EDITORIAL

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A New Approach for Genetic Factors Influencing Periodontitis

Nowości dotyczące czynników genetycznych zapalenia przyzębia

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Abstract

Periodontitis is a variety of conditions which affect the tissues surrounding the tooth. The pathological process results from a distortion of balance between dental plaque bacteria and immunological system of the host. Moreover, the onset and the course of periodontitis are modulated by the impact of genetic mechanisms mutually with risk factors. Genetic influence on the periodontitis might be divided into the following groups: single nucleotide polymorphisms: Il-1β and CD14 receptor; inherited immunodeficiencies: benign familial neutropenia, leukocyte adhesion deficiency, Chediak-Higashi syndrome, Kostmann disease; connective tissues disorders: keratoderma, Ehlers-Danlos syndrome, hypophosphatasia, Marfan syndrome and familial immunodeficiencies (**Dent. Med. Probl. 2013, 50, 2, 145–151**).

Key words: single nucleotide polymorphisms, benign familial neutropenia, leukocyte adhesion deficiency, Down syndrome.

Streszczenie

Zapalenie przyzębia jest dużą grupą schorzeń tkanek podtrzymujących ząb. Proces patologiczny wynika z zaburzenia stanu dynamicznej równowagi między bakteriami zasiedlającymi płytkę nazębną a układem immunologicznym gospodarza. Ponadto początek oraz przebieg zapalenia przyzębia jest modulowany przez wpływ współwystępujących czynników ryzyka oraz wiele mechanizmów genetycznych. Wpływ czynników genetycznych na etiopatogenezę zapalenia klasyfikuje się następująco: polimorfizm pojedynczych nukloetydów: IL-1β oraz receptora CD14; wrodzone niedobory odporności: rodzinna neutropenia, zespół zaburzonej adhezji leukocytów, zespół Chediaka-Higashiego, choroba Kostmanna; zaburzenia tkanki łącznej: keratoderma, zespół Ehlersa-Danlosa, hipofosfatazja, zespół Marfana oraz dziedziczne zespoły zaburzonej odporności (**Dent. Med. Probl. 2013, 50, 2, 145–151**).

Słowa kluczowe: polimorfizm pojedynczych nukleotydów, rodzinna neutropenia, zespół zaburzonej adhezji leukocytów, zespół Downa.

Periodontitis is a multifarious group of conditions affecting the tissues supporting the tooth. The onset of periodontitis results from the disruption of the dynamic balance between dental plaque bacteria and immunological system of the host [1–5]. Periodontitis takes place under favorable conditions for bacterial proliferation and suppression of immunity. According to Socransky classification, etiological factors of periodontitis might be classified into the microbiological complexes based on their clinical association with severity of periodontitis [6]. According to the current scientific reports, the crucial pathogens accountable for the onset and the course of chronic periodontitis are the following: *Porphyromonas gingivalis, Tannerella forsythia* and *Treponema denticola* [7].

Clinically the ongoing periodontitis is manifested by the following signs: increased probing depth, loss of connective tissue attachment, tooth mobility and pathological teeth migration and finally bleeding on probing, which is the sign of active inflammation [1, 2, 8]. On the molecular level etiopathogenesis of periodontitis begins with the activation of CD14 macrophage receptor by the endotoxin of Gram (–) bacteria [9]. The activation signal is then transduced through the cell membrane through toll-like-receptor type 4 (TLR4), its activation triggers specific pathways of gene expression (NLRP) [10]. Subsequently activated tyrosine kinases induce nuclear transcriptional factors, among which the most important one is nuclear factor of light chain enhancer (NF-κB). The NF-κB acts with a promoter DNA sequence of nod-like receptor proteins 3 complex (NLRP3) [11–13]. The main function of the NLRP complex is the activation of caspase 1 which subsequently acts on a preinterleukin 1 forming a fully active interleukin 1 β (Il-1β). The Il-1β is the main cytokine responsible for the activation of inflammatory mechanisms not only in periodontitis but also in general systemic diseases (infective endocarditis, atherosclerosis, chronic pancreatitis) [14–16]. Interleukin 1 β secreted by macrophages located in periodontal tissues stimulates fibroblasts to produce matrix metallo-proteinases (MMPS) and prostaglandin E_2 (PGE_2) [17]. The MMPS are zinc-enzymes which activity results in the breakdown of the connective tissue, whereas PGE_2 activates osteoclasts and favors bone tissue remodeling. The mentioned mechanisms constitute the theoretical basis for the observed clinical manifestations of periodontitis: loss of connective tissue attachment and osteolysis of alveolar process. Loss of tissues supporting the tooth increases their mobility and leads to pathological migration, and if the condition remains untreated, it eventually results in tooth exfoliation.

The onset and course of periodontitis depends on the presence of risk factors such as: age, gender, tobacco smoking, alcohol abuse, genetic factor and patients compliance [18]. Up-to-date studies put special emphasis on the role of genetic factors in the diagnostics and monitoring the course of the disease [19]. Moreover it seems that genetic inheritance plays a key role in a comprehensive treatment plan, especially when orthodontic and implanto-prosthetical therapy is necessary to avoid adverse effects such as gingival recession and perimplantitis [20].

Genetic Syndrome-Related Periodontitis

Many genetically inherited diseases also include among their manifestations various forms of periodontitis. These syndromes, not surprisingly, are chiefly caused by gene mutations influencing immunological system and connective tissue. As it is widely known, periodontitis results from the disruption of a dynamic balance between host immunological system and bacterial agents. Therefore, mutations debilitating immunity of the host facilitate bacterial colonization and invasion in many tissues, including periodontium. On the other hand, periodontium is made of different types of connective tissue – that is why diseases disrupting its structure also facilitate bacterial invasion into morphologically pathological tissue. The common clinical feature of periodontitis of all these disorders is an early onset and an aggressive course.

The first group of familial disorders (those affecting host immunity) include: benign familial neutropenia, leukocyte adhesion deficiency, Chediak-Higashi syndrome, Kostmann syndrome. Another group of inherited disorders affects connective tissue and include: Papillon-Lefevre syndrome, Heim-Munk syndrome, Ehlers-Danlos syndrome, hypophosphatasia, Marfan syndrome. Periodontitis is also one of oral manifestation of the Down syndrome, which will be discussed in detail below.

Inherited Immunodeficiencies

Benign familial neutropenia (BFN) is inherited in an autosomal dominant way. The gene mutation involved in this disease is not known; however, the precise locus was identified – 16q22 [21]. The mutation leads to decreased neutrophile count and subsequently to general susceptibility to bacterial diseases, some of which might be life-threatening. It is not surprising that periodontitis, also caused by bacteria, affects patients with BFN more frequently than the general population [22]. The severity of the disorder varies, as does the neutrophile count observed in laboratory tests. The patients are more susceptible to gingival inflammation and attachment loss; however, they respond more favourably to oral hygiene improvement than the control group [22]. The periodontitis' onset may take place in prepuberty. Other oral manifestation include, but are not limited to, oral ulceration, candidal infections and angular stomatitis [23].

Leukocyte adhesion deficiency (LAD) is an autosomal recessive disorder characterized by defects in neutrophil adhesion, chemotaxis and phagocystosis [24]. They are caused by mutations in three different genes – *ITGB2, SLC35C1, FERMT3*. The mutation of the first one of them is the most

common cause of LAD (subtype LAD1) and encodes integrin β-2 subunit. The other two (GDP-fucose transporter-1 and kindling-3) are responsible for LAD2 and LAD3 respectively. All three LAD subtypes lead to recurrent bacterial infections beginning in the neonatal period, delayed wound healing, impaired pus formation and delay in umbilical cord sloughing. In the oral cavity we may find periodontitis (prepubertal age patients) involving gingival hyperplasia and bone destruction [25].

Chediak-Higashi syndrome (CHS) is caused by defects in phagocytosis arising on the basis of inefficient microtubule polymerization. Autosomal recessive mutation in *LYST* gene (encoding vesicular trafficking protein) is responsible for the clinical manifestation of the disease [26]. Since phagocytosis is one of the main factors in innate immunity, through which macrophage and neutrophils remove bacteria and cellular debris, its disruption leads to frequent bacterial and fungal infections – *S. aureus* being the most common pathogenic species [27]. Periodontitis associated with CHS occurs in young patients and has generalized and aggressive course [28].

Kostmann disease is inherited in an autosomal recessive manner. The molecular basis of the disease is the mutation in *HAX1* gene, encoding HCLS associated protein X-1. HAX1 is shown to be interacting with interleukin-1a [29]. Chronic sever neutropenia is detected soon after birth and numerous aggressive infections follow [30]. *A. actinomycetemcomitans* is found to be overgrown in dental flora, and aggressive periodontitis results, probably as a result of lack of antibacterial peptides normally secreted by neutrophils [31].

Connective Tissue Disorders

Keratoderma, caused by mutations in cathepsin C gene (*CTSC*), is a manifestation of two clinically and genetically related syndromes: Papillon-Lefevre and Heim-Munk syndromes [32]. Oral microflora is severely disrupted in these conditions and early-onset periodontitis follows [33].

Ehlers-Danlos syndrome is a group of ten disorders resulting from genetic defects of collagen synthesis. Among various manifestations of the disease, oral cavity symptoms begin with gingival bleeding, then rapid destruction of periodontal tissues occurs. Intra-familial variability is pronounced; therefore, the age of periodontitis onset may vary greatly. Type VIII is most commonly associated with periodontal manifestations [34, 35]. It is worth noting than ligneous periodontitis (periodontitis with fibrinoid material deposition) is associated with the classic type of Ehlers-Danlos syndrome and does not occur when no collagen mutations are present [36].

Hypophosphatasia [37] is a metabolic bone disease. Inheritance might be autosomal recessive or dominant depending on the variant. A molecular defect of tissue non-specific alkaline phosphatase (TNSALP) is responsible for the disorder [38]. This enzyme is tethered to the outer surface of osteoblasts and chondrocytes. Normally it hydrolyzes many various substances including inorganic pyrophosphate and B6 vitamin. Accumulation of inorganic pyrophosphate inhibits the mineralization of the bones.

Marfan syndrome is only hypothetically associated with sever periodontitis; however, connective tissue diseases conferring susceptibility to periodontitis seem to confirm this hypothesis. Fibrillin-1 mutation causing Marfan syndrome is responsible for the defective formation of elastic fibers. Currently, more than 600 possible mutations have been described [39].

Down Syndrome

Down syndrome might be caused either by meiotic nondisjunction event leading to trisomy of the chromosome 21 or by Robertsonian translocation (familial Down syndrome), where additional genetic material is inherited from one of the parents.

The prevalence of periodontitis is higher in patients with Down syndrome than in control group [40]. The greater susceptibility to periodontitis is caused by endogenous and exogenous factors. The host factors include elevated activity of oxidative burst in peripheral macrophages and neutrophils [41], reduced expression of STAT and Interferon Regulatory Factor 1 [42], increased activity of MMP-2 and MMP-8 even before inflammation is manifested [43], on the other hand, patients with Down syndrome evince higher levels of bacterial colonization of the oral cavity, with increased proportions of *S. noxia*, *P. acnes, S. mitis* and *S. oralis* as compared with control group [44]. From these information it is clear that pathogenesis of periodontitis in Down syndrome results from immunological dysfunction leading to more extensive bacterial colonization of oral cavity.

Single Nucleotide Polymorphism (SNP)

Gene polymorphisms play a key role in the current research studies. DNA sequence of several genes which are expressed during inflammation

Table 1. Classification of genetic syndromes in correlation with inheritance and proposed pathomechanism of periodontitis

Tabela 1. Podział zespołów genetycznych w powiązaniu ze sposobem dziedziczenia i proponowanym patomechanizmem zapalenia przyzębia

Disorder (Zaburzenie)	Inheritance (Sposób dziedziczenia)	Gene (Gen)	Periodontitis mechanism (Oddziaływanie w zapaleniu przyzębia)	References (Piśmiennictwo)
Benign familial neutropenia (Rodzinna neutropenia)	autosomal dominant	unknown, located in 16q22	immunodeficiency	[21–22]
Leukocyte adhesion deficiency (Zespół zaburzonej adhezji leukocytów)	autosomal recessive	ITGB2, SLC35C1, FERMT3	immunodeficiency	[21–23]
Chediak-Higashi syndrome (Choroba Chediaka--Higashiego)	autosomal recessive	LYST	immunodeficiency	[26–28]
Kostmann disease (Choroba Kostmanna)	autosomal recessive	HAX1	immunodeficiency	[29–31]
Papillon-Lefevre and Heim-Munk syndromes (Zespoły Papillona-Lefevre'a i Heim-Munka)	autosomal recessive	CTSC	connective tissue disruption	[32–33]
Ehlers-Danlos syndrome (Zespół Ehlersa-Danlosa)	autosomal recessive or autosomal dominant	various	connective tissue disruption	[34–36]
Hypophosphatasia (Hipofosfatazja)	autosomal recessive or autosomal dominant	TNSALP	connective tissue disruption	[37–38]
Marfan syndrome (Zespół Marfana)	autosomal dominant	FBN1	connective tissue disruption	[39]
Down syndrome (Zespół Downa)	see text	chromosome 21	immunological imbalance	[41–44]

were taken into account as possible factors which are responsible for increased or decreased protein expression as well as activation of enzymes and interleukins.

Interleukin 1 β

Interleukines are a group of pleotropic cytokines which are responsible for modulating inflammatory processes [45]. The group of type 1 interleukines consists of more than five types, from which the most important in pathogenesis is Il-1β [46]. In the course of periodontitis interleukin 1β is secreted by macrophages in response to the stimulation of Gram (–) bacterial endotoxin. According to the allelic discrimination studies performed by the means of RT-PCR there have been identified several polymorphisms which influence *Il-1β* gene expression. They can be divided into the two groups: promoter and exons sequence polymorphisms. In the first group the following are included [47–49]:

– RS 16944: –511 C > T

whereas in coding sequence we distinguish [50]:

– RS 1143634: +3953 G > T
– RS 11436340: +3954 C > T

The variants of interleukin gene listed above were analyzed according to the diagnosis (chronic or aggressive periodontitis), gender and risk factors. Patients with homozygous genotype TT (RS 1143634) constituted the largest, non-smoking group with severe chronic periodontitis, whereas in the control this genotype was present in 23% of subjects [47, 51]. On the other hand, in the group of patients with aggressive periodontitis homozygotes TT (RS 11436340) were more prevalent [52]. These conclusions suggest that different coding sequence polymorphisms of *IL-1β* gene impact the course of chronic and aggressive periodontitis in the non-smoking individuals. The SNP of promoter region assessed in many studies was considered to be *in vivo* unfunctional in various types of periodontitis. However, in the studies performed on individuals belonging to black and mulattos, it was found that RS 16944 can be taken into account as a putative risk factor only for chronic periodontitis [50, 53]. In the group of smoking individuals with severe periodontitis, the RS 1143634 was found in 58% of patients [47].

Results of these tests confirm theoretical mechanisms of periodontitis etiopathogenesis. Moreover, novel theories suggest that selected single

nucleotide polymorphisms together with local factors and addictions mutually modulate the onset and course of the disease.

CD 14 Receptor

The CD14 is the receptor located on the macrophages' cell membrane and is a part of a human innate immunity [54]. The key role of CD 14 is to detect and join Gram(–) bacterial endotoxin and activate TLR4 receptor in order to transduce the signal through cell membrane [55]. On the other hand, reticuloendothelial cells secrete soluble form of this receptor, but only CD14 associated with cell membrane, in the presence of lipopolisacharide binding protein (LBP) is biologically fully active [56]. Up-to-date SNP of CD14 gene promoter are taken into account as a possible risk factors in periodontitis [10, 57, 58]:

- –1359 G > T
- –260 C > T

The transition of cytosine to the thymine occurring in the promoter position exerts a positive influence on gene expression and results in an increased production of transmembrane and soluble form of CD14 [59]. Thus, individuals with –260 TT genotype are considered to have exaggerated (hyperreactive) immunological response. In clinical studies, individuals with chronic periodontitis and type –260 TT genotype were significantly more frequently diagnosed with chronic periodontitis. Moreover, the genotype mentioned above was associated with bronchial asthma in other studies [60]. Results of this study show that this SNP acts systemically and is functional. On the other hand, the impact of the first polymorphism is associated with gender of the patient. In research studies, it was proven that females with this SNP develop first symptoms of periodontitis in the developmental age [10, 61].

Conclusions

Despite an overwhelming amount of research on etiopathogenesis of periodontitis, the genetic impact on the onset and course of the diseases is not yet fully understood. The following are taken into account: single nucleotide polymorphisms, inherited immunodeficiencies, connective tissues disorders and familial immunodeficiencies.

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