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ПАТОГЕНЕТИЧЕСКАЯ ВЗАИМОСВЯЗЬ ИММУНОЛОГИЧЕСКИХ НАРУШЕНИЙ ПРИ ХРОНИЧЕСКОМ ГЕНЕРАЛИЗОВАННОМ ПАРОДОНТИТЕ И РЕВМАТОИДНОМ АРТРИТЕ

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Pathogenetic Relationship of Immunological Disorders in Chronic Generalized Periodontitis and Rheumatoid Arthritis

Резюме

Патогенетическое единство механизмов прогрессирования хронического пародонтита и ревматоидного артрита подтверждается общими звеньями иммуновоспалительных реакций.

Повреждение тканей пародонта опосредовано цитотоксическими эффектами вырабатываемых бактериями Porphyromonas gingivalis ферментов и их метаболитов. Нейтрофилы способствуют развитию пародонтита и участвуют в его прогрессировании, рекрутируя Т-хелперы 17 (Th17) и способствуя накоплению плазматических клеток в поражённых тканях. Активация иммунокомпетентных клеток способствует генерации активных форм кислорода, инициирующих свободнорадикальное окисление липидов, что в сочетании с невозможностью их нейтрализации вследствие сниженного антиоксидантного потенциала приводит к развитию оксидативного стресса.

Связь между ревматоидным артритом и хроническим пародонтитом была в центре внимания многочисленных исследований, что обусловлено их общими патогенетическими механизмами. Хроническое воспаление, связанное как с ревматоидным артритом, так и с хроническим пародонтитом, сходно по преобладающему адаптивному иммунному фенотипу, дисбалансу между про — и противовоспалительными цитокинами. Значимым является вовлечение микроорганизма Porphyromonas gingivalis в генерацию антител к цитруллинированным пептидам у пациентов с ревматоидным артритом. Общность эпитопа (SE)-кодирующего аллель HLA-DRB1, связывающего цитруллинированные пептиды, может служить основанием для утверждения генетической предрасположенности и взаимопотенцирования данных заболеваний. Таким образом, имеющаяся взаимосвязь хронического пародонтита и ревматоидного артрита обосновывает необходимость проведения исследований, направленных на разработку новых методов в диагностике, лечении и профилактике рассматриваемых заболеваний с целью разобщения общих патогенетических механизмов воспалительных реакций и процессов остеорезорбции, приводящих к стойким функциональным и органическим расстройствам.

Ключевые слова: *пародонтит, ревматоидный артрит, цитокины, воспалительный ответ, остеорезорбция*

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Abstract

The pathogenetic mechanisms of progression of chronic periodontitis accompanied with rheumatoid arthritis is confirmed by the common parts of immune-inflammatory reactions.

Damage to periodontal tissues is indirectly made by cytotoxic effects of enzymes and their metabolites produced by Porphyromonas gingivalis bacteria. Neutrophils contribute to the progression of periodontitis and participate in its amplification by recruiting T-helper cells 17 and contributing to the accumulation of plasma cells in the affected tissues. Activation of immunocompetent cells promotes the generation of reactive oxygen species that initiate free radical oxidation of lipids, which, combined with the inability to neutralize them due to reduced antioxidant potential, leads to the development of oxidative stress.

The connection between rheumatoid arthritis and chronic periodontitis has been the focus of numerous studies, due to their common pathogenetic mechanisms. Chronic inflammation associated with both rheumatoid arthritis and chronic periodontitis is similar in its prevailing adaptive immune phenotype, an imbalance between pro- and anti-inflammatory cytokines. The involvement of the Porphyromonas gingivalis microorganism in the generation of antibodies to citrullinated peptides in patients with rheumatoid arthritis is significant. The similarity of the epitope (SE) encoding the HLA-DRB1 allele, binding citrullinated peptides, can act as a basis for the approval of the genetic predisposition and mutual potential of these diseases. Thus, the proven connection between chronic periodontitis and rheumatoid polyarthropathies determines the significance of the analysis of the data obtained and substantiates the need for strategic research aimed at developing new methods in the diagnosis, treatment and prevention of the diseases for the purpose of breaking and separation of the common pathogenetic mechanisms of inflammatory reactions and osteoresorption processes leading to persistent functional and organic disorders.

Key words: *periodontitis, rheumatoid arthritis, cytokines, inflammatory response, osteoresorption*

Conflict of interests

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ACPA — antibodies to citrullinated peptides, IL — interleukin, IL-1β — interleukin-1β, MMP — matrix metalloproteinases, PPAD — peptidyl arginine deaminase, RA — rheumatoid arthritis, RANKL — membrane-bound receptor activator of nuclear factor kappa-β, ROS — reactive oxygen species, TNF — tumor necrosis factor

Introduction

Periodontal inflammatory diseases are one of the most challenging socially-significant pathologies in the world [1]. Their prevalence in the world is about 98 % and they are one of the main causes of tooth loss [2]. According to the World Health Organization (WHO), the incidence of periodontal diseases peaks at 35–45 years; in recent years, such diseases have increasingly been found in younger individuals [3]. The prevalence of periodontal diseases in Russia has age-related features. In particular, their incidence in patients at the age of 32 is 48.2 %, in patients aged 45 — up to 86 %, and in patients aged 65 — 100 % [4].

Currently, odontogenic infection is thought to play an important role in the development of somatic pathology [5]. Periodontal pathogens, increased synthesis of pro-inflammatory cytokines contribute to the development of a systemic response and/or a number of systemic autoimmune diseases; rheumatic diseases with joint damage are of the greatest significance among such conditions. In this group, rheumatoid arthritis has the strongest pathogenetic relationship with inflammatory periodontal diseases [6].

The NHANES (National Health and Nutrition Examination Survey) showed that the prevalence of chronic periodontitis, as measured by the number of missing

teeth, was four times higher in patients with rheumatoid arthritis (RA) [7]. This conclusion is supported by epidemiological and case-control studies, which have demonstrated that patients with active RA have a significantly higher prevalence of chronic periodontitis (defined by various parameters, including bleeding, gingivitis, and increased probing pocket depth) compared to patients without RA [8]. In addition, the prevalence of RA in patients with chronic periodontitis is higher than among those without such pathology [6].

Confirmation of the pathogenetic relationship between chronic periodontitis and rheumatoid arthritis requires pointing out the much higher prevalence of rheumatoid arthritis in patients with chronic periodontitis (3.95 % compared to 1 % in the overall population) [9]. Interestingly, with high activity of rheumatoid arthritis, the increase in the RBC sedimentation rate and the increase in the level of C-reactive protein correlate with a more severe degree of periodontal bone resorption [8].

There are similar genetic factors in patients with chronic periodontitis and rheumatoid arthritis that contribute to the development of these pathologies. More than 50 % of the risk of developing RA is associated with genetic factors, and the most significant genetic association in RA is the SE-coding gene HLA-DRB1, which contributes more than 80 % susceptibility to periodontal tissue damage [7].

Immunological aspects of the development of chronic periodontitis

According to some sources, there are about 700 microorganisms in the oral cavity [10]. Microbiological aspects of the pathogenesis of chronic periodontitis are the colonization of gingival pockets, mainly by gram-negative anaerobic bacteria *Porphyromonas gingivalis* together with *Agregatibacter actinomycetemcomitans*, etc. Under the conditions of impaired microbiota composition in combination with the effects of certain immune cells, the above component is brought into action as a pathological component [7]. *P. Gingivalis* are primarily localized on the supragingival surface of teeth and in the subgingival fissure, causing the destruction of periodontal supporting tissues by the produced enzymes — proteinases, hemolysins, peptidyl-arginine deaminases (PPAD) — and reacting with cellular components [11]. These enzymes and metabolites (alkaline and acid phosphatases, volatile sulfur compounds — hydrogen sulfide, methyl mercaptan and dimethyl sulfide) have cytotoxicity as a result of the inhibition of phospholipase A_2 and protein synthesis. The severity of the inflammatory reaction is determined by local and general, specific and nonspecific resistance [12]. Microorganisms form a dental plaque 24–48 hours after brushing is stopped. The supragingival part of dental plaque is predominantly represented by gram-positive microorganisms, and the subgingival part — by gram-negative microorganisms. [13]. The antigenic load and effect of toxins increase the permeability of the epithelium of the gingival sulcus and hypersecretion of sulcular fluid, which potentiates a further increase in capillary permeability, together with the effects of bacteria and leukotoxins. Phagocytes enter the connective tissue and gingival fluid [14].

Periodontal damage starts as an acute inflammation characterized by an increase in the number of neutrophils that migrate into the gingival fissure through the periodontal epithelium and have the capacity for biosynthesis of chemokines and cytokines with pro-inflammatory, anti-inflammatory and immunoregulatory properties. Neutrophils can induce the recruitment of interleukin-17-producing CD4-positive T helper cells 17 at the site of infection or inflammation by releasing chemokines. In addition, they may promote the proliferation and differentiation of B cells into plasma cells, which are responsible for antibody production. Activated neutrophils express the activator of the membrane-bound receptor for nuclear factor kappa-β (RANKL), a key osteoclastogenic cytokine, thereby promoting bone resorption by osteoclasts [15]. These latter ideas suggest that neutrophils may contribute to the development of periodontitis, not only by initiating damage but also by participating in its progression [15].

Macrophages are an important source of pro-inflammatory cytokines such as interleukin-1β (IL-1β), tumor necrosis factor (TNF), matrix metalloproteinases (MMP), and prostaglandin E2 [16], which play an important role in the development of inflammation. Also, an increase in their level in gingival tissue and gingival fissure fluid is observed in patients with chronic periodontitis [17].

According to current concepts, the chronization of the inflammatory process primarily contributes to the hyperproduction of non-specific body defense factors by cells: pro-inflammatory cytokines (IL-1β, IL-6, IL-8, IL-18, TNF) in response to the action of pathogenic microorganisms [18].

Due to the chemotactic action of pro-inflammatory mediators, periodontal tissues are infiltrated by neutrophils and macrophages. Their subsequent secretory degranulation leads to the release of matrix metalloproteinases (MMP), which are important in the development and maintenance of chronic inflammation [19]. MMP are Zn^{2+} and Ca^{2+}-dependent endopeptidases, which are catabolism enzymes for most extracellular matrix proteins. Collagenase-1 (MMP-1) is responsible for the cleavage of type I collagen. It is produced mainly by fibroblasts, as well as such cells as macrophages, monocytes, osteoblasts, endothelial cells, and chondroblasts. Several studies showed increased levels of MMP-8 and MMP-9 in periodontal tissues [20].

MMP-8 (collagenase-2) plays a critical role in the final stages of the development of chronic periodontitis and remodeling of periodontal tissues. It is secreted mainly by neutrophils and their precursors, as well as fibroblasts, monocytes, macrophages, plasma cells, and differentiated granulocytes [19]. It should be noted that an increased level of MMP-8 (up to 65 ng/mL) in gingival fluid was found in patients with severe chronic periodontitis, as well as patients with untreated forms of aggressive types [21]. Some authors established that Il-1β and tumor necrosis factor (TNF) contribute to excessive production of MMP-9 (collagenase-4), which stimulates increased permeability, damage to the structure of tooth tissues, and tooth decay [22].

The generation of pro-inflammatory cytokines by lymphocytes and the direct effect of the enzymes produced by bacterial cells on collagen structures [18] play an essential role in the destructive processes of the periodontium.

Free radical oxidation processes [23] play a significant role in the etiopathogenesis of chronic periodontitis. Due to an excessive inflammatory response to bacterial plaque, tissue destruction occurs, which leads to increased generation of reactive oxygen species (ROS) by WBC [24]. The cytotoxic effect of ROS is brought into action in the peroxidation of lipid structures of both cell membranes and the extracellular matrix. ROS peroxidation disrupts the physicochemical properties of proteins, which leads to the manifestation of oxidative degradation and protein aggregation. Impaired functions of proteins as the components of transport and enzyme systems of cells result in the impaired constancy of the internal environment [25]. In addition, ROS can cause depolymerization of the extracellular matrix (particularly glycosaminoglycans) and enzymes (particularly MMR) [26].

Lack of control over lipid peroxidation (LPO) reactions not only causes impaired metabolic processes, but also contributes to the development of structural changes in tissues and suppression of body defense mechanisms [25]. According to several reports, LPO activation results in the destruction of the intermediate epithelium and periodontal tissues, leading to pathological tooth mobility. Also, due to the activation of free radical oxidation processes, regeneration processes are impaired, periodontal pockets and bone resorption develop [26].

With periodontitis, there is a decreased activity of key enzymes of the body's antioxidant defense: catalase, superoxide dismutase, glutathione peroxidase, cytochrome oxidase. An increase in sulfhydryl groups is observed, which indicates the cleavage of proteins. In addition, the triggering of free radical oxidation processes is indicated by an increased level of active products of thiobarbituric acid in gingival fluid; these are the main products of the free radical peroxidation of polyunsaturated fatty acids [27].

Pathogenetic relationship between chronic periodontitis and rheumatoid arthritis

The unity of general pathological processes in the progression of periodontitis and rheumatoid arthritis, i.e., concomitant action of cellular and humoral immunity through cytokine regulation (IL-1β, IL-6, IL-8, IL-18, TNF), as well as the role of LPO in the destruction of collagen structures, extracellular matrix of subgingival spaces, as well as the predominant activation of osteoclasts, confirm the possibility of interdependence and mutual potentiation of these pathological conditions [28].

Exposure to certain environmental factors, such as smoking, genetic background (HLA-DRB1-SE), gut microbiome, P. gingivalis infection, and more recently, A. actinomycetemcomitans (microbial dysbiosis), leads to local changes in proteins due to citrullination [28, 29].

P. Gingivalis causes the activation of proteases and peptidyl-arginine deaminase (PPAD), which generates citrullinated proteins via post-transcriptional removal of the guanidine group of terminal arginine from proteins (keratin, felargin, collagen, fibrin) and triggers the synthesis of antibodies to citrullinated proteins (ACPA), which are represented by antibodies to cyclic citrullinated peptide (ACCP), modified citrullinated vimentin (AMCV), and some other antibodies [30, 31].

The consequence of impaired tolerance to citrullinated proteins is the triggering of the activation of immunocompetent cells (dendritic cells, macrophages, T and B lymphocytes), which triggers the subsequent production of pro-inflammatory cytokines and, as a result, the activation of type 1 T helper cells (Th1) and Th17 cells. Their stimulation results in the production of interferon-γ (IFN-γ), IL-2, IL-17, IL-21, TNF, leading to the activation of B lymphocytes, which are subsequently transformed into plasma cells responsible for the production of autoantibodies of the IgG isotype [32]. Therefore, the received signal against citrullinated epitopes in joints leads to increased expression of rheumatoid factor (RF) and antibodies to citrullinated peptides, which contributes to the development of immune complexes. The resulting immune complexes are phagocytized by neutrophils and macrophages of the synovial membrane, which leads to damage to neutrophils, the release of lysosomal enzymes, histamine, serotonin, kinins, prostaglandins, leukotrienes and the development of exudative and proliferative changes in the synovium and cartilage. Damage to the joint tissues by immune complexes leads to further autoantibody production and contributes to the chronicity of the inflammatory process [7].

Hyperproduction of pro-inflammatory cytokines (TNF, IL-1, IL-6, IL-17) leads to the increased production of RANKL. Moreover, TNF can bind to the type 1 TNF receptor on the surface of osteoclasts, thereby stimulating osteoclastogenesis [33].

Notably, *A. actinomycetemcomitans* leads to the hypercitrullination of neutrophils and the activation of citrulline enzymes, which are also involved in the impaired immune tolerance to host molecules. These immune complexes intensify the inflammatory process, which can aggravate the course of rheumatoid arthritis. Also, autoantibodies may contribute to the inflammatory process by direct activation of osteoclasts by interacting with citrullinated vimentin, which is expressed on the membrane of osteoclast precursors, leading to bone and cartilage damage (Fig. 1) [7].

The activation of mast cells that secrete heparin and serotonin should be noted. It leads to exudative and proliferative inflammation of the synovial membrane of joints (synovitis), which is characterized by the production of lymphocytic infiltrates, accumulation of macrophages, development of neoangiogenesis, proliferation of synovial membrane cells and fibroblasts, with the formation of an aggressive tissue — pannus. [33, 34]. Synovitis causes changes to the cellular structure of synovia due to the increased number of macrophage-like (MLS) and fibroblast-like synoviocytes (FLS). MLS produce chemokines and growth factors, which leads to the activation of local FLS expressing IL-6, prostanoids, MMP, as well as chronic synovitis [35].

Therefore, citrullination of proteins may represent a biological mechanism that strengthens mutual influence between rheumatoid arthritis and chronic periodontitis.

Wagner et al. (2015) proposed a "two-hit" model of the impact of chronic periodontitis on rheumatoid arthritis: the first "hit" is initiated by an increase in the prevalence of PAD-producing *P. gingivalis* in the periodontal microenvironment, which increases local citrullination of peptides and the generation of antibodies to citrullinated proteins. The second "hit" is represented by the cross-reactivity of periodontal-generated ACPA to antigens that are in the microenvironment of a joint, which further exacerbates chronic autoimmune inflammation caused by rheumatoid arthritis [36].

In addition, there are similar genetic factors in patients with chronic periodontitis and rheumatoid arthritis that contribute to the development of these pathologies. It is possible that several common genetic disorders are associated with increased susceptibility to these diseases. One of the potential genetic mechanisms linking rheumatoid arthritis and chronic periodontitis is a common epitope (SE)-coding HLA-DRB1 allele [37]. HLA-DRB1 alleles that encode the major histocompatibility complex class II beta chain can bind citrulliniropeptides, which can increase the immunogenicity of autoantigenic citrullinated arthritis peptides [38, 39].

Therefore, a growing number of experimental and clinical studies has undoubtedly demonstrated that there is a strong link between rheumatoid arthritis and chronic periodontitis (Figure 2) [7].

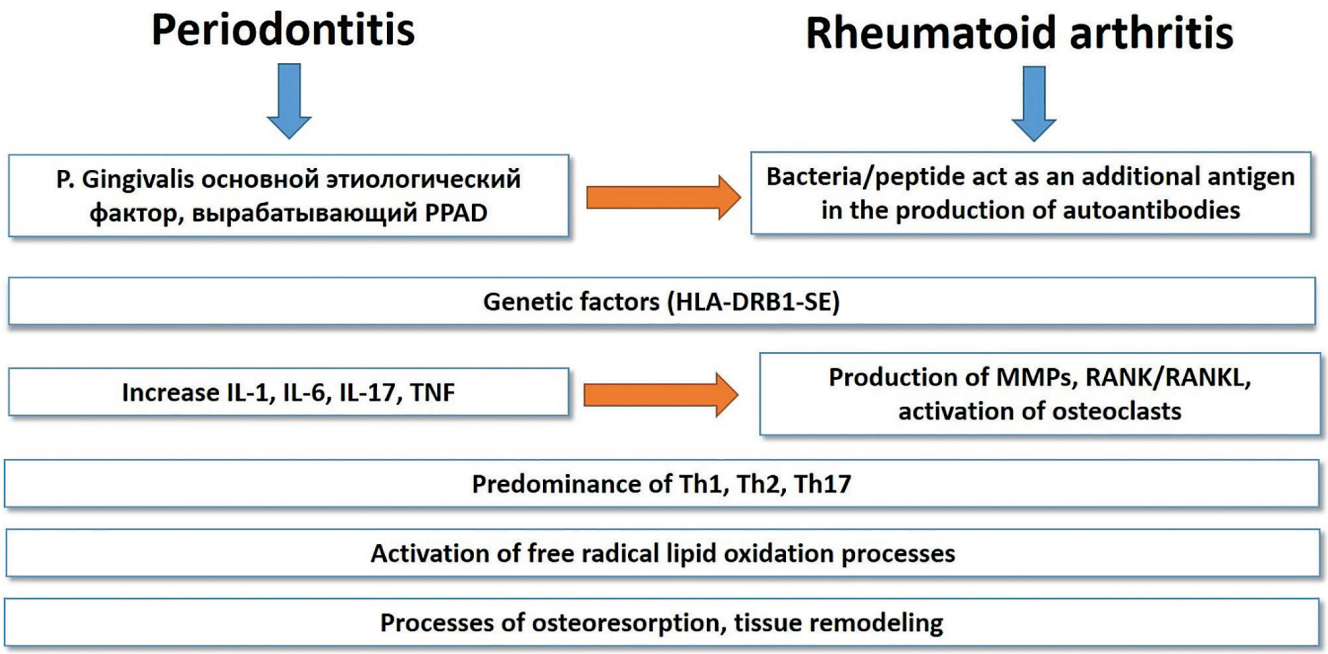

Figure 1. *The main factors of the formation of chronic generalized periodontitis and rheumatoid arthritis [7]*

Notes. PPAD –peptidyl-arginine deiminase; Th1 — T-helper cell type 1; Th2 — T-helper cell type 2; Th17 — T-helper cell type 17; IL-1 — interleukin-1; IL-6 — interleukin-6; TNF — tumor necrosis factor; IL-17 — interleukin-17; RANK-L — receptor activator of nuclear factor kappa-β; MMP — matrix metalloproteinase

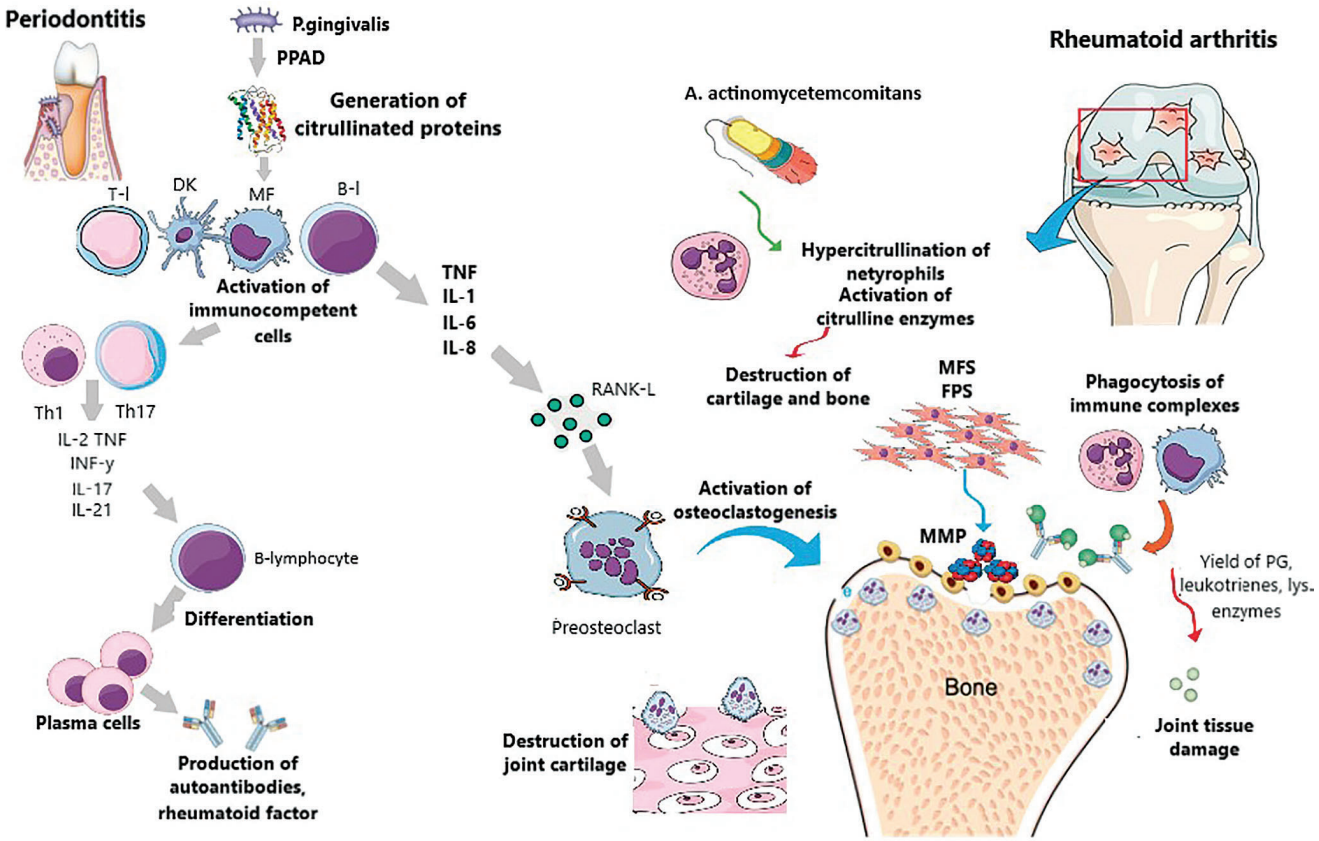

Figure 2. *Pathogenetic connection of chronic generalized periodontitis and rheumatoid polyarthritis [7]*

Notes. PPAD — peptidyl-arginine deiminase; T-l — T-lymphocyte; DK — Dendritic cell; MF — macrophage; B-l — B-lymphocyte; Th1 — T-helper cell type 1;Th17 — T-helper cell type 17; IL-1 — interleukin-1; IL-2 — interleukin-2;IL-6 — interleukin-6;IL-8 — interleukin-8; TNF — tumor necrosis factor; IL-17 — interleukin-17;IL-21 — interleukin-21; RANK-L — receptor activator of nuclear factor kappa-β; MFS — macrophage-like synoviocytes; FLS — fibroblast-like synoviocytes; MMP — matrix metalloproteinase; PG — prostaglandins

Conclusion

The presented summarized studies make a strong case for a pathogenetic relationship between the mechanisms of progression of chronic periodontitis and rheumatoid arthritis.

The correlation between both diseases is confirmed by the high incidence of the combination of both pathologies in the population, the presence of a common epitope (SE) encoding HLA-DRB1 allele, the production of cross-reacting antibodies that cause the combined effect of autoimmune and inflammatory processes, leading to systemic effects of cytokines at the body level, which explains the increased risk of this pathology in chronic periodontitis.

The link between rheumatoid arthritis and chronic periodontitis is due to the infection of periodontal tissues with *P. Gingivalis,* leading to the activation of proteases, PPAD and the production of citrullinated proteins, impaired tolerance to which leads to the activation of immunocompetent cells. Such triggering of autoaggressive reactions is critical in the development of rheumatoid arthritis in chronic periodontitis. Several proinflammatory cytokines (TNF, IL-1, IL-6, IL-17) increase the production of RANKL and stimulate osteoclastogenesis inducing bone resorption.

Further study of the mutual influence of these pathologies will allow developing new methods for diagnosing and managing these nosologies and preventing their progression at the early stages of their development. Good oral hygiene and timely detection of the initial stages of periodontitis can prevent the possible development of rheumatoid arthritis in individuals with a genetic predisposition to this pathology. Available evidence of the presence of systemic inflammation makes a strong case for introducing genetically engineered biological preparations into the treatment algorithms for these diseases. The identification of close relationships will facilitate the development and manufacturing of agents that will have an effect on both RA and chronic periodontitis. The summarized study results indicate the need for close interaction between dentists and rheumatologists, as well as for screening immunological examination of individuals with chronic periodontitis, especially those of early working age, in order to prevent the development or slow down the progression of rheumatoid arthritis.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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