of immunological response by presenting bacterial antigens to the effector cells of the immune system. On the basis of many studies a genetic test was developed, embracing the polymorphism of genes encoding cytokines and their receptors. Patients carrying the allele 2 of IL-1β gene are six times more prone to periodontal diseases as compared to the allele 1 of IL-1β gene. So, we can expect the new therapeutic protocols.

Key words: *periodontitis, host response, immune system, genetic determinants.*

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The studies performed to date aimed mainly at exploring the patomechanisms and factors associated with periodontitis development and natural history. The results of these studies enabled us to systematize the factors influencing host susceptibility to periodontal diseases. They were distinguished into phenomenons one cannot modify, called risk determinants, and the exact risk factors. All of them modulate host immunologic reaction, making oral tissues prone to periodontal diseases. The risk determinants include age, gender, social status and genetic determinants. The other group comprised true risk factors: smoking, stress, diabetes, osteoporosis and diseases characterised by congenital or aquired immune deficiencies. One of the important groups of factors determining the etiopathogenesis of periodontitis is genetic factors. The antigens of periodontal pathogens can modulate host response in different ways. Matsuyama has observed human gingival epithelial cells, colonized by *Actinobacillus actinomycetemcomitans* strains. In the aftermath of IFN-γ stimulation these cells exhibited increased expression of MHC class II genes, as well as B cells surface antigens, B7-1 (CD80). These molecules presented antigen to T cells, binding to the specific CD4+ receptor on their surface, thus stimulating humoral immune response. Interestingly, no CD4+ receptors activation was observed in lack of periopathogenic A. actinomycetemcomitans strain in gingival epithelial cells [1]. On the other hand, Schreiner et al. have stated, that the possibility of *A. actinomycetemcomitans* colonization depends on exact sequence of 14 genes in locus called tad (tight-adherence). According to these authors, rats inoculated with *A. actinomycetemcomitans* exhibiting mutation within tad locus developed no immune response or alveolar bone loss [2]. The studies performed by Srisatjaluk *et al*. have proven, that the proteolytic *enzymes* inside membrane vesicles of *Porphyromonas* gingivalis can inhibit the IFN-γ-mediated expression of HLA-DR-α gene, as well as transcription of CIITA (a transactivator of class II MHC genes). As a result the *P. gingivalis* bacteria impair cell functions and inhibit host immune response [3]. Both the innate and adaptive immunological reactivity can be modified by genetic factors. It is the particular genotype that determines the susceptibility or resistance to periodontal disease. Many studies have supported the hypothesis of genetic implications in the etiopathogenesis of periodontitis, genetic poly-

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morphism being emphasized as a distinctively important phenomenon. Special attention should be paid to the genes encoding major histocompatibility complex (MHC) antigens; in humans it is referred to as a human leukocyte antigens (HLA) system. The HLA molecules play a significant role in the progress of immunological response by presenting bacterial antigens to the effector cells of the immune system. The MHC genes exhibit marked polymorphism, which means high level of allelic diversity. The DR allele, encoding the polipeptide chain α of heterodimer HLA-D, belonging to MHC class II, could determine increased susceptibility to infection [4]. On the surface of many cell types there are specific glycoprotein receptors, which play an important role in the regulation of inflammatory processes in periodontal tissues. Their role was extensively studied in the past years. The expression of these receptors on the cell surface, i.e. on the neutrophiles, is one of the determinants of effective phagocytosis. In the aggressive periodontitis an impaired migration and adhesion functions of neutrophiles was observed. This defect results from point mutations and leads to the lack of Mac-1, LFA-1 and p-150,95 (CD 11/18) receptors expression on the neutrophilic leukocyte surface membrane. It is referred to as a leukocyte adherence deficiency I (LAD I) syndrome [5]. The other important molecules, that are expressed on the neutrophiles and determine the antigen-antibody complex recognition, are the FcγR receptors for IgG. There are three distinct kinds of IgG receptors: FcγRI (CD64), exhibiting high avidity against immunoglobulin, and low avidity receptors FcγRII (CD32) and FcγRIII (CD16). There are two structural forms of FcγRII: FcγRIIA, expressed on the phagocytic cells, and FcγRIIB on B cells. The presence of high avidity receptor leads to increased immunoglobulin synthesis and as a consequence to the tissue degradation. Also FcγRIII is expressed in two distinct forms, of which FcγRIIIA is present mainly on NK cells and FcγRIIIB on neutrophils. Both forms of FcγRII and FcγRIII receptors were proven to exist in two different allotypes of different avidity against IgG, clinically presenting as different susceptibility to infection [6]. The polymorphic FcγRIIA (R131 and H131), FcγRIIIA (V158 and F158) and FcγRIIIB (NA1 and NA2) were subject of many studies. Kobayashi have observed higher avidity of the FcγRIIIB-NA1 against IgG1 and IgG3 complexes, as compared to the FcγRIIIB-NA2. It determines the capability of phagocytosis of the *P. gingivalis* bacteria cells opsonised by immunoglobulins, as well as the local release of free oxygen radicals by the neutrophils. In a study on patients suffering from chronic periodontitis the clinical attachment loss was found to progress faster in those exhibiting FcγRIIIB-NA2 allele (both homozygotes and heterozygotes) than in patients with FcγRIIIB-NA1 allele [7]. In another study a polymorphic FcγR-FcγRIIIB-NA2 receptor was found to be significantly more prevalent in patients with aggressive periodontitis, as compared to chronic periodontitis and healthy control. Moreover the coincidence of FcγRIIIB-NA2 and FcγRIIIA-158F genotypes was found more frequently in aggressive periodontitis [8]. The results obtained by Kobayashi were further supported by Sugity study. The FcγRIIIB-NA1 form was more effective towards IgG1/IgG3 as compared to the FcγRIIIB-NA2. Moreover in patients with no signs of periodontal disease the more prevalent form is FcγRIIIB-NA1, suggesting that FcγRIIIB-NA2 could predispose to periodontitis [9]. In another study on Caucasian population the FcγRIIIA-V158 and FcγRIIA-H131 were found to present more frequently in the periodontitis group than in the control group [10]. Another receptor exhibiting genetic polymorphism that can be of importance in the etiopathogenesis of periodontal disease is vitamin D receptor (VDR). Vitamin D is responsible for the proper bone metabolism. The active form of vitamin, 1,25-dihydroxycholecalciferol, stimulates synthesis of bone matrix proteins and its' mineralization, as well as monocytes and macrophages production. The biological activity of vitamin D results from binding to the VDR. Vitamin D receptor exhibits genetic polymorphism. Some of the alleles lack the specific DNA sequences, recognized by Apa I, Bms I, Taq I and Fok I restriction endonucleases. In a study on Japanese patients with chronic periodontitis and Taq I polymorphism a more frequent presence of the allele lacking the sequence digested by restriction endonuclease as compared to the healthy control was observed [11]. Some other authors, investigating the effect of VDR polymorphism on periodontitis, have found the higher prevalence of periodontal tissue inflammation in patients presenting 27823*CC allele [12]. Yet another cellular receptor with genetic polymorphism of biological significance is N-formyl peptide (fMLP) receptor. The fMLP receptor has structural similarity with bacterial products stimulating the chemotaxis of neutrophils. There are two known polymorphisms in the fMLP receptors at base 329 T to C and base 378 C to G [13]. Another receptor studied for the correlation between genetic polymorphism and periodontitis is receptor for advanced glycation end products (RAGE). The interaction between RAGE and monocytes leads to an increased cytokine production, while the interaction between RAGE and fibroblasts decreases collagen synthesis. In patients with periodontitis a polymorphic allele with a single base change at base 1704 (G to T) was more prevalent then in a healthy control group [14]. In another study a correlation between CD14 encoding gene and periodontitis was assessed. CD14 is a glycoprotein receptor, present on the cell surface neutrophiles, monocytes, macrophages, fibroblasts etc. It recognises the bacterial lypopolysaccharides bound to a specific protein binding LPS, present in the circulation. Gene encoding the CD14 molecule can be present in one of two polymorphic forms: at base 159 (C to T) and at 1359 (G to T). More frequent 159*C allele presence was stated in Caucasians suffering from periodontal disease as compared to the healthy controls [15]. Other studies have assessed the polymor-

phism of metaloproteinases (MMP) genes. Metaloproteinases are enzymes directly responsible for collagen deterioration as a result of inflammatory processes in periodontal tissues. One of the objects of the studies was polymorphism of MMP-1-encoding gene, distinguished by deletion or addition of G at base 1607. The alleles were defined as 1G and 2G, respectively. Allele 2G was found to be more frequent in Caucasians with chronic periodontitis then in a healthy control group [16]. Keles *et al*. have been investigating the single nucleotide polymorphism of the metalloproteinase 9 (MMP-9) encoding gene at base 1562. They have observed the correlation between this allele and prevalence of periodontal disease [17]. On the basis of many studies a genetic test was developed, embracing the polymorphism of genes encoding cytokines and their receptors. Patients carrying the allele 2 of IL-1β gene are six times more prone to periodontal diseases as compared to the allele 1 of IL-1β gene [18]. The subsequent studies have shown a significantly higher prevalence of IL-1β+3953 allele in aggressive periodontitis then in healthy control group [19]. Other reports have shown that allele 2 IL-1β+3953 is over-represented in chronic periodontitis. Moreover there is a higher prevalence of allele 1 TNF-α-308 in periodontitis patients as compared to those suffering from gingivitis [20]. The risk of exacerbation of periodontitis is over 12 times higher in the patients with chronic periodontitis presenting specific IL-1α+4845/ IL-1β+3953 genotype [21]. Another group has compared two groups of patients: the first one exhibiting IL-1α-889, IL-1β+3953 genotype (referred to as PST(+) (periodontitis susceptibility trait), that was believed to be more susceptible to periodontitis, and the other designated as PST(–). The peripheral monocytes isolated from both PST(+) and PST(+) group secreted comparable amount of IL-1β upon stimulation with bacterial lipopolysaccharides [22]. On the other hand, the analysis performed by means of polymerase chain reaction (PCR) has not revealed any significant difference between periodontitis and healthy controls as to the prevalence of polymorphic IL-1α-889, IL-1β+3953 genes [23]; other studies did not support the differences between specific TNF-α genotype (referred to as A+ genotype), comprising the polymorphic alleles TNF-α-376, TNF-α-308, TNF-α-238 and TNF-α+489, in patients with periodontitis and control group. Moreover there was no significant difference of alveolar bone loss between patients with A+ genotype and those without these particular polymorphic forms of TNF-α gene [24]. Similarly, Endo et al. have not observed the correlations mentioned above, neither for the same genetic alleles, nor for the polymorphic forms of tumor necrosis factor gene: TNF-α-1031, -863, -857 [25]. According to the subsequent studies, the monocytes isolated from peripheral blood of patients suffering from aggressive periodontitis and possessing the TNF-α-308 allele secrete significantly higher levels of TNF-α then the control group [26]. The genetic diversity of IL-1β may influence the course of periodontal disease by means of its linkage to other genes. The IL-1β-encoding gene is located within chromosome 2, in close proximity to IL-1β and IL-1Ra genes. Thus some specific haplotypes can be associated with the etiopathogenesis of periodontitis. The correlation between IL-1Ra level and distinct IL-1β alleles (i.e. IL-1β+3953 and IL-1β-511) was a subject of a recent study. Seventy-five out of 200 healthy subjects presenting with IL-1β-511 genotype have also exhibited allele 2 of IL-1Ra gene. This percentage was significantly increased as compared to the control group. Also the IL-1 receptor antagonist level in the peripheral blood was significantly higher in those possessing the allele 2 of IL-1Ra gene. On the other hand, the IL-1β+3953 genotype coexisted twice less often with allele 2 IL-1Ra gene [27]. Tai *et al*. have shown that the patients with aggressive periodontitis carry the polymorphic IL-1RN (VNTR) gene significantly more often than the control group. Still in these patients no correlation was found between IL-1β+4845, IL-1β-511 or IL-1β+3953 genotype and aggressive periodontitis prevalence [28]. Another study has also not supported the correlation between IL-1α-889, IL-1β+3953, IL-1β-511, TNF-α-308 or IL-1RN and aggressive periodontitis [29]. On the basis of evidence presented above, one can expect the emergence of new, customized therapeutic protocols, based on the genetics of periodontal disease. Much hope is being placed on the potential of genetic therapy, i.e. modified techniques of gene transfer and genetic reprogramming of the target cells [30].

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