УДК 616.314.18-002.4-002.2:616.72-002:616.517]-092
https://doi.org/10.20538/1682-0363-2022-4-183-192

Pathogenetic aspects of the development of psoriatic arthritis in people with generalized chronic periodontitis

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ABSTRACT

The pathogenetic mechanisms of progression of chronic periodontitis and psoriatic arthritis have common components in immune and inflammatory responses.

The pathogenesis of chronic periodontitis involves interaction of microbial and immunological components. As a chronic immune-mediated inflammatory disease and a consequence of an infectious trigger that originally affects gingival soft tissue, periodontitis is typically characterized by periodontal destruction and damage to adjacent connective tissues. Neutrophils contribute to the development of periodontitis and participate in its progression by recruiting T helper 17 cells and stimulating synthesis of the receptor activator of the nuclear factor kappa-β ligand (RANKL), contributing to bone resorption.

Macrophages as producers of proinflammatory cytokines (interleukin (IL)-1β, IL-6, IL-22, IL-23, tumor necrosis factor (TNF)), free radicals, and matrix metalloproteinases contribute to the chronic course of the disease. Tissue destruction results in generation of reactive oxygen species by neutrophils, which, against the background of a decrease in the antioxidant potential, leads to development of oxidative stress. These processes together lead to tooth mobility, formation of periodontal pockets, and bone resorption.

The key factors in the formation of psoriatic arthritis against the background of periodontitis are overproduction of proinflammatory cytokines in target tissues (skin, joints, gingival microflora) and development of an excessive systemic immune response to the microbiota inhabiting the epithelial and periodontal tissues. A statistically confirmed correlation of the progression of periodontal destruction with the presence of psoriatic arthritis proves the significance of the effects of inflammation as a background for the progression of a comorbidity. Increased IL-17 synthesis plays a crucial role in the development of immune responses of pathological bone remodeling and bone resorption in periodontitis and psoriatic arthritis.

Keywords: periodontitis, psoriatic arthritis, cytokines, free radical oxidation, inflammatory response, bone resorption

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

For citation: Poryadin G.V., Zakhvatov A.N., Parshina A.Yu. Pathogenetic aspects of the development of psoriatic arthritis in people with generalized chronic periodontitis. *Bulletin of Siberian Medicine.* 2022;21(4):183–192. https://doi.org/10.20538/1682-0363-2022-4-183-192.

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Патогенетические аспекты взаимосвязи хронического генерализованного пародонтита и псориатического артрита

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РЕЗЮМЕ

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

Патогенез хронического пародонтита заключается во взаимодействии микробного и иммунологического компонентов. Как хроническое иммуновоспалительное заболевание и следствие инфекционного триггера, который первоначально поражает мягкие ткани десен, пародонтит классически характеризуется разрушением периодонта и окружающих соединительных тканей. Нейтрофилы способствуют развитию пародонтита и участвуют в его прогрессировании, рекрутируя Т-хелперы 17 и стимулируя синтез активатора мембраносвязанного рецептора ядерного фактора каппа-β (RANKL), способствуя остеорезорбции.

Макрофаги как продуценты провоспалительных цитокинов (интерлейкин (IL)-1β, IL-6, IL-22, IL-23, фактор некроза опухоли), свободных радикалов, матриксных металлопротеиназ способствуют хронизации процесса. Деструкция тканей влечет за собой генерацию нейтрофилами активных форм кислорода, что на фоне снижения антиоксидантного потенциала ведет к развитию оксидативного стресса. Данные процессы в совокупности ведут к формированию патологической подвижности зубов, пародонтальных карманов, процессам остеорезорбции.

Ключевым фактором в формировании псориатического артрита на фоне пародонтита является гиперпродукция провоспалительных цитокинов в тканях-мишенях (кожа, суставы, микросреда десен) и развитие чрезмерного системного иммунного ответа на микробиоту, населяющую поверхность эпителия и ткани пародонта. Статистически подтвержденная корреляция развития деструкции пародонта с наличием псориатического артрита доказывает значимость эффектов воспалительного процесса как фона для развития коморбидной патологии. Повышенный синтез IL-17 выполняет ключевую роль в развитии иммунных реакций патологического костного ремоделирования и остеорезорбции при пародонтите и псориатическом артрите.

Ключевые слова: пародонтит, псориатический артрит, цитокины, свободнорадикальное окисление, воспалительный ответ, остеорезорбция

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Порядин Г.В., Захватов А.Н., Паршина А.Ю. Патогенетические аспекты взаимосвязи хронического генерализованного пародонтита и псориатического артрита. *Бюллетень сибирской медицины.* 2022;21(4):183–192. https://doi.org/10.20538/1682-0363-2022-4-183-192.

INTRODUCTION

Currently, inflammatory periodontal diseases are some of the urgent and socially sensitive problems of health care [1]. About 95% of the adult population in the world suffer from this pathology, which, in the absence of proper and timely treatment, leads to defects in the dentition, thereby reducing the ability to work and decreasing the quality of life of the population [2–6]. The prevalence of periodontal disease in Russia is about 85%, 53% of the population have initial manifestations of inflammations, and 12% have moderate and severe inflammation [7–9].

In chronic periodontitis, systemic lesions occur that involve not only periodontal tissues, but also other organs and systems, which leads to disruption of various components of homeostasis, including the immune system [10]. The inflammatory process and increased synthesis of proinflammatory cytokines result in the development of a number of systemic autoimmune pathologies, of which rheumatic diseases and severe forms of psoriasis with joint damage have the greatest significance [11].

Despite the widespread interest in periodontitis and systemic disorders over the past decade, only a few studies have considered the association between psoriatic arthritis (PsA) and chronic periodontitis [12, 13].

The analysis of the conducted studies showed an increase in the frequency of periodontitis in patients with PsA. For example, in Denmark, a large cohort study of 6,428 patients who were diagnosed with PsA revealed that the frequency of periodontitis in this group of patients was significantly higher than in the control group [14]. C. Ancuta et al. (2017) showed a significant decrease in the intensity of the disease and an improvement in the periodontal condition in patients with PsA 6 months after the initiation of anti-cytokine therapy [15].

The association between chronic periodontitis and PsA is bidirectional. An increased risk of psoriasis was noted in patients with chronic periodontal diseases [13, 15–17]. This suggests the existence of common mechanisms that determine mutual aggravation of the course of these common diseases.

IMMUNOPATHOGENESIS OF CHRONIC GENERALIZED PERIODONTITIS

The pathogenesis of chronic generalized periodontitis is multifactorial and is considered to be a result of an ongoing cross-interaction of bacterial, immunological, inflammatory, and genetic factors [18]. As a chronic immune-mediated inflammatory disease and a consequence of an infectious trigger that originally affects gingival soft tissue, periodontitis is typically characterized by periodontal destruction and damage to adjacent connective tissues [19].

Microbiological aspects of the development of chronic periodontitis consist mainly in colonization of the periodontal pockets by gram-negative microorganisms, the most significant of which are *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Tannerella forsythia,* and *Treponema denticola* [17].

The inflammatory response is triggered by the interaction of resident cells with bacterial biofilm attached to the tooth surface, which, via fixation, makes it impossible for the immune system to destroy gram-negative microorganisms, thereby increasing damage to periodontal tissues [20]. The epithelium of the periodontal ligamnent is the first periodontal structure to experience bacterial exposure [21]. Production of the main enzymes (proteinase, peptidyl-arginine deiminase (PPAD), hemolysins) and metabolites (methyl mercaptan and dimethyl sulfide) by gram-negative anaerobic microorganisms contributes to destruction of fibronectin and laminin and hydrolysis of collagen. It facilitates passage of bacteria through the periodontium into the gingival connective tissue, where they stimulate gingival epithelial cells and fibroblasts to trigger initial inflammatory responses [22].

Resident periodontal cells detect bacterial pathogen-associated molecular patterns (PAMP) [23], which connect to toll-like receptors (TLR4/2), triggering the recruitment of protein kinases. It ultimately causes activation of proinflammatory transcription factors, such as nuclear factor kappa B (NF-kB) and activator protein-1 (AP-1), stimulating the expression of genes responsible for synthesis of proinflammatory cytokines, thereby leading to an increase in inflammation [24]. In addition, gingival fibroblasts stimulate destruction and disorganization of the fibrous component of the extracellular matrix by increasing the production and activity of matrix metalloproteinases (MMP) [25].

Due to migration of immunocompetent cells into the subgingival space, infiltration of periodontal tissues by neutrophils occurs, which leads to an increase in synthesis of cytokines and chemokines with proinflammatory and anti-inflammatory properties [22]. Neutrophils induce recruitment of CD4+ T helper 17 (Th17) cells responsible for the production of IL-17 and stimulate synthesis of the receptor activator of the nuclear factor kappa-β ligand (RANKL), which leads to bone resorption by osteoclasts [25].

Macrophages are important sources of pro-inflammatory cytokines, such as interleukin (IL)-1, tumor necrosis factor (TNF), MMP, and prostaglandin E2 [26], which are elevated in the gingival tissue of patients with chronic periodontitis [25]. Studies have shown a direct correlation of macrophage infiltration with the severity of periodontitis, which significantly contributes to the degradation of the collagen matrix in the connective tissue of the periodontium [27].

Macrophages can undergo classical (M1) or alternative (M2) activation. M1 macrophages are induced by microbial agents or Th1 cytokines and exhibit high phagocytic capacity and increased expression of proinflammatory cytokines and costimulatory and antimicrobial molecules. In contrast, M2 macrophages are induced by Th2 cytokines and secrete high levels of IL-10 and transforming growth factor-β1 (TGF-β1). Consequently, they have immunoregulatory properties and promote cell proliferation and tissue regeneration [28]. In experimental models of periodontitis, the presence of both M1 and M2 macrophages was noted, but with the predominance of M1 macrophages, which indicates the activation of the immune response with increased production of proinflammatory cytokines [27].

When the inflammatory process becomes chronic, lymphocytes penetrate into periodontal tissues, releasing inflammatory and immune molecular mediators that change the balance of bone metabolism, determining the transition from gingivitis to periodontitis [25]. Activation of adaptive immunity has a great impact on bone loss associated with B and T lymphocytes, since these cells are the main cellular sources of RANKL during periodontal inflammation [28].

RANKL is a cytokine belonging to the TNF family that can bind to receptors on membranes and stimulate osteoclast differentiation, cell fusion and activation, which results in bone resorption [28]. Osteoblasts and bone marrow stromal cells predominantly express membrane-bound RANKL which induces osteoclastogenesis through cell contact with osteoclast precursors. Activated T and B cells produce both membrane-bound and soluble RANKL [22]. Soluble RANKL can induce osteoclastogenesis independently of the direct contact between infiltrating lymphocytes and osteoclast precursors on the bone surface. RANKL is an osteoclast activator and a molecular signal directly responsible for bone resorption. It interacts with the associated RANK receptor on the surface of osteoclasts and their precursors, which triggers its recruitment on the bone surface with subsequent activation of cells [29].

Osteoprotegerin (OPG) is a soluble protein that has the ability to block biological functions of RANKL by competitive inhibition [30]. In periodontitis, an increase in RANKL / OPG promotes the recruitment of osteoclast precursors, which contribute to bone resorption via the interaction with proinflammatory cytokines expressed by Th1 lymphocytes [29].

In addition, Th1 lymphocytes play an important role in the emergence and progression of periodontitis by increasing the level of interferon γ (IFNγ) [24]. IL-1ß and TNF secreted by Th1 lymphocytes cause vasodilation, stimulate activation of endothelial cells, increase the production of chemokines, participate in activation of neutrophils, and stimulate secretion of MMP [25]. Th2 lymphocytes are the main cellular source of IL-4, which promotes secretion of IgE by plasma cells and alternative activation of macrophages via the IFN-dependent pathway.

Lipid peroxidation processes play a significant role in the pathogenesis of chronic periodontitis [31]. Progressive periodontal destruction entails generation of reactive oxygen species (ROS) by neutrophils and subsequent peroxidation of lipid structures in cell membranes [32]. Insufficient antioxidant potential of cells, manifested by the inability to neutralize ROS, leads to development of oxidative stress, formation of metabolic disorders, and development of secondary destructive changes [32]. In such conditions, a violation of regeneration, formation of periodontal pockets, and progression of bone resorption are noted [30].

IMMUNOPATHOGENETIC ASPECTS OF PSA DEVELOPMENT

Psoriatic arthritis is a chronic progressive inflammatory process associated with psoriasis, characterized by predominant localization in the tissues of the musculoskeletal system and leading to the development of erosive arthritis, intra-articular osteolysis, and spondyloarthritis [33].

Etiological factors underlying the development of PsA are currently insufficiently studied. The disease develops following a complex interaction of genetic, immunological, and environmental factors [34]. About 40% of patients with PsA have this disease in the family history, and, therefore, the risk of developing this disease in such patients increases by 27–50 times [35, 36]. In recent years, studies have been conducted to identify genetic markers of PsA, during which the antigen of the histocompatibility complex HLA-B27 was detected in every third patient [33–36]. Genetic associations in PsA include HLA-B*08:01, HLA-B*27:05, HLA-B*38:01, HLA-B*39:01, HLA-B*57:01, and HLA-C*06:02 [36]. HLA-B27 is associated with axial lesion, whereas HLA-B38 and HLA-B39 are associated with polyarthritis [37]. Non-HLA genes associated with PsA include IL-23R [34].

Bacterial infection, smoking, obesity, stress, and trauma are environmental factors that increase the risk of developing PsA, especially in young people [38]. PsA is considered a T-cell-mediated disease in which cellular immunity is activated in the skin and synovia, followed by overproduction and imbalance of key pro- and anti-inflammatory cytokines, such as TNF, IL-1ß, IL-6, IL-12, IL-17, IL-23, and chemokines [39].

A genetic predisposition in combination with environmental factors (bacterial infection, mechanical injury) initiate a chronic inflammatory process affecting primarily the tissues of the joints [38]. Repeated mechanical injury contributes to formation of inflammatory infiltrates consisting of monocytes, dendritic cells, neutrophils, and T cells in the synovial membrane [40]. Dendritic cells release IL-12 and IL-23, which leads to differentiation of naive T cells into Th1 and Th17, respectively, and to a decrease in the production of regulatory T (Treg) cells [41]. Abnormal activation of the IL-23 / Th17 axis is the dominant pathology in PsA. IL-23 triggers the activation of tyrosine kinase 2 (TYK2) and Janus kinase 2 (JAK2) signaling pathways, which promote phosphorylation and activation of the signal protein STAT3 (signal transducer and activator of transcription 3). It increases the expression of the transcription factor RORγt, which stimulates the production of IL-17, IL-21, IL-22, granulocyte-macrophage colony stimulating factor (GM-CSF), and tumor necrosis factor (TNF), thereby contributing to tissue inflammation [42]. In addition to IL-23, the differentiation of naive T cells into Th17 cells is stimulated by IL-1ß, IL-6, and transforming growth factor β (TGFβ) [41].

In PsA, enthesis is considered to be the initial focus of inflammation, which spreads to other periarticular and articular structures, leading to the development of synovitis, dactylitis, spondylitis, and osteitis [43]. An important early mediator of enthesitis is prostaglandin E2 (PGE2), which causes vasodilation and facilitates recruitment of neutrophils from the bone marrow to tendon-to-bone attachment sites. Neutrophils increase inflammation by releasing proteases and ROS. PGE2 also promotes IL-17 production by T cells [44].

Inflammation in extra-articular structures, i.e. extensor tendon enthesitis and peritendon inflammation, progresses to intra-articular inflammation, taking the form of synovitis [43]. Synovitis in PsA is characterized by hyperplasia of the mucous layer with an increase in the number of fibroblast-like synoviocytes and macrophages, hypervascularization of tortuous arteries, and the presence of hyperemic villi and subsynovial infiltrate consisting of T cells, B cells, neutrophils, mast cells, and monocytes / macrophages. Elongated, dilated, thick, and tortuous vessels indicate increased angiogenesis [45, 46]. In the synovial membrane in PsA, high expression of IL-17A and IL-17 receptors is noted, where the cytokine IL-17A is directly involved in bone and cartilage destruction [44].

Remodeling is a unique feature of PsA [46]. In PsA, IL-17 enhances osteoclastogenesis, whereas IL-22 promotes osteoblastogenesis. Thus, the presence of a balance between IL-17, IL-22, and IL-23 is necessary to maintain bone homeostasis [47]. Prominent signs of PsA are subchondral perienthesial edema and diffuse bone marrow edema [45]. The subenthesis bone in PsA exhibits increased vascularity and hyperosteoclastic cystic and erosive changes [47]. Physiologically, bone homeostasis is maintained by a balance between osteoclasts capable of bone resorption and osteoblasts responsible for osteoblastogenesis. In systemic inflammation, stimulation of CD14+ monocytes by macrophage colony stimulating factor (M-CSF), TNF, and RANKL leads to the formation of osteoclast precursors in peripheral blood.

In addition, IL-23 and IL-17 independently induce osteoclast formation in myeloid cells [43]. In the subchondral bone, binding of the receptor activator of nuclear factor kappa B (RANK), present on the surface of monocytes / macrophages, to membrane-bound RANKL, present on the surface of Th17 cells, stimulates differentiation of monocytes / macrophages into osteoclasts [47]. Activated osteoclasts begin to secrete enzymes of bone matrix degradation: acid phosphatases, matrix metalloproteinase-9 (MMP-9), and cathepsin K (CatK), which promote bone resorption. In addition, the osteoclast-associated receptor (OSCAR) located on the surface of monocytes, after TNF induction, potentiates the action of RANKL, thereby enhancing osteoclastogenesis [46]. RANKL also increases the activation of T cells and their production of proinflammatory cytokines, including TNF, IL-1β, IL-6, IL-15, IL-17, and IL-23 [45].

In PsA, IL-22 induces osteoproliferation in the enthesis and periosteum by activating STAT3 on osteoblasts, causing the formation of new bone tissue, manifested by fusion of peripheral joints, enthesophytes, spurs, ankylosis, syndesmophytes in the axial skeleton, and changes in the sacroiliac joints [43, 47].

Proinflammatory cytokines secreted in PsA can stimulate chondrocytes to produce destructive

proteases, which leads to proteoglycan loss, damage to collagen bundles with concomitant release of cartilaginous oligomeric matrix protein (COMP). COMP, a glycoprotein belonging to the family of thrombospondins, is one of the components of the articular cartilage extracellular matrix. An increased level of COMP in the synovial fluid and serum contributes to remodeling and restoration of cartilage [48].

PATHOGENETIC RELATIONSHIP BETWEEN CHRONIC PERIODONTITIS AND PSORIATIC ARTHRITIS

A number of authors consider joint damage in PsA in the context of periodontitis to be a complex interaction of immunological and inflammatory phenomena involving bacterial infection [12, 35]. Psoriasis can occur in genetically predisposed people with an abnormal innate and / or adaptive immune response to components of oral microbiota in chronic periodontitis (such as *Porphyromonas gingivalis*), which can cause various psoriasis manifestations [49]. In addition, a certain composition of the microbiota in the body folds in patients with inverse psoriasis may also play a role in triggering local inflammation in the periodontium [50].

A closer look indicates an association between the immunopathogenesis of diseases: hypersecretion of proinflammatory cytokines produced by activated T lymphocytes and other mononuclear cells (monocytes, macrophages); increased proliferative activity of fibroblasts in the synovial membrane and periodontium, their ability to secrete platelet growth factors; increased collagenolytic activity of MMR and increased tissue proteolysis, disruptions in humoral immunity (autoantibodies to nuclear antigens, cytokeratins); pathological remodeling of bone tissue [49, 51].

The interaction between innate and adaptive immunity in chronic periodontitis, which maintains chronic inflammation, leads to dysregulation and overproduction of various proinflammatory cytokines, such as TNF, IL-17, IL-1β, IL-22, and IL-23 [49, 52]. Activation of IL-23R receptors induces phosphorylation of Jak2 and Tyk2 protein kinases, which mediate activation of STAT3 and RORγ transcription factors, thereby contributing to Th17 cell differentiation. The resulting Th17 cells produce IL-17, a powerful proinflammatory cytokine [52].

IL-17 and TNF induce synthesis of MMP in the synovial fluid and cartilage, which mediates loss of collagen structures and erosion-like changes in the cartilage surface. It also stimulates production of IL-1 and TNF by macrophages, induces secretion of IL-6 and IL-8 by synovial fibroblasts, and promotes recruitment of neutrophils and other immune cells into the synovial membrane [53]. IL-17 stimulates synthesis of RANKL in osteoblasts and its ligation with RANK in osteoclast precursors, contributing to the differentiation and activation of osteoclasts [30]. Mature osteoclasts, being bone resorbing cells, secrete lysosomal enzymes, thereby leading to destruction of the bone matrix. [53]. Therefore, Th17-mediated induction of osteoclastogenesis plays an important role in the pathogenesis of bone and cartilage destruction in PsA [49].

In addition, lymphocytic infiltration in PsA is localized not only on the skin or joints, but also in isolated blood cells, thereby confirming the presence of a systemic inflammatory response in such patients [55].

The production of TNF by macrophages promotes activation and recruitment of immune cells to the synovial membrane and synovial hyperplasia and induces secretion of MMR involved in cartilage degradation. Besides, together with other angiogenic factors, it promotes formation of new blood vessels [56]. TNF is responsible for regulation of genes responsible for synthesis of IL-1, interferon γ, granulocyte – macrophage colony stimulating factor (GM-CSF), IL-6, proinflammatory chemokine IL-8, and other inflammatory mediators [53]. It is assumed that angiogenesis and development of oxidative stress due to an increase in ROS production are apparently present in the early phase of diseases and can be considered as important processes linking periodontitis and PsA [50].

Therefore, PsA and periodontitis are chronic inflammatory diseases with similar pathophysiological mechanisms: overproduction of proinflammatory cytokines in target tissues (skin, joints, gingival microenvironment) and development of an excessive systemic immune response to the microbiota inhabiting the surface of the epithelium and periodontium [52]. Impaired interaction of innate and adaptive immunity present in chronic periodontitis leads to systemic overexpression of proinflammatory cytokines (TNF, IL-17, IL-1β, IL-22, and IL-23) and differentiation of Th0 into Th17, which play an important role in mutual aggravation of these pathologies. In addition, among the common pathophysiological mechanisms in the development of these pathologies, pathological bone

remodeling and bone resorption can be distinguished [49, 54].

CONCLUSION

Based on the studies listed above, it is possible to confirm the presence of a pathogenetic relationship between chronic periodontitis and PsA. Significance of the prevalence of the hyperergic systemic inflammatory response in both cases and the unity of the cytokine profile and bone resorption processes also confirm this statement.

A key factor in the formation and progression of PsA against the background of periodontitis is a disturbance in the interaction of innate and adaptive immunities, leading to overexpression of proinflammatory cytokines (TNF, IL-17, IL-1β, IL-22, and IL-23) and differentiation of Th0 into Th17. It further leads to increased synthesis of IL-17, which plays a significant role in the initiation of immune responses in PsA. IL-17 stimulates production of IL-1 and TNF by macrophages, secretion of neutrophil-attracting IL-6 and IL-8 by synovial fibroblasts, and induces synthesis of RANKL by them and osteoblasts, thus mediating secretion of osteoclastogenic factors (TNF and IL-1ß) and pathological bone remodeling and bone resorption (Figure) [31, 33, 45–47]. The statistically confirmed correlation between the development of periodontal destruction and the severity of PsA proves the commonality of immunological and inflammatory processes in the development and mutual aggravation of the studied comorbidity [6, 7, 9, 14].

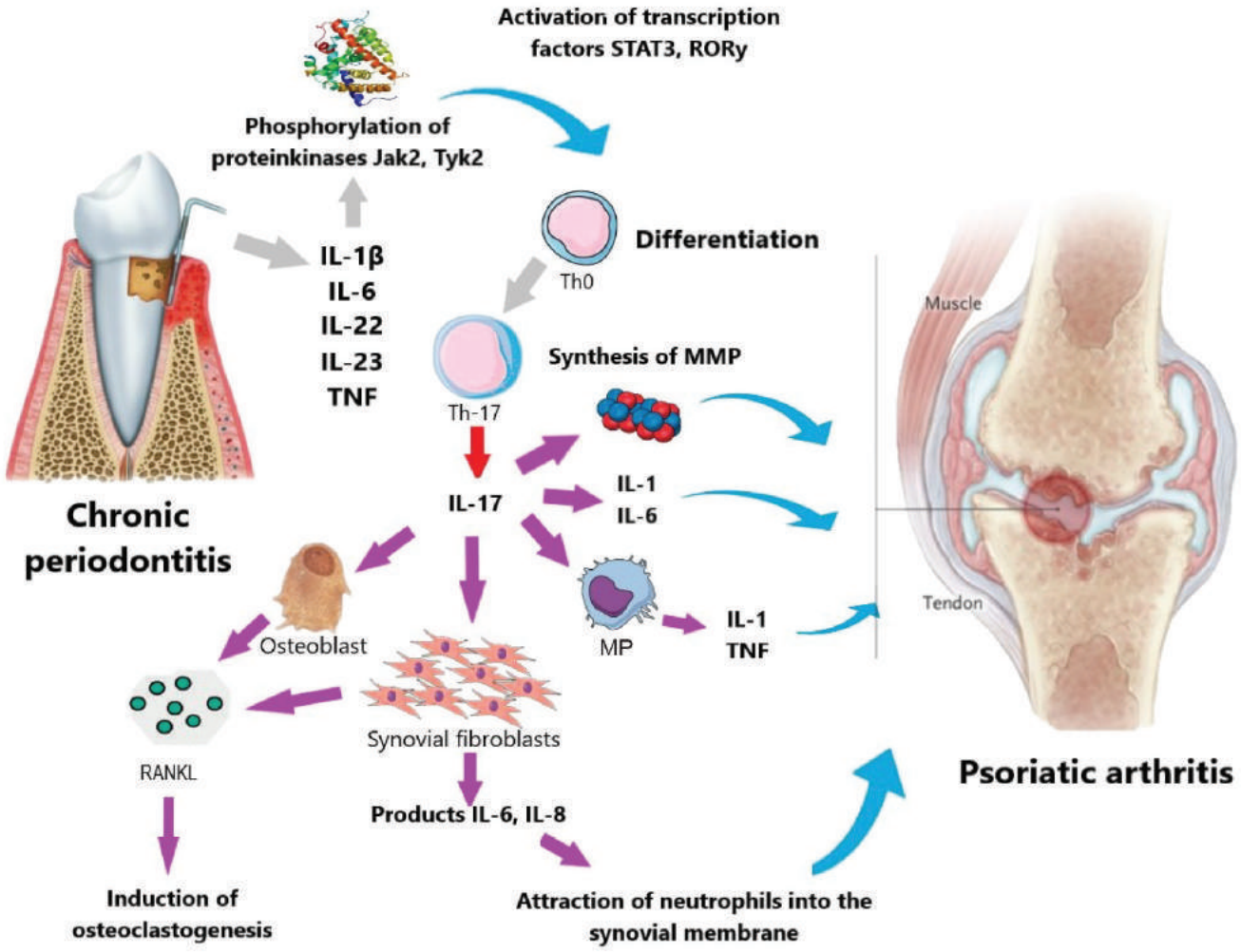

Figure. Pathogenetic relationship of chronic generalized periodontitis and psoriatic arthritis [31, 33, 45–47]. IL-1β – interleukin-1β; IL-1 – interleukin-1; IL-6 – interleukin-6; IL-8 – interleukin-8; IL-22 – interleukin-22; IL-23 – interleukin-23; TNF – tumor necrosis factor; Th0 – undifferentiated T helper cell; Th17 – T helper 17 cell; IL-17 – interleukin-17; MMP – matrix metalloproteinase; MP – macrophage; RANKL – receptor activator of nuclear factor kappa-β

Therefore, the established pathogenetic relationship makes it possible to develop new methods of early diagnosis, treatment, and prophylaxis for early detection and prevention of the progression of these pathologies. Close collaboration between dentists and rheumatologists for prescribing complex therapy for these diseases, as well as screening immunological examinations of people (especially working-age population) with chronic periodontitis will allow for early detection and prediction of the development of psoriatic arthritis.

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Received 04.02.2022;
approved after peer review 16.05.2022;
accepted 09.06.2022