Autoimmune processes participate in oral pathologies

Udział procesów autoimmunologicznych w patologiach jamy ustnej

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Abstract

Autoimmune diseases are mostly chronic disorders with acute periods and remissions. This group of disorders consists of 70 entities and has a high prevalence, with 5% of the world’s population affected. The aim of this paper was to present, basing on the contemporary literature, the impact of autoimmune mechanisms on the diseases affecting only oral cavity or in which oral cavity is one of many localizations. The localization and features of identified autoantigens, the character of effector mechanisms in these diseases, suggested endo- and exogenous factors leading to the abolition of self-tolerance were described. The issues were presented in respect to systemic lupus erythematosus, Sjögren’s syndrome, pemphigus, pemphigoid, Behçet’s disease, chronic ulcerative stomatitis and periodontitis. This knowledge has great importance in the diagnosis and therapy of these diseases (Dent. Med. Probl. 2004, 41, 2, 267–276).

Key words: autoimmune disease, oral cavity, autoantigens, autoantibodies.

Streszczenie


Słowa kluczowe: choroby autoimmunizacyjne, jama ustna, autoantygeny, autoprzeciwieństwa.
Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune multiorgan disease, involving skin and mucous membranes. Among 11 criteria of SLE introduced by American Rheumatological Association, two are mentioned, which can be verified also by a dentist: oral ulceration and a butterfly-like facial erythema. The disease manifests by autoantibodies production, circulating immune complexes and periodic uncontrolled activation of the complement. Among the identified SLE autoantigens there are: double stranded DNA, nuclear ribonucleoproteins (RNPs), Ro and La in nucleolar and cytoplasmic ribonucleoproteins, histones, protein p53 [3].

SLE affects mostly women in the reproductive years, who between 20–40 years of age develop SLE 9 times more often then men [3, 4]. In the remaining age range the female: male ratio is reduced to 3 : 1 [4]. The female predominance in this disorder indicates a potential role of hormonal factors. SLE can also concern infants and develops as a result of passive transfer of antibodies (mainly Ro/SS-A, often with La/SS-B) from mother to foetus [5]. Mother can suffer from SLE, Sjögren’s syndrome, or other connective tissue disease.

Attention draws the familiar coincidence of this disease. It is known that statistically in 5–10% of SLE patients’ close family will develop its symptoms [6]. SLE patients more often have HLA-DR2 (relative risk 5.8) [6].

Patients with SLE have recurrent vascular changes in different organs (skin, kidneys, brain, joints, lungs, serous membranes and alimentary duct). Histopathological findings are not homogeneous, they can be divided into 2 categories: inflammatory and thrombotic [4]. Inflammatory changes are associated with the complement activation in the presence of immune complexes or without their effect. Thrombotic lesions are usually linked with the presence of circulating antiphospholipid antibodies. Immune complexes deposited in the skin and internal organs initiate inflammatory processes, leading to tissue destruction and release of new intracellular autoantigens and production of new complexes.

About 1% of SLE patients can have rarely observed complement deficiency [7]. 98% of patients with autosomal recessively inherited C1q deficiency develop its symptoms [7]. Less spectacular is the association between C4, C1r/s deficiency and SLE. C2 deficiency contributes to the development of lupus-type disease in 1/3 of patients.

Among environmental factors photosensitivity especially to ultraviolet radiation (UV) plays the major role in the development of skin lesions and in the aggravation of systemic disease symptoms of SLE. Many studies show the presence of apoptosis dysregulation [8, 9]. In these conditions extracellular or nuclear antigens can be the source of autoantibodies formation. UV radiation in healthy people causes changes in the DNA of spinous and basal layer. In case when the mechanisms responsible for DNA repair fail, keratinocytes get into the state of apoptosis, and the forming apoptotic bodies are phagocytised, what prevents from the organism’s immune response. In lupus predisposed subjects in the UV radiation leads to apoptosis or its dysregulation in the epidermal and skin cells [8, 9]. Extracellular presence of the nucleus substance indicates the apoptosis dysregulation in its final phase [8]. Immunoglobulins present in the dermal-epidermal junction prove the interaction between them and the fragments of destroyed cells, which become epidermal autoanti-
gens. Phagocytosis of nuclear substance by macrophages and its presentation to lymphocytes CD4 enables the antinuclear antibody production. As long as serum if free of circulating antinuclear antibodies, process has a local character. With their presence the disease is becoming systemic.

SLE is characterised by a dysfunction of suppressor lymphocytes, function and number defect of NK cells and polyclonal B cell activation, leading to autoantibodies and also non-specific γ-globulins production [7, 10]. Such polyclonal activator can be Epstein-Barr virus (EBV) [11]. The literature presents a case of SLE development immediately following the diagnosis of EBV-induced infectious mononucleosis [12].

Among SLE clinical subgroups there is also one induced by medications. The factors are most often hydralazine, hydantoin, sulphonamids, procainamide, d-penicillamin, gold salts, hormonal pills, isoniasid and chlorpromazine. Among clinical symptoms dominate skin lesions, joints’ pain and serositis. The patients’ serum contain antihistone antibodies, there is lack of antibodies against native DNA and normal complement concentrations are found [3].

**Sjögren’s Syndrome**

Sjögren’s syndrome (SS) may occur in the context of other autoimmune diseases (rheumatoid arthritis, SLE, scleroderma, mixed connective tissue disease) and is then described as secondary Sjögren’s syndrome (SSS). Prevalence of SS is high, with about 0.8–3% of the population affected, mostly females, which suffer 9 times more often [13–15]. It starts usually in the fourth and fifth decade. The advantage of women in SS development points to the potential role of hormonal factor in the disease aetiopathogenesis.

A hypothesis has been drawn, which assumes the participation of somatostatin (hypothalamic hormone which controls the secretion of somatotropin) deficiency in the SS development [16]. It is a multifunctional peptide, which reduces lymphocyte activity, gastric and intestinal secretion, activates hypothalamic-pituitary axis and anti-inflammatyory action.

As for now a series of autoantigens have been revealed, from which a part is used in the disease diagnosis. Among them are non-organ-specific autoantigens SS-A/Ro, SS-B/La and SS-56, which can also be associated with other autoimmune disease [13–15]. Antibodies against SS-A/Ro, SS-B/La are detected in 40–70% and 25–40% of patients respectively. Their titre show correlation between disease symptoms and presence of extra-glandular symptoms [13]. Other autoantigens, which are organ-specific are α-fodrin, β-fodrin and muscarine receptor M3 [13]. Their role in the initiation and aggravation of SSS symptoms is not clear, however antibodies directed against muscarine receptor may participate in the loss of salivary function associated with this disease. Newly detected autoantigen – ICA69 is a protein of unknown function that is expressed in neurons and pancreatic B cells and in salivary and lacrimal glands [17]. Often detected antibodies are: rheumatoid factor, antinuclear antibodies against histones and ssDNA and cryoglobulins [13].

The characteristic feature of SSS is the genetic predisposition. The familiar presence and strong relation with HLA DR3 antigens (relative risk 9.7) can be observed [13]. Patients from different ethnic groups show different HLA gene association. HLA class II allele association has been reported to differ among anti-Ro/SS-A positive subjects according to the presence or absence of coexisting anti-La/SS-B. Certain HLA haplotypes were associated with different level of autoantibodies diversification in SS patients. Stronger correlation was observed between anti-Ro/SSA antibodies and DR3/DR2, than that to the disease itself. Antibodies against Ro/SSA and La/SSB showed relation with DR3 and DQA1 antigens [13]. SS patients with alleles DQ1/DQ2 have much more severe disease than patients with in any other combination of HLA-DQ alleles. The DR3-DQ2 haplotype was proposed as a possible marker of more active immune response in Finnish SS patients [13].

Among exogenous factors, which can have influence on the SSS development are viral infections. Salivary glands are a place of latent viral infections. Potential viral triggers include a number of viruses: EBV, CMV, HTLV-1, HHV-6, HCV, HIV [13]. Some immunoreactive regions within La/SS-B protein have similar sequences with proteins of EBV, HHV-6, HIV-1. It seems reasonable to suspect, that these viruses can promote autoantibody production.

The other infectious factor potentially taking part in the SSS etiopathogenesis is the role of *Helicobacter pylori* infection. Despite conflicting reports concerning participation of this bacteria in SSS pathology, its eradication can improve clinical condition of the patients with SSS [13].

The pathognomonic histological feature of salivary gland biopsies in the course of SS is the focal infiltration of mononuclear lymphoid cells, replacing glandular epithelium. Immunohistologic analysis shows that these infiltrations comprise mainly of lymphocytes T (70–80%) and B (20–25%), rarely of macrophages [13, 14]. The majority of T cells are lymphocytes CD4+ showing
activation features, with a CD4/CD8 ratio well over two [14]. Lymphocytes T are activated, what is expressed with HLA-DR and CD95 molecule expression [18]. According to the present hypothesis, the destruction of tissues in SS is concerned with the aggravation of apoptosis in the epithelia, what helps autoantigen presentation activating lymphocytes and cytotoxic effect of released by their mediators. Research on the cytokine spectrum produced by lymphocytes Th1 and Th2 show increased value of cytokines from both groups in the lymphocyte infiltration of glandular tissue, with the predominance of secreted by Th1 cells [18]. Polyclonal hyperactivity of lymphocytes B is one of the most crucial etiopathological phenomena in this syndrome. It manifests by hypergamma-globulinemia, presence of circulating immune complexes and various organ-specific and non-organ-specific autoantibodies [19].

**Pemphigus**

Pemphigus is an autoimmune blistering disease affecting skin and mucous membranes. Intraepidermal and intraepithelial blisters appearing during its course are the effect of dissociation of intercellular connections in epidermis and epithelium. It is due to binding autoantibodies directed against adhesive molecules in the intracellular spaces of epidermis or epithelium. These molecules are called cadherins-transmembrane adhesive molecules forming desmosomes, the most important structures, which define keratinocyte cohesion [20].

There are many pemphigus subtypes, which differ from each other with the clinical manifestation, and so the depth of blister formation in the epidermis, what has the association with the type and localization of antigen recognized by autoantibodies, course, prognosis and response to treatment. Among pemphigus clinical subtypes there are two major groups: pemphigus vulgaris (PV) with its variant pemphigus vegetans and pemphigus foliaceus (PF) comprising of pemphigus erythematosus and pemphigus foliaceus. Apart from two major groups there are also rare subtypes such as: pemphigus herpetiformis, paraneoplastic pemphigus (PNP), IgA pemphigus and pemphigus-erythema annulare-like. Oral lesions occur mainly in the course of pemphigus vulgaris and its variant – pemphigus vegetans, paraneoplastic pemphigus and in 20% of cases with pemphigus herpetiformis [21].

In the pemphigus etiopathogenesis great role is ascribed to genetic predisposition (population with HLA-DR4-DQB living in the Mediterranean basin and Israel) and exogenous factors such as UV, burns, stress, viral infections, drugs or diet [21, 22]. Probably the genetic predisposition can be associated with the genes which code immunoglobulins [21]. Diet rich of phenols (mango, cachew nuts, mustard) and thiol groups (onion, garlic, leek) can cause pemphigus aggravation and resistance to treatment [21, 22]. Also some drugs with active thiol groups in the molecule such as D-penicillamin, captopril can aggravate its course or even induce pemphigus in a healthy subjects [21, 22].

PV begins in the 2 or 3 decade. Because it often begins with non-specific oral erosions, which preceed for about 6–12 weeks skin lesions, it is often diagnosed at late stage. The PV antibodies are directed against autoantigen desmoglein 3 (Dsg3) cadherin with 130 kD molecular weight, which greatest expression is in the lower parts of epithelium, however for PF it is Dsg1 (160 kD) present in upper parts [20, 23]. Newly introduced detecting methods showed that the serum of PV patients reacts only with Dsg3 or with Dsg3 and Dsg1, while serum from PF patients reacts only with Dsg1 [22]. Some studies report cases of PV to PF and vice versa exchange with the simultaneous change of serum antibodies against Dsg3 to Dsg1 or Ds1 to Dsg3 [24, 25].

Pemphigus herpetiformis is atypical pemphigus described for the first time in 1975 by Jablońska et al. [acc. 26]. It is characterized by the presence of vesicles, blisters and papules in a herpetiform pattern, localized on the erythematous basement. Skin lesions are accompanied by itching and burning sensations, and in some cases also erosions on mucous membranes are observed. This disease is difficult in diagnosis because of the atypical clinical symptoms. In immunofluorescence examination IgG deposits are observed in the epithelium and basement membrane, and in some cases C3 complement depositions were observed [26]. More frequent localization of IgG in upper parts of epidermis confirms, that pemphigus herpetiformis is usually a variant of pemphigus foliaceus. Interesting is the fact that apart from knowing the antigens, which are Dsg1 and 3, there are totally different clinical symptoms. Probably antibodies recognize epitopes which have less important function in the intracellular adhesion, that is why acantholysis is not observed [26]. They are able to induce inflammatory process by activating complement.

Paraneoplastic pemphigus (PNP) was separated as an independent syndrome coinciding with lymphoproliferative neoplasms. About 80% of PNP cases are linked with only three neoplasms: non-Hodgkin’s lymphoma, chronic lymphocytic leukemia and Castelman’s disease [27–31]. Other
cases are less commonly associated with retroperitoneal sarcomas, thymoma and Waldenstrom’s disease [31, 32]. PNP is the most severe pemphigus subtype. It is characterized by suprabasal acantholysis, dyskeratosis, basal layer vacuolar changes and necrosis of keratinocytes [28–31]. PNP mostly affects oral and genital mucous membranes [28–34]. Clinical symptoms are resembling severe pemphigus or erythema multiforme. Additionally lichen planus-like skin lesions are observed, which do not occur in other forms of pemphigus [28–31]. Autoantibodies directed against proteins from the plakin family are present in the nonstratified epithelial and therefore in the course of PNP destruction of respiratory and intestine epithelium may be observed, in contrast to PV [31, 33]. In PV antibodies react only with squamous epithelia. In PNP autoantibodies are directed against different desmosomal components. They are proteins, which belong to the plakin family: desmoplakin I (250 kD) and desmoplakin II (210 kD), which are intercellular components of the desmosome, envoplakin (210 kD), protein 230 kD – antigen pemphigoid bullous BPAG1 – hemidesmosome constituent located completely intracellularly, periplakin (190 kD) [20, 29, 31]. Plakins are cytoplasmic proteins lying along the cellular membrane, linking keratinocytes and desmogleins. Among antibodies found in PNP attention has been drawn to those directed against high molecular weight plakin, known also as plectin or HDI (466 kD) [29, 30]. Last research studies show the presence of antibodies for Dsg3 and Dsg1, which expression is associated with the aggravation of lesion on mucous membranes and skin respectively [27, 29–31]. Among closely not identified antigens is transmembrane glycoprotein 170 kD [29, 34]. Antibodies directed against this antigen alone are sufficient for the clinical expression of PNP.

**Pemphigoid**

Pemphigoid is an autoimmune blistering disorder characterized by subepidermal blisters on skin and rarely by subepithelial blisters on oral mucous membranes. The hallmark of this disease is the presence of autoantibodies against hemidesmosomal proteins BP180 and BP230 [35–38]. Antibodies against BP230 are present in 70% of examined sera in pemphigoid patients, 55% of sera show presence of antibodies against BP180, and only 30% against both proteins [20]. The reaction of these epitopes with autoantibodies leads to deposition of immunoglobulin deposits and or complement constituents on the dermal-epidermal junction. Other autoantigen detected in a group of patients with pemphigoid is plectin, a large protein of 516 kD molecular weight with a wide tissue distribution, which is also a cytoplasmic hemidesmosomal constituent [39].

Pemphigoid autoantibodies belong to class IgG4 and are directed against BP180, which uses protein kinase C to lead the signal inside the cell. These antibodies activate the release of IL-6 and IL-8 from keratinocytes [36]. Pathogenicity of IgG4 antibodies is still discussed. On one hand it is believed that they have blocking features to IgG1 which have proinflammatory features, on the other hand this subpopulation has ability to block the intracellular concentration of Ca2+ ions by IgG subclasses [36]. Antibodies IgG4 target epitopes on both intra- and extracellular domains of BP180 [35].

Most of the patients with pemphigoid have increased serum IgE antibodies and eosinophil levels [40]. IgE are directed against intracellular hemidesmosomal antigen BP230. Eosinophils are the predominant cells of the lesional infiltrate. They could play crucial role in the dermal-epidermal separation through the release of their cytoxic proteins granulations and enzymatic mediators [40]. Probably Th2 and CD8+ Tc2 lymphocytes’ effects are responsible for the increased IgE levels in patients, what was suggested in patients with atopic dermatitis [40–42]. The IgG4 skin depositions correlate with the increase of IgE serum level [40]. The association between IgE and IgG4 was indicated on the molecular level [40]. The important part in this diseases can play Th2 lymphocytes, since they stimulate IgG1 and IgE production by B lymphocytes [44]. The animal model of pemphigoid was used to investigate neutrophils, mast cells, macrophages and lymphocytes contribution and their functional relationship in the immunopathogenesis of this disease [44]. Obtained results revealed that mainly macrophages are responsible for the blister formation, mast cells activate macrophages, which initiative neutrophil recruitment.

Mucous membrane pemphigoid (MMP) is an autoimmune blistering disease of ocular, oral and genital mucous membranes. Apart from localization from the classical bullous pemphigoid it can be distinguished by having the tendency to result in fibrosis. In its course subepithelial blisters and deposition of immunoglobulins and complement along the basement membrane zone (BMZ) can be observed. At the present it is suggested that MMP is not a single entity, but a group of different subsets such as pure ocular cicatricial pemphigoid (OCP) and pure oral pemphigoid (OP) [45]. Skin lesions appear in about 30% MMP patients.
To date, a series of autoantigens were isolated, which form hemidesmosomes or are a part of basal cells. The hemidesmosome constituents are: transmembrane protein collagen-like bullous pemphigoid antigen 180 (BPAG2 or collagen XVII) and plaque protein-antigen of bullous pemphigoid 230 (BPAG1) [35, 37, 38]. Other autoantigens can be proteins which bind basal cells below the hemidesmosomes. They are laminin 6 and α chain of laminin 5 (epiligrin), β4 integrin and type VII collagen and mucosal antigen 168 kD [35, 37, 46].

Many studies show that in the MMP pathogenesis haplotype DBQ1*0301 is necessary [45, 47]. It may have a role in T-cell recognition of basement membrane antigens, resulting in the production of anti-BMZ IgG antibodies [48].

Serum of the minority of patients contains IgG and IgA antibodies, which bind constituents of dermal-epidermal junction. This leads to complement fixation, leukocyte infiltration with basal cells keratinocytes detachment from BMZ. Their pathogenic character is confirmed by correlation of the reaction of circulation IgG and IgA antibasement membrane antibodies with the aggravation of disease symptoms [35, 48, 49].

**Behçet’s Disease**

Behçet’s disease (BD) is a multisystemic inflammatory disorder with a chronic recurrent course. Typical criteria are recurrent: oral aphthae, recurrent genital ulcerations, eye lesions (iritis, uveitis). Less characteristic manifestations include arthritis, gastrointestinal disturbances, epididymitis, pulmonary changes, glomerulonephritis, endocarditis, changes in the central nervous system (50–52). Disease is a chronic recurrent vasculitis concerning small and medium vessels with accompanying perivascular necrosis.

The etiology is presumed to be multifactorial. It consists of genetic predisposition, immune system dysregulation and endothelial cell dysfunction.

For the specific genetic predisposition states the atypical geographic distribution of disease and its close association with the major histocompatibility complex – allele HLA-B51 (HLA-B5101–5106) (relative risk 6.3) [53, 54]. The geographic distribution of disease encounters mainly countries spanning from Mediterranean basin to Far East, which lie between latitudes 30° and 45° north [53]. Geographic occurrence of HLA-B51 among healthy people covers the global disease distribution. This connection suggests, that genetic risk factors were propagated by migrant traders along the Silk Road 2000 years ago, what lead to the synonym of Silk Road disease [53]. More likely explanation is that such distribution of genes was associated with demographic movements across Asia and the Beringia Landmass about 10–13 thousands years ago [53]. Last studies concerning genetic determination of BD show new association between MHC loci, and also genes out of this complex. They are allelic variants of within TNF gene region and within the MHC class1-polymorphism i.e. allele MICA6 [53, 54]. The association with the V factor gene mutation on first chromosome (Leiden mutation) was also revealed, which is associated with the retinal vascular occlusion and with polymorphism of intracellular adhesion molecule gene ICAM [53].

Among environmental factors Huluci Behçet himself postulated a viral (HSV-1) trigger of for this disease [53, 54]. Serum antibodies to HSV-1 and circulating immune complexes with HSV-1 are both reported to be raised in patients [53, 54]. It is possible that viral factor could be the trigger for this disease, although there is still lack of evidence.

The immune background of BD is shown in reports concerning the influence of heat shock proteins (HSP), alterations in the neutrophil and macrophage activity, expression of numerous cytokines secreted by lymphocytes Th1. The influence of HSP65 on BS pathogenesis is confirmed by: the increased concentrations of IgA against HSP65, presence of antibodies to oral epithelial antigens, cross-reactivity between polyclonal antibodies to HSP and *Streptococcus sanguis* with oral epithelium antigens [acc. 54]. HSP65 can induce lymphocytes γδ to accumulate in erosive lesions and then to stimulate the local and systemic secretion of IFN-γ and TNF-α [55]. Interaction of HSP with T αβ lymphocytes could also contribute to hyperactivation of lymphocytes Th1 secreting IL-2, which increased serum titres could be observed in disease’s active periods [54]. In the erosion formation participate neutrophils, which chemotaxis, phagocytosis, oxygen and non-oxygen bactericidal mechanism are clearly activated in this disease [54]. Consecutively monocyte and macrophage hyperactivity explains the increased levels of proinflammatory cytokines (IL-1, IL-6, IL-8, TNF-α) in patients with active BD.

The specific IgM to endothelial cell membrane-bound antigen 44 kD can be responsible for typical vascular lesions in the course of this disease [54]. Biding of the circulating IgM complexes to their endothelial receptor induces type III immunological reaction, with epithelial cells cytokine synthesis, what then stimulates the flow and accumulation of inflammatory cells. Circulating immune complexes together with the enhanced neutrophil migration can be responsible for systemic and mucosal lesions in BD. Increased
levels of NK cell were observed in peripheral blood of patients with active disease [55]. Additionally enhancement of coagulation and thrombosis was noted [56].

**Chronic Ulcerative Stomatitis**

Chronic ulcerative stomatitis (CUS) was described as a new disease entity in 1990 by Jaremko et al. [acc. 57]. This disease is characterized by the presence of erosions and ulcers with healing difficulty, mainly appearing on the tongue and desquamative gingivitis. Clinical features are similar to those of erosive lichen planus. In about 14% of patients skin characteristics for lichen planus are present. CUS mostly affects women over 50 years of age, and respond to treatment with hydroxychloroquine (in dosage of 250 mg daily in 5 day therapeutic courses with 5 days intervals) [58].

The immunological marker of CUS is the presence of serum high titres of antinuclear antibodies (SES-ANA) directed against the nuclear antigens of basal and spinous layer of the epithelium [59]. They are detected in indirect immunofluorescence method using various stratified epithelial tissues e.g. monkey or guinea-pig oesophagus as the antigen substrate [58, 59]. Deposits of IgG in keratinocytes nuclei (granular pattern), not detectable on conventional substrates for ANA, which are Hep2 and mouse’s kidneys, are observed in direct immunofluorescence of lesional oral mucosa. In consecutive examinations using immunoblotting technique in the sera of CUS patients a molecule in the range of 70 kD from the nuclei of epithelial cells. Autoantigen was named CUS protein (CUSP) [61]. The analysis of cDNA sequence for this protein revealed great homology e.g. to p53 tumor suppressor and p73 putative tumor suppressor genes and to p53-like gene, KET variant [57]. The p53-like genes, p73 and the several KET splicing variants probably have pathologic significance [57]. It has not been established in what way autoantibodies binding CUSP induce the disease, however the association of these antigens with CUSP is clear. It was noted that titres of the antibodies against CUSP not always correlate with the intensity of disease symptoms [57]. They were not detected in sera of patients with other autoimmune diseases (systemic lupus, dermatomyositis) and typical oral pathologies (aphthous stomatitis, lichen planus). CUSP is believed to be an essential epithelial regeneration and developmental factor and the presence of specific antibodies for this protein is responsible for the problems with wound and chronic ulceration healing.

**Periodontitis**

Periodontitis is not an autoimmune disease. However, in its pathogenesis the influence of the autoimmune process on the disease course can be detected. Series of studies have pointed to collagen type I as the main autoantigen in this disease [62–65]. Significantly higher levels in gingival extracts compared to serum levels of class IgG and IgA antibodies against collagen type I could be detected, what was explained as local synthesis of these antibodies in the active periodontal tissues damage periods [62]. The main source of immunoglobulins seem to be B CD5 cells, but at the time of formation of inflammatory process of periodontal tissues there is an exchange of classes from natural antibodies IgM to IgG and IgA [65]. Anusaksathien et al. [62] examined the serum level of class IgG antibodies directed against 12 autoantigens (DS-DNA, SS-DNA, human and bull thyroglobulin, myoglobin, transferrin, myosin, actin, human collagen type I, proteoglycan, cytochrom C and foetus antigen) in patients with periodontitis. Increased titres of collagen I were only observed. Other studies revealed that in 90% of sera and in all analysed samples of gingival cervical fluid from patients with periodontitis IgG class antibodies against desmosomal proteins (desmoplakin 1 and 2) and glycoproteins – desmoglein 1, 2 and 3 were present [66]. It is suggested that some of the so far described autoantigens, for example collagen I and desmosomal proteins exposed or released from periodontal structures (as a result of bacterial destruction) are the factors influencing the polyclonal activation of lymphocytes B and synthesis of specific for these structures antibodies [62–66]. These observations indicate the secondary nature of autoimmune processes induced by periodontal tissue destruction. Autoantibodies can influence the apical migration of junctional epithelium and periodontal pocket formation and can counteract the reattachment of connective tissue to root surface in the period of periodontal treatment. Govze and Herzberg suggested, that periodontal diseases have a multifactor model of autoimmune processes [66]. They are initiated by polyclonal bacterial activators, inducing expansion of autoreactive lymphocytes B leading to class IgG antibody synthesis. Many pathogenic for periodontium bacteria e.g. Porphyromonas gingivalis and Fusobacterium
show the properties of polyclonal activators of lymphocytes B. Along in the lasting process lymphocyte B activation is supported by autoantigen stimulation coming from destroyed tissues e.g. collagen, desmosomes of junctional epithelium. The research model showed the highest production of antibodies against collagen, when collagen I and bacterial polyclonal activators were available in destroyed periodontal tissues [63]. The influence of microorganisms could rely on the adjuvant action, increasing the autoantibody reaction to main autoantigens exposed in the course of periodontal tissue destruction.

In patients with periodontitis serum concentration of antibodies against neutrophils’ cytoplasm (ANCA) [67] and against human and bacterial heat shock proteins (HSP) were examined [68]. It does not look as these epitopes had a greater significance in escalating and the clinical course of periodontitis. Interestings are the observations, which point to significantly increased serum titres of anti-cardiolipin antibodies anti-β2-glycoprotein I in the course of generalized periodontitis (chronic or aggressive) [69]. Probably they cross react with the chosen sequence of arg-gingipain protease of Porphyromonas gingivalis. Postulated pathogenicity of these autoantibodies is defined by the activation of endothelial cells, induction of oxygen-mediated injury due to their reactivity with oxidized low density lipoproteins β (LDL) or interference with natural anticoagulants [69]. Induction of antiphospholipid antibodies formation in generalized periodontitis can have serious systemic implications as earlier described escalated susceptibility to atherosclerosis and increased probability of preterm low-birth-weight labour dependent on the periodontal status.

References


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