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Identity of the pathogenesis, genetic and epigenetic mechanisms of osteoarthritis and rheumatoid arthritis development

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ABSTRACT

Osteoarthritis is characterized by heterogeneity of clinical manifestations and, in some cases, a severe progressive course. In this regard, it is important to identify new molecular targets for the treatment of the disease. To determine the role of autoimmune processes, general genetic and epigenetic changes in osteoarthritis and rheumatoid arthritis, as well as to identify osteoarthritis-specific ribonucleic acids (microRNAs), potential targets for targeted therapy, information was searched using scientific platforms PubMed, Scopus, ResearchGate, RSCI over the past 10 years. Although the pathogenesis of rheumatoid arthritis and osteoarthritis differs, evidence has been obtained that identical pathological immune reactions are involved in the mechanism of osteoarthritis and disruption of the expression of 26 identical genes with identical changes in the levels of 13 of them. Changes in the expression of the same microRNAs (miR-140, miR-149, miR-25, miR-146a, miR-16, miR-23b) were detected in osteoarthritis and rheumatoid arthritis. Molecular genetic studies make it possible to find new markers of pathological immune reactions in osteoarthritis, which can be used to treat the disease and prevent its rapid progression, as well as to design targeted therapy using gene expression products as targets. MicroRNAs associated with osteoarthritis and rheumatoid arthritis and involved in the pathogenesis of both diseases may become promising targets for targeted therapy of osteoarthritis and rheumatoid arthritis.

Keywords: inflammation; immune reactions; microRNA; osteoarthritis; rheumatoid arthritis.

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Идентичность патогенеза, генетических и эпигенетических механизмов развития остеоартрита и ревматоидного артрита

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АННОТАЦИЯ

Остеоартрит характеризуется гетерогенностью клинических проявлений и, в ряде случаев, тяжёлым прогрессирующим течением. В связи с этим актуально выявление новых молекулярных мишеней для лечения заболевания. Для определения роли аутоиммунных процессов, общих генетических и эпигенетических изменений при остеоартрите и ревматоидном артрите, а также для выявления специфических для остеоартрита рибонуклеиновых кислот (микроРНК), потенциальных мишеней для таргетной терапии, проведён поиск информации с использованием научных платформ PubMed, Scopus, ResearchGate, RSCI за последние 10 лет. Хотя патогенез ревматоидного артрита и остеоартрита различаются, получены данные о вовлечении в механизм остеоартрита идентичных патологических иммунных реакций и нарушении экспрессии 26 идентичных генов с идентичным изменением уровней 13 из них. Выявлены изменения экспрессии одних и тех же микроРНК (miR-140, miR-149, miR-25, miR-146a, miR-16, miR-23b) при остеоартрите и ревматоидном артрите. Молекулярно-генетические исследования позволяют находить новые маркёры патологических иммунных реакций при остеоартрите, которые можно использовать для лечения болезни и предотвращения её быстрого прогрессирования, а также для проектирования таргетной терапии с использованием в качестве мишеней продуктов экспрессии генов. Ассоциированные с остеоартритом и ревматоидным артритом микроРНК, вовлечённые в патогенез обоих заболеваний, могут стать перспективными мишенями для таргетной терапии остеоартрита и ревматоидного артрита.

Ключевые слова: воспаление; иммунные реакции; микроРНК; остеоартрит; ревматоидный артрит.

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INTRODUCTION

Osteoarthritis is the most common type of arthritis and is characterized by irreversible cartilage loss with synovitis development [1] and bone remodeling [2]. The incidence of osteoarthritis is 10.7% in people aged >20 years, 29.3% in those aged >50 years [3], and 40% in those aged >70 years, indicating the disease association with age [4]. Severe cases of osteoarthritis account for 2% in high-income countries and 17% in middle- and low-income countries [5]. Osteoarthritis of the knee and hip joints ranks eleventh among the leading factors of disability worldwide [5].

Currently, despite its slow progression, osteoarthritis remains an unsolved problem because standard treatment methods do not stop the progression of the disease, which often leads to the need for joint replacement at a late stage [6]. An epidemiological analysis conducted in Russia revealed that in 2019 alone, 147,061 primary knee and hip replacement surgeries were performed, and complications in the form of implant-associated infection were noted in 2.91% of cases [6]. This indicates the need for new approaches in the diagnosis and treatment of osteoarthritis, which can avoid severe complications and the need for arthroplasty.

It is crucial to focus on the role of immune responses in the disease development and progression because inflammation is considered a key pathophysiological process in osteoarthritis, and irreversible cartilage loss is caused by a developing inflammation [1].

With aging and osteoarthritis, there is decrease in the expression of Kruppel-like transcription factors KLF2 and KLF4, which control inflammatory responses. KLF2 and KLF4 provide protection against uncontrolled degradation and inflammation by activating genes of the main components of cartilage and the extracellular matrix, such as *SOX9* and *COL2A1*, and by suppressing the catabolic and inflammatory genes *MMP13, iNOS*, and *IL6* [7].

Impaired expression of transcription factors during aging [7], which leads to an age-associated increase in the risk of osteoarthritis [3, 4], is caused by epigenetic changes in the body, including histone modification with chromatin structure changes, deoxyribonucleic acid (DNA) methylation, and interference of ribonucleic acid (RNA) with noncoding RNA [8].

Drivers of epigenetic factors [9] and sources of noncoding RNA [10] are transposons. These are specific DNA loci characterized by movement to new loci of the genome using the cut-and-insert mechanism (DNA transposons) or "copy and paste" (retroelements) [10]. Hyperactivation of retroelements is considered a crucial cause of aging [11], because with age occurs an imbalance in the immune system with the development of autoimmune aseptic inflammation and hyperproduction of interferon in response to the expression products of retroelements [12].

With aging, the inhibitory effect of histone Sirt6 on deacetylase retroelements is weakened, which leads to their pathological activation [13]. Moreover, low Sirt6 levels are determined in synovial inflammation against osteoarthritis, which is accompanied by polarization of M1 macrophages with the release of pro-inflammatory cytokines into them. Increased Sirt6 expression improves the condition of the cartilage and stops the progression of osteoarthritis [1].

This indicates the presence of common mechanisms of aging and osteoarthritis, when regular epigenetic changes (weakening of Sirt6 action) with age lead to pathological reactions of specific cells (macrophages in the joints), causing pathology associated with aging and osteoarthritis.

Macrophages, which play a role in inflammatory reactions, are involved in the pathogenesis of osteoarthritis and rheumatoid arthritis (RA). M1 macrophages are activated during inflammatory processes under the influence of interferon γ and toll-like receptors. Following activation, they secrete a large number of pro-inflammatory cytokines, namely, interleukin (IL)-1β, IL-6, and IL-12, tumor necrosis factor α (TNF-α), reactive oxygen species, and inducible nitric oxide synthase [14].

Obtained data indicate the relationship between pathologically activated retroelements during aging and immune reactions causing osteoarthritis. The role of retroelements in the pathogenesis of autoimmune reactions has been described [15]; thus, an assumption on the significance of these reactions in the development of osteoarthritis can be deduced.

The study of the common epigenetic mechanisms of osteoarthritis and RA may become the basis for a new understanding of the pathogenesis of osteoarthritis with the identification of the most significant ways of preventing and treating the disease. Retroelements induce epigenetic regulation; hence, data on their participation in the mechanisms of osteoarthritis development are beneficial for further development of targeted therapy for the disease.

INTERFERON INVOLVEMENT IN THE DEVELOPMENT OF OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

Interferon γ affects the mechanisms of osteoarthritis in various ways, including by activating protein kinase R, which is involved in inflammation [2]. In experiments, the treatment of articular cartilage with interferon γ caused its degradation phenotype mediated by protein kinase R with increased expression of key inflammatory mediators (tumor necrosis factor (TNF)α, IL-6), matrix-degrading enzymes (MMP-13), and transcription factors protein kinase R and STAT1 [2]. In the blood plasma and synovial fluid of patients with osteoarthritis, a significant change in the level of IP-10 (interferon-γ inducible protein) was determined compared to those of healthy controls [16].

TIM3 gene (T-cell immunoglobulin and mucin domain-containing protein 3) polymorphisms are associated with the risk of osteoarthritis, which may be due to increased

expression of interferon γ by $CD4^+$ T lymphocytes, as the TIM3 protein involved in the immune response is expressed in response to interferon γ [17]. Increased *STING* gene expression has been found in tissues of individuals and mice with osteoarthritis. The protein product of the *STING* gene is an interferon stimulator and promotes MMP13 and aggrecanase-2 (ADAMTS5) production, suppresses aggrecan and collagen II expression, and enhances apoptosis and aging of chondrocytes, owing to activation of the NF-κB signaling cascade [18].

Similar to osteoarthritis, the role of interferon has been determined in the pathogenesis of RA, wherein interferon is involved in the JAK/STAT signaling pathways [19]. A meta-analysis of gene expression conducted in 2014 revealed the differential expression of 371 genes in individuals with RA, systemic lupus erythematosus, and systemic scleroderma compared with healthy controls. Among the identified genes, the most reliable difference was determined in the interferon response genes [20]. In this regard, the efficacy of some JAK inhibitors (i.e., filgotinib, baricitinib, and upadacitinib) for the treatment of RA is due to the suppression of interferon [21], which induces pro-inflammatory $HLA\text{-}DR^+CD90^+$ synovial fibroblasts [22]. Moreover, the role of interferon III (λ) in the pathogenesis of RA has been described, which promotes the expression of toll-like receptors and production of pro-inflammatory cytokines [23].

A meta-analysis conducted in 2022 showed an association between *IFN-γ* +874 T/A polymorphism with RA and systemic lupus erythematosus in Asian and Arab populations [24]. $CD4^+$ T lymphocytes are critical in the pathogenesis of RA, and it has been proven that interferon-γ production in these cells is significantly increased at an early stage of RA and is associated with a worse prognosis [25].

Interferon involvement in the pathogenesis of RA became the basis for the development of treatment methods for the disease with an effect on interferon. Thus, menthone, which inhibits the transmission of type I interferon signals, promotes Tyk2 ubiquitination and suppresses local inflammatory processes in RA [26]. Interferon production in patients with RA is reduced by baminercept (a fusion protein of lymphotoxin-β with an immunoglobulin receptor), which blocks lymphotoxin-αβ/LIGHT [27].

The nature of changes in interferon I and II concentrations can be used to determine sensitivity to anti-TNF therapy in RA, which is promising for use in clinical practice [28]. Furthermore, interferon activation plays a role in the pathogenesis of osteoarthritis [2, 17, 18]. Therefore, menthone, baminercept, and anti-TNF therapy may be used in the treatment of severe cases of osteoarthritis with progressive destruction of articular cartilage to prevent irreversible changes requiring joint replacement.

Owing to the presence of common pathogenetic mechanisms of osteoarthritis and RA, the influence of identical immune mechanisms of osteoarthritis should be considered, which could form basis for new methods of therapy.

ROLE OF AUTOIMMUNE PROCESSES IN THE DEVELOPMENT OF OSTEOARTHRITIS

A change in interferon activity plays a role in the pathogenesis of osteoarthritis and RA, and osteoarthritis is characterized by the identity of etiopathogenesis with autoimmune diseases in relation to damage to joint structures. The concept of osteoarthritis as a degenerative process has been replaced by data on the primary role of immune disorders at the level of the synovial membrane, which (similar to changes in RA) hypertrophies with the recruitment of macrophages and lymphocytes, as well as with angiogenesis and proliferation of fibroblasts. In the osteochondral unit, chondrocyte proliferation in the deep zones occurs, as well as loss of extracellular matrix and chondrocytes in the superficial zone, vascularization and ingrowth of neurons through the boundary between calcified and noncalcified cartilage, and remodeling of the subchondral bone (with sclerosis, cysts, and osteophytes) [29].

In 2014, a genome-wide gene expression profile analysis revealed the role of the oxidative phosphorylation genes *ATP6, SCO2, CYTB, DN1, COX1,* and *ANT1* in the etiopathogenesis of osteoarthritis and RA. It was shown that biological pathways associated with the functioning of the immune system, apoptosis, and inflammation are involved in osteoarthritis and RA development [30]. Additionally, cartilage destruction due to inflammation has been shown to be central to the pathogenesis of osteoarthritis and is mediated by matrix-degrading enzymes [31].

Osteoarthritis shares several pathogenetic features with RA, including synovial activation with the release of pro-inflammatory cytokines into the synovial fluid. Preterm senescence and dedifferentiation of chondrocytes occurs in osteoarthritis and RA, which may explain the homing of the pannus to the cartilage in RA [32].

Although osteoarthritis is not considered an autoimmune pathology, there is evidence of a role for immunopathological processes in osteoarthritis, identical to RA, systemic scleroderma, systemic lupus erythematosus, and Sjögren's syndrome. In these diseases and in osteoarthritis, abnormal expression of galectins (a family of glycan-binding proteins that regulate innate and adaptive immune response and participate in cell invasion, migration, adhesion, and proliferation) is determined [33].

Autoantibodies to homocysteinylated alpha 1 antitrypsin (Hcy-A1AT) were detected in the blood serum of 15% of patients with osteoarthritis; these antibodies are specific for patients with seropositive (87.1%) and seronegative (75.7%) RA. In healthy individuals, these autoantibodies were not detected [34].

In 2023, a multiomic analysis revealed a pleiotropic effect of the expression of the gene of the major histocompatibility complex of the immune system *HLA-DPB2* in the development of osteoarthritis of the knee joint, mediated by changes

in the methylation of this gene [35]. In patients with RA, a correlation was found between disease severity and probability of the lymphomyeloid pathotype with *HLA-DPB2* expression [36].

Vitamin D_3 reduces the activity of Th1 cells and increases immunotolerance. Vitamin D_3 deficiency leads to an imbalance in the interactions between Th1/Th17 and Th2 and Th17/Th reg and can be the cause of autoimmune processes (including RA) and osteoarthritis. This indicates the presence of common pathogenetic links between osteoarthritis and RA and the possibility of using RA treatment methods (replenishment of vitamin D_3 deficiency) in treating osteoarthritis [37].

The role of increased IL-17 expression in autoimmune diseases and osteoarthritis has been noted, which may be considered as a target for the treatment of these diseases [38]. The anti-inflammatory molecule progranulin (an endogenous TNFα antagonist due to competitive binding to TNFR) slows down osteoarthritis progression; however, in RA patients, it is detected in elevated concentrations in the blood serum compared with healthy individuals. This indicates that although autoimmune processes may play a role in the pathogenesis of osteoarthritis, the mechanism of its development differs from that of RA [39].

Studies of single-cell communication and signaling pathways have shown that in osteoarthritis, collagen and laminin pathways are predominant, whereas in RA, cadherin 5, neurotrophin, and epidermal growth factor pathways are prevalent [40]. Genetic changes in these processes can be considered in determining the specific pathological immune mechanisms of osteoarthritis development.

COMPARISON OF GENE ASSOCIATION WITH IMMUNE REACTIONS IN OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS

Modern genetic studies allow determining the role of allelic variants of genes (polymorphisms) in the development of the disease and identifying the features of expression of specific genes that play a role in local pathogenetic processes in osteoarthritis. Synovial macrophages are crucial in the pathogenesis of osteoarthritis. The genes *C5AR1, FCGR2B, IL1B, IL6, IL10,* and *TYROBP* are associated with joint infiltration in patients with osteoarthritis [41].

A study on potential risk genes for cartilage infiltration by immune cells in osteoarthritis determined a significant influence of the genes *GPR137B, HLA-DMB,* and *PTGS1* [42]. Notably, among the immune system genes associated with osteoarthritis, an association with RA was determined for allelic variants of the *GPR137B* gene [43]. Moreover, *HLA-DMB* was found to be a prognostic factor for RA [44]. An association was determined between RA and the polymorphic variants of *C5AR1* [45], *IL1B* [46], and *IL10* [47] genes.

In 2023, an integrated bioinformatics analysis of the accumulated results on the association of allelic variants of various genes with osteoarthritis was published. Eight immune system-related genes associated with osteoarthritis and metabolic syndrome were identified (i.e., *FZD7, IRAK3, KDELR3, PHC2, RHOB, RNF170, SOX13,* and *ZKSAN4*) [48]. In RA patients, lower *IRAK3* expression levels by $CD14^+$ monocytes were noted compared with controls [49]. In RA, significantly higher levels of antibodies to the transcription factor SOX13 were observed [50]. Evidence was obtained for the role of the small vesicular GTPase RHOB in pathogenic autoantibody production and RA progression [51].

In a 2023 study, differential expression of 181 genes was detected in macrophages, mast cells, B lymphocytes, and CD4 T lymphocytes of the synovial membrane of patients with osteoarthritis compared with healthy controls. Four of these genes were specific to the immune system (i.e., *DUSP1, JUN, MYC,* and *NFKBIA*) and may be used as therapeutic targets for osteoarthritis [52].

In a 2023 study, five immune system genes were found to be characterized by differential expression (i.e., *EDNRB, IL1R1, PGF, SCD1,* and *TNFSF11*) in joints affected by osteoarthritis [53]. In RA, decreased *DUSP1* expression under the influence of miR-101 contributed to cartilage degradation [54]. Additionally, changes in *EDNRB* expression in RA are directly involved in pain perception [55]. Allelic variants rs3917318, rs956730, and rs1049057 of the *IL1R* gene are associated with RA risk [56]. Increased *PGF* expression was determined in mouse models with RA compared with normal animals [57].

Several studies have identified the genes associated with immune infiltration and involved in the pathogenesis of osteoarthritis, namely, *KLF9, EPYC* [31], *GABARAPL1, TNFAIP3, ARNTL, JUN* [58], *GREM1, NRP1, VEGFA, FYN, IL6R* [59], *CDKN1A, DDIT3, MAP1LC3B, MYC* (involved in immune system functioning) [60], *LPCAT3,* and *PGD* (involved in ferroptosis) [61]. In the synovial tissue of patients with RA, miR-218-5p expression was higher than the norm, which contributes to *KLF9* inhibition, affecting apoptosis and autophagy [62]. In RA, the differential expression of *GABARAPL1*, which regulates autophagy, was determined [63].

In 2022, a meta-analysis showed that rs2230926 and rs5029937 of the *TNFAIP3* gene are associated with the risk of developing RA [64]. In RA patients, elevated TNFα levels cause increased *ARNTL* expression in fibroblasts of affected joints [65]. Additionally, increased *GREM1* expression (encoding a bone morphogenetic protein antagonist) was found in the joints of patients with RA, which promotes proliferation, survival, migration, and invasion of fibroblast-like synoviocytes [66]. In RA, *VEGFA* contributes to the regulation of migration, invasion, and angiogenesis in the miR-200a-3p/KLF6/VEGFA pathway [67].

Furthermore, a significant difference in *FYN* gene expression was determined in patients with RA compared with controls [68]. An association was noted between rs2228145 polymorphism of the *IL6R* gene and RA development [69].

Bioinformatic analysis methods showed changes in the expression of the *CDKN1A* gene in RA, which is involved in autophagy [63], and *MYC* and *MAP1LC3B* genes, which show immunopathological significance [70]. Synovial mast cells regulate inflammation in RA by *PGD* hyperproduction [71].

The *BCL6, EPHA3, MCL1, PIM1,* and *SLC16A7* genes were found to be associated with aging and osteoarthritis. An analysis of immune infiltration showed that these genes correlate significantly with specific immune cells and participate in immune signaling pathways [72]. In RA patients, a change was noted in the expression of *BCL6* in the affected tissue by $CD4^+$ T lymphocytes [73].

In RA, nuclear factor-κB and phosphatidylinositol 3-kinase/Akt-1 signaling pathways are activated in joints, which promotes the expression of genes that cause inflammation and cartilage damage and anti-apoptotic molecules such as MCL1 [74]. Increased *PIM1* expression has been detected in the peripheral mononuclear cells ($CD4^+$ T cells) and synovial T lymphocytes of RA patients [75].

In 2021, an extensive cytokine analysis of synovial fluid of patients with osteoarthritis showed high GITRL, CEACAM-1, FSH, EG-VEGF, FGF-4, PIGF, Cystatin EM, and NT-4 protein levels. Bioinformatic analysis demonstrated that most of these proteins are involved in altering leukocyte functions, with differentially expressed proteins IL-18, CXCL1, CTLA4, MIP-3b, CD40, MMP-1, THBS1, CCL11, PAI-1, BAFF, aggrecan, angiogenin, and follistatin located at the center of protein–protein networks [76].

Moreover, allelic variants of the immune system genes *CTLA4-rs231775, CTLA4-rs5742909* (cytotoxic T-lymphocyte-associated protein 4), and *CD28-rs1980422* are associated with a predisposition to RA [77]. In osteoarthritis, changes in gene expression associated with immune reactions in the affected joints were determined, which are also associated with RA. This indicates certain pathogenetic links between osteoarthritis and RA and the role of autoimmune processes in the pathogenesis of osteoarthritis and potential use of drugs for targeted therapy of RA in the treatment of severe progressive forms of osteoarthritis.

However, a differentiated approach and the use of only those molecules as targets, whose nature of association with RA is similar, are required. Table 1 presents 26 genes associated with immune reactions in osteoarthritis and RA. Thirteen of these genes showed different patterns of association, which were related to the pathogenesis features of each disease.

Thus, in osteoarthritis, a decrease was found in the expression of the anti-apoptotic genes *BCL6, MCL1,* and *PIM1* [72], whereas in RA, an increase in their levels was established [73–75]. This is associated with the pathological role of the proliferation of fibroblast-like and immune cells for pannus formation in RA [78], whereas in osteoarthritis, a decrease in chondrocyte proliferation contributes to progression of the disease due to the loss of cartilage tissue [72]. Thus, identical strategies for targeted therapy of osteoarthritis and RA can be applied to 13 genes, the changes in which coincide for both diseases (Table 1).

ROLE OF MICRORNAS IN THE DEVELOPMENT OF OSTEOARTHRITIS AND AUTOIMMUNE PATHOLOGY

Differences in the expression of specific microRNAs were determined between patients with osteoarthritis and healthy people and between different samples of cartilage of the same patient with osteoarthritis. Thus, in a study of 130 articular cartilage samples from 1 patient, differential expression of 142 microRNAs was determined between the affected and intact cartilage. These differences may indicate compensatory epigenetic processes aimed at restoring damaged cells and the participation of these microRNAs in apoptosis and inflammation [79].

In 2017, an integrative bioinformatics analysis of osteoarthritis-associated microRNA expression patterns revealed a significant increase in miR-23b-3p, miR-27b-3p, miR-211-5p, and miR-16-5p levels and a decrease in miR-25-3p and miR-149-5p levels [80].

Notably, miR-23b is associated with inflammation and autoimmune diseases. Microarray analysis of microRNA in fibroblast-like synoviocytes showed increased miR-23b expression in RA patients, which was confirmed by quantitative polymerase chain reaction. The level of this microRNA in blood plasma was higher in RA patients with anorexia and decreased during treatment; thus, the use of miR-23b as a biomarker of RA activity was proposed.

The targets of miR-23b are the genes *Marcksl-1* (encodes a protein that affects adhesive junctions and cytoskeleton regulation) and *NF-κB* (a transcription factor that regulates immune response gene expression) and the messenger RNA of genes encoding endothelial cell inflammatory factors [78]. Furthermore, increased miR-16-5p expression was detected in plasma samples from RA patients compared with controls, indicating the role of this microRNA in disease initiation and progression [81]. MiR-16-5p induces a regulatory effect on the expression of genes of matrix metalloproteinases *MMP8* and *MMP1* and protein kinase ERK1/2 [82].

In peripheral mononuclear cells of RA patients, decreased miR-25-3p expression was noted [83], which regulates the expression of *VEGFR2, ZO-1,* and *Claudin5* in endothelial cells owing to the target effect on KLF2 and KLF4, thus promoting angiogenesis [84]. MiR-149-5p and miR-let-7c-5p suppress the transcription of TNFα, IL-1β, and IL-6 in patients with osteoarthritis and RA compared with controls. The anti-inflammatory drugs indomethacin, celecoxib, and dexamethasone and ibuprofen and methotrexate suppressed the synthesis of pro-inflammatory cytokines by increasing miR-149-5p and miR-let-7c-5p expression [85].

In 2023, a meta-analysis reported that most studies on osteoarthritis used articular cartilage, wherein activation of miR-146a-5p and miR-34a-5p and decreased expression of miR-127-5p and miR-140-5p were detected most frequently [86]. Moreover, a meta-analysis conducted in 2018 revealed

Table 1. Identical genes influencing immune responses and associated with osteoarthritis and rheumatoid arthritis

Gene name	Gene protein product and function	Role in osteoarthritis [author]	Role in osteoarthritis [author]
ARNTL	AHR nuclear translocator-like protein activates genes whose expression is regulated by circadian gene products	Low expression in osteoarthritis [58]	Increased expression in fibroblasts of affected joints [65]
BCL6	A POZ/BTB zinc finger protein family member and enhances chondrocyte proliferation	Decreased expression in NK, mast, and dendritic cells [72]	Differentially increased expression [73]
C5AR1	C5a anaphylotoxin receptor expressed by immune cells and a chemical attractant and inflammation mediator	Increased expression in affected joints correlated with macrophage infiltration [41]	Increased levels promote inflammatory processes [45]
CDKN1A	CDKN1A Cyclin-dependent kinase inhibitor 1A, regulates DNA replication in the S-phase and is involved in the repair of damaged DNA and affects autophagy	Reduced expression [60]	Differential expression [63]
CTLA4	Cellular receptor for immunoglobulins	Increased expression [76]	Association with the rs231775 allele [77]
DUSP1	Inhibits proliferation and inflammatory response and protects cartilage by suppressing MMP-13 and activating MAPK	Low expression in the immune infiltration of the joint [52]	Low expression promotes cartilage degradation [54]
EDNRB	Endothelin receptor type B, coupled to the G protein, which activates the phosphatidylinositol/calcium system	Increased expression is associated with immune cell infiltration [53]	Involved in pain perception [55]
FYN	Proto-oncogene, a membrane-bound tyrosine kinase that controls cell growth	Negative association with M1 macrophage joint infiltration [59]	Increased expression [56]
GABARAPL1	GABA receptor type A-related protein and regulates autophagy	Low expression in osteoarthritis [58]	Differential expression in RA [63]
GPR137B	G protein-coupled receptor 137B and regulates TORC1 signaling and GTPase activity	Increased expression [42]	Association of replication signals in the vicinity of the gene [43]
GREM1	Bone morphogenetic protein antagonist	Associated with immune cell joint infiltration [59]	Promotes proliferation, survival, migration, and invasion of fibroblast-like synoviocytes [66]
HLA-DMB	Major histocompatibility complex class II proteins, DM beta	Increased expression [42]	Associated with severe disease [44]
KLF9	Transcription factor that inhibits mRNA expression when bound to the GC box and activates when bound to GC box tandem repeats	Increased expression is associated with immune cell infiltration [31]	Low expression suppresses apoptosis and autophagy [62]
IL1B	Pro-inflammatory cytokine produced by immune cells	Increased expression in affected joints and correlated with macrophage infiltration [41]	Associated with the risk of RA development [46]
IL6R	Interleukin-6 receptor, pro-inflammatory signaling	Negative association with joint infiltration by M1 macrophages [59]	Associated with the risk of RA development [69]
IL10	Anti-inflammatory cytokine produced by immune cells	Increased expression in affected joints and correlated with macrophage infiltration [41]	Increased levels are associated with high seropositivity for rheumatoid factor and antibodies to cyclic citrullinated peptide [47]
IRAK3	Interleukin-1 receptor-associated kinase	Expressed by immune cells [48]	Low expression by $CD14^+$ monocytes [49]
MAP1LC3B	Subunit of MAP1A and MAP1B proteins associated with neuronal microtubules and involved in autophagy	Decreased expression [60]	Promotes immunopathological processes [70]
MCL1	MCL1 apoptosis regulator and required for survival of fibroblasts, macrophages, and lymphocytes	Decreased expression in NK and mast cells [72]	Increased expression [74]

Table 1 (continued).

MYC	Transcription factor and regulates apoptosis and cellular transformation	Decreased expression [60]	Promotes immunopathological processes [70]
PGF	Placental growth factor, a member of the VEGF subfamily, and promotes angiogenesis	Increased expression is associated with immune cell infiltration [53]	Increased expression causes pathological angiogenesis in the joint [57]
PIM1	Key regulator of apoptosis and stimulates differentiation and proliferation	Decreased expression in mast cells [72]	Increased expression [75]
RHOB	Small vesicular GTPase RHOB and activates IL-1β, LPS, and TNFα	Increased expression in osteoarthritis promotes inflammation [48]	Induces autoantibody synthesis [51]
SOX13	Autoimmune antigen and modulates inflammatory response	Increased expression in osteoarthritis promotes inflammation [48]	Induces autoantibody synthesis [50]
TNFAIP3	TNF-induced zinc finger protein and edits ubiquitin and is involved in immune and inflammatory responses	Low expression in osteoarthritis [58]	Associated with the risk of RA development [64]
VEGFA	Vascular endothelial growth factor A	Association with joint infiltration of CD8+-naive T cells [59]	Promotes migration and invasion of immune cells and angiogenesis [67]

Note: DNA, deoxyribonucleic acid; GABA, γ-aminobutyric acid; GTP, guanosine triphosphate; mRNA, matrix ribonucleic acid; VEGF, vascular endothelial growth factor; IL, interleukin; TNF, tumor necrosis factor.

Table 2. Changes in the expression of specific microRNAs in osteoarthritis and rheumatoid arthritis

MicroRNA	Changes in expression in osteoarthritis [author]	Changes in expression in rheumatoid arthritis [author]	Mechanism of action of microRNA [author]
miR-140	Decrease [86]	Decrease [90]	Inhibition of messenger RNA of the genes *Smad3, ADAMTS-5,* and *HDAC4* [90]
miR-146a	Increase [86]	Increase [87]	Regulation of *Fox-P3, IL-10,* and *TGF-β* expression [89]
miR-149	Decrease [80]	Decrease [85]	Suppressing *TNF- α, IL-1β,* and *IL-6* expression [85]
miR-16	Increase [80]	Increase [81]	Regulation of the expression of genes *MMP8, MMP1,* and *ERK1/2* [82]
miR-23b	Increase [80]	Increase [78]	Regulation of the expression of genes *Marcksl-1* and *NF-κB* [78]
miR-25	Decrease [80]	Decrease [83]	Suppressing *KLF2* и *KLF4* expression [84]

Note: RNA, ribonucleic acid.

that miR-146a levels are significantly higher in RA patients than in healthy controls [87]. A critical role of miR-146 in the development of juvenile idiopathic arthritis and autoimmune uveitis has been determined [88].

MiR-146a is a primary regulator of the immune response and is involved in RA pathogenesis. In experiments on mice, it was noted that exosomes obtained from mesenchymal stem cells and transduced by miR-146a increased *Fox-P3, IL-10,* and *TGF-β* expression [89]. Additionally, a significant decrease in miR-140 expression was detected in mice with RA compared with controls. The target of this microRNA is the matrix RNA of the *Smad3, ADAMTS-5,* and *HDAC4* genes. Further, miR-140 affects the histone deacetylase HDAC4, leading to hyperacetylation of the matrix protein with the regulation of cartilage development and homeostasis [90].

Thus, microRNAs, whose expression is significantly associated with the development of osteoarthritis, exhibit identical level changes in RA patients, which indicates the prospects for designing targeted therapy for these two diseases using six specific microRNAs as targets (Table 2).

Moreover, the results indicate possible coinciding epigenetic pathways in the development of RA and osteoarthritis. In contrast to the association with the expression of specific protein-coding genes, identical changes in the levels of which were determined only for half of the genes, the identical nature of the association of microRNAs may be due to the presence of multiple targets of these molecules (microRNAs regulate the expression of messenger RNAs of various genes).

In addition, microRNAs can cause the restructuring of stem cells into differentiated ones with cartilage tissue

regeneration. Their use in clinical medicine is promising. In rat experiments, cartilage regeneration was demonstrated by suppressing aging when miR-29b-5p microRNA was delivered to joints using synovial stem cells (which differentiated into chondrocytes) [91].

In osteoarthritis, a decrease in miR-17 expression in chondrocytes was determined. Moreover, miR-17 deficiency contributes to osteoarthritis progression. In mice experiments, miR-17 induction by growth differentiation factor or miR-17 administration prevented osteoarthritis by simultaneously affecting nitric oxide synthetase-2 , ADAMTS5, and metallopeptidase-3/13. MiR-17 was expressed at high levels in superficial and middle chondrocytes of normal articular cartilage and maintains a physiological balance between catabolism and anabolism, potentially by restricting HIF-1α signals [92].

CONCLUSION

Analysis of studies published in the databases PubMed, Scopus, ResearchGate, and RSCI in the past 10 years revealed that cartilage destruction in osteoarthritis is caused by inflammation, and immunopathological processes identical to RA are involved in the disease etiopathogenesis. These include hypertrophy of the synovial membrane with the recruitment of lymphocytes and macrophages, fibroblast proliferation, and angiogenesis.

Identical genes (i.e., *ATP6, SCO2, CYTB, DN1, COX1,* and *ANT1*) and biological pathways associated with apoptosis, inflammation, and immune system functioning have been found to be involved in the pathogenesis of osteoarthritis and RA. In osteoarthritis, as in autoimmune diseases, abnormal expression of galectin, autoantibodies to Hcy-A1AT, imbalance of interactions between Th1/Th17 and Th2, Th17/Th reg in vitamin D_3 deficiency, expression of IL-17 by T lymphocytes, and changes in methylation of the *HLA-DPB2* gene were determined. The listed immune disorders can be significant factors in the progression and aggravation of the severity of osteoarthritis; therefore, they are promising molecular targets for targeted therapy of the disease.

Genetic studies have shown an association of many genes with the development of pathological immune responses in osteoarthritis, with 26 of them also associated with RA and 13 had coinciding expression changes (*C5AR1, CTLA4, DUSP1, EDNRB, GPR137B, GREM1, HLA-DMB, IL1B, IL10, PGF, RHOB, SOX13,* and *VEGFA*) and 13 had opposite changes. This indicates the potential use of determining the levels of specific molecules in the synovial fluid for the differential diagnosis of these diseases. Additionally, 13 molecules with identical expression changes can be used as targets for targeted therapy of RA and osteoarthritis.

In this regard, microRNAs are the most promising. Analysis of scientific literature data showed that in RA and osteoarthritis, miR-140, miR-149, and miR-25 expressions decrease and miR-146a, miR-16, and miR-23b levels increase. This indicates the presence of common epigenetic mechanisms of these diseases and possibility of using identical methods of targeted therapy for osteoarthritis and RA.

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