Genij Ortopedii. 2022. Vol. 28, no. 2. P. 289-295.

Review article

https://doi.org/10.18019/1028-4427-2022-28-2-289-295

Immunogenetic aspects of osteoarthritis (literature review)

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Abstract

Inflammation plays critical role in the onset and progression of osteoarthritis (OA), a joint disease affecting more than 10 % of the world's population. Exporing immunological mechanisms of osteoarthritis is essential. The present paper is a literature review of immunogenetic aspects of the pathogenesis of the disease. The study is aimed at analysis and summary of information concerning the immunogenetics and molecular mechanisms of osteoarthritis. **Material and methods** The original literature search was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.org) with subsequent selection of articles, analysis and synthesis of information. **Results and discussion** Mutations in proinflammatory cytokine and receptor genes, metalloprotease genes, HLA genes and in the anti-inflammatory cytokine (*IL-4*) gene, polymorphisms in phospholipase and *IL-2* genes are more common for OA patients than for healthy subjects. Epigenetic regulation in OA include a decreased methylation of the promoters of proinflammatory cytokine and metalloprotease genes and a decreased methylation of NF-κB-sensitive *iNOS* enhancer sites. OA patients show an increased activity of histone acetylases in the *IL-6* promoter area. In contrast, the expression of anti-inflammatory cytokines is decreased due to the reduced activity of the SIRT1 deacetylase.

Keywords: osteoarthritis, inflammation, immunogenetics, pathogenesis, cytokines

For citation: Kazantsev Yu.A., Urazaeva A.T., Mustafin R.N., Deriabina S.S. Immunogenetic aspects of osteoarthritis (literature review). *Genij Ortopedii*, 2022, vol. 28, no 2, pp. 289-295. https://doi.org/10.18019/1028-4427-2022-28-2-289-295

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease affecting more than 10 % of people worldwide [1]. The Global Burden of Disease Study 2017 estimated the epidemiological patterns of hip osteoarthritis from 1990 to 2017 published in 2019 indicating the age-standardised point prevalence and annual incidence rate of OA in 2017 with an increase of 9.3 % and 8.2 % from 1990, respectively [2]. The figures indicate an increased relevance of research on the pathophysiology of OA. Evidence suggests that OA is associated with inflammation using criteria to distinguish pathological and physiological processes [3]. Immunological and immunogenetic status and associated molecular mechanisms is of a role for OA patients.

The study is aimed at analysis and summary of recent publications on immunogenetics and molecular mechanisms of osteoarthritis.

MATERIAL AND METHODS

The original literature search was conducted on key resources including Scientific Electronic Library (www.elibrary.ru) and the National Library of Medicine (www.pubmed.com). Inclusion criteria were publications on the immunogenetics of OA (genetic and epigenetic regulation) in English or in Russian, level of evidence I–III. The phrases used for the query were "osteoarthritis immunogenetis", "osteoarthritis epigenetics", "inflammation in osteoarthritis", "molecular mechanisms of osteoarthritis", "pathogenesis of osteoarthritis", "epidemiology of osteoarthritis", "risk factors for osteoarthritis". Most of the articles were published between 2010 and 2021 and the time range for the search was extended for particular cases.

RESULTS

1. Pathogenesis of osteoarthritis

OA is a group of diseases in which all of the components of the joint are affected with underlying mechanisms of impaired reparation, "mechanical stress" and chronic inflammation in the joint [4]. OA is characterized by cellular stress and degradation of the extracellular matrix that occur with macro- or microdamages activating abnormal adaptive repair responses including pro-inflammatory pathways of the immune system [1].

OA is 2 times more likely to affect women with the incidence increasing with age [1, 2, 5, 6]. There are some joint characteristics that distinguish normal age-related and pathological changes in OA. Normal aging

is associated with loss of articular cartilage thickness and a reduced content of glycosaminoglycans (GAGs), and local fibrillation is typical for OA related damage to the cartilage surface. The density of chondrocytes in cartilage tissue normally decreases with age, and on the contrary, clusters of chondrocytes are likely to form at the sites of tissue damage in OA. Normal age-related chondrocytes are characterized by decreased expression of genes including those responsible for the synthesis of the extracellular matrix, and higher activity of chondrocytes is accompanied by an increased intensity of both anabolic and catabolic processes in OA [3]. OA also causes inflammation and hypertrophy of the synovium which is not typical for normal aging of the joints [3] due to mononuclear cell infiltration and production of inflammatory cytokines which leads to synovitis in OA prior to visible cartilage degradation [7]. The histopathology of OA also includes increased collagen breakdown and rupture of the collagen network, rupture and fragmentation of the cartilage matrix and chondrocyte hypertrophy. OA is associated with increased cortical thickness and the remodeling with greater porosity and less cortical rigidity that is likely to increase onward. The subchondral cancellous bone decreases with changes in the architecture.

Osteophytes, bone marrow lesions, bone cysts accompanied by deformity and thinned structure are characteristic for the condition [8]. Taken together, these changes at the tissue level lead to such clinical manifestations as joint deformity, narrowing of the joint space, pronounced contractures with resultant pain, limited mobility and, finally, disability of patients [1, 2]. The inflammatory process plays a significant role in the pathogenesis of OA, which raises the question of the immunogenetic profile of OA patients.

2. Hereditary factors for OA

OA is a multifactorial disease in which both environmental factors and genetic predisposition play a role. In twin studies, the contribution of the hereditary factor to the development of OA of the hip joint in women was estimated at 58 % [9], of the knee and wrist joints at 39–65 % (also in women) [10]. A retrospective study of 9058 twin pairs conducted between 1987 and 2014 in Norway, showed that genetic factors play a decisive role in the development of hip OA in 73 % and knee OA in 45 % [11]. Since the immune component of osteoarthritis is an “excessive” inflammatory process, the disease is associated with mutations in the genes of pro-inflammatory interleukins, primarily *IL-1* [12]. Activation of Toll-like receptors (TLRs) in OA triggers the synthesis of IL-1, which causes the activation of such transcription factors as NF-κB, p38MAPK and c-Jun N-terminal kinase (JNK) [13]. Activation of the transcription factors promotes the expression of multiple genes that produce other cytokines, chemokines, adhesion molecules, inflammatory mediators and enzymes. IL-1β has a variety of pathogenic effects on cartilage including inhibition of cartilage regeneration, increased degradation by enzymes and direct adverse effects on chondrocytes. In joint cells, IL-1β is able to induce the own secretion in an autocrine manner stimulating the synthesis of other cytokines, TNFα, IL-6, IL-8, and the CCL5 chemokine [14].

OA patients have an increased expression of IL-1 receptors (an average of 4.069 binding domains per cell in OA, while normal is 2.315) [15]. A meta-analysis based on 1269 cases associated this increase in expression with mutations in the IL-1 genes (*IL1B* and *IL1RN*) [16]. Although there is a strong relationship between an increased expression of genes encoding proteins of the IL-1 family and the severity of OA there is evidence that IL-1 cannot be the cause of direct destruction of articular cartilage [17]. According to another meta-analysis, there is no significant association between increased expression of *IL-1* and OA [18].

IL-6 is a pro-inflammatory cytokine the increased level of which in the synovial fluid in OA has been reported since the end of the last century [19]. IL-6 is associated with the transmission of an intracellular signal in two ways: classical signaling is produced due to the binding of IL6 to the membrane IL6 receptor (mIL6R), trans-signaling is due to the binding of the IL6 complex and the soluble IL6 receptor to the membrane glycoprotein (gp) gp130 which allows initiating the transmission of an IL6-dependent activation signal in cells that do not express mIL6R. Both signaling pathways lead to the activation of JAK (Janus family tyrosine kinase) tyrosine kinase (JAK1, JAK2 and Tyk2) which causes the recruitment and phosphorylation of latent transcription factors STAT1 (signal transducers and activators of transcription 1) and STAT3, which regulate the synthesis of a wide range of pro-inflammatory mediators [20].

An association between single nucleotide polymorphisms in the *IL-6* gene and the risk of OA is reported. The effect of *IL-6* on the onset and the course of OA is determined by polymorphic variants of the promoter [21]. Thus, a recent study of six key SNPs of the promoter region of the *IL-6* gene showed that the risk of OA is significantly higher in patients with the "susceptibility haplotype" (GGGGCT) and is significantly lower in patients with the "protective haplotype" (CGAGGC) [22].

IL-17 is synthesized by a special subpopulation of Th17 T helpers and is another important pro-inflammatory cytokine that can play a role in the inflammation in OA cases [23]. IL-17 works in two ways. Transcription of IL-17A target genes which play a key role in inflammation and the body's defense against infections is activated through the canonical pathway. The transcription factor NF-kβ of the mitogen-activated

protein kinase (MAPK) pathways is triggered through exposure to *IL-17* and lipocalin synthesis is activated. *IL-17* can have a synergistic effect on tumor necrosis factor (TNF) [24]. The second non-canonical pathway leads to the stabilization of transcribed mRNAs that encode cytokines and chemokines and are unstable under normal conditions. TNF stimulates the initiation of transcription of mRNA of the chemoattractant protein CXCL1 (chemokine (C-X-C motif) ligand) and IL-17 stabilizes synthesized mRNA [25]. Different studies (Vrgoc G. [26] and Jiang L. [27]) showed a pronounced association of single nucleotide polymorphisms in the *IL-17* genes with an increased risk of OA. Three meta-analyses performed in the Chinese population demonstrated a close relationship between OA and the presence of certain polymorphisms in the *IL-17A* and *IL-17F* genes (rs2275913 and rs763780, respectively) [28, 29, 30]. However, the authors indicated the need to verify the statement in studies on other ethnic populations. Tumor necrosis factor alpha (TNFα), one of 19 ligands in the tumor necrosis factor superfamily, along with IL-1β, is considered a key inflammatory cytokine involved in the pathophysiological processes in OA. TNFα is secreted similarly to IL-1β and the elevated concentration is observed in the same elements (synovial fluid, synovial membrane, cartilage and subchondral bone) where elevated levels of IL-1β are also found [31, 32].

The effect of TNFα coincides with the action of IL-1β in most cases, and there is a pronounced synergy between the two cytokines, which is the result of activation of the same group of intracellular signaling pathways, which in turn triggers similar effects increasing inflammation and catabolism in tissue joints [32, 33]. TNFα blocks the synthesis of proteoglycan components, proteoglycan-binding proteins and type II collagen by chondrocytes [34]. As described previously, chondrocyte death is induced and chondroprogenitor cell migration is disrupted depriving cartilage of regeneration [35]. The effect of TNFα and IL-1β on the decrease in the efficiency of the respiratory chain and the decreased ATP produced in mitochondria located in chondrocytes was observed; in addition to that, the potential of the mitochondrial membrane decreases [36]. An increased risk of a more severe OA in TNFα polymorphisms has been established [37]. The M196R polymorphism of the TNFR2 gene encoding the TNF-R2 receptor protein can predetermine the development of OA due to increased TNFα receptors on the surface of chondrocytes, which leads to disruption of their functions due to excessive activation of mTNFα [38]. The substitution of G for A at position -308 in the *TNF* gene significantly increases the risk of OA. It is assumed that the SNP increases the expression of TNF mRNA, which increases the inflammatory response and predisposition to OA [39].

There is also evidence that mutations in TNF genes can create mutually reinforcing inflammatory cascades in conjunction with mutations in other genes, such as *ADAMTS-7*, which expresses the enzyme *ADAMTS-7* which promotes cartilage degradation by inducing the activity of metalloproteases - zinc- dependent proteins that cleave the extracellular matrix [40]. Increased expression of these proteins can also be caused by changes in the genes of the metalloproteases. The -77G > A (rs2252070) substitution in the MMP-13 gene increases the synthesis of the MMP-13 metalloprotease by 30 % significantly aggravating the inflammatory process in OA [41].

OA patients demonstrate differences in the genes of human leukocyte antigens (Human Leukocyte Antigens, HLA). It is a group of surface and transmembrane receptor proteins that are part of the major histocompatibility complex (MHC). Mutations associated with OA are found in *HLA-DRB1*01* and *HLA-DRB1*07* [42]. The DRB1 protein is part of the HLA-DR, the major histocompatibility complex receptor (MHC II), which is present on antigen-presenting cells (APCs) and binds to the T-cell receptor (TCR). Increased expression of DRB1 was also reported in the studies of knee and hip OA performed using full transcriptome association analysis (TWAS) [43]. The HLA-DRB1*0101 haplotype is associated with a general increased risk of OA [44], and the HLA-DRB1 haplotypes are associated with different localizations of OA with DRB*10 and DRB*12 being associated with osteoarthritis in the joints of the distal upper limb, while DRB*07 and DRB*04, with OA in other localizations [45]. Studies based on genome-wide association screening (GWAS) show that single nucleotide substitutions of cytosine for thymine (rs7775228 and rs10947262) in the genes encoding the DQ2 receptor on antigen-presenting cells, *HLA-DQ2*, also increase the likelihood of knee OA [46]. Changes in anti-inflammatory cytokine genes may also cause the risk of OA. Interleukin-4 (IL-4) is a cytokine that has an anti-inflammatory effect when exposed to chondrocytes. IL-4 is activated under mechanical stress and primarily affects surrounding cells, triggering intracellular mechanisms that reduce the activity of matrix metalloproteinases [47]. Known variants of *IL4* in the form of variable number of tandem repeats (VNTR) 3 introns are associated with an increased risk of OA [48]. The rs1805015 (S503P) and rs1801275 (Q576R) polymorphisms in the IL4 receptor (*IL4R*) genes were found to be associated with an increased risk of OA. This may be due to a disruption in the interaction of the receptor with intracellular mediators STAT-6 and IRS (insulin receptor substrate), and the conduction of the intracellular signal [49]. The predisposition to OA in patients with mutations in the *IL4R* gene is 2.4 times higher than in patients with the *IL4R* gene without

them [50].

According to the GWAS (Genome Wide Association Study), genes responsible for a high risk of developing OA are generally not associated with an increased risk of rheumatoid arthritis (RA). Most of the genetic risk factors for OA are associated with the genes of collagens, pro-inflammatory interleukins, metalloproteases, and cartilage growth factors [51]. Genes of receptors and intracellular mediators of T-lymphocyte signaling pathways are mainly associated with an increased risk of developing RA [52], and *STAT1* (Signal transducer and activator of transcription 1) and *IL7R* genes allow differentiation of RA from OA [53] (the IL-7 receptor gene). The main function of the genes is to stimulate the differentiation of T-lymphocytes [54]. There are also genes that affect the pathogenesis of both RA and OA: the expression of the *PLCH2* and *PLCB1* genes responsible for the synthesis of phospholipase C was found to be increased in both RA and OA, however, the effect of phospholipase C on the pathogenesis of these disease has not been fully established [55]. The *IL2, AKT1, TP53* (tumor protein 53) genes are associated with the risk of both RA and OA. The *IL2* gene product is a pro-inflammatory cytokine and has an activating effect on cellular immunity, AKT1 helps prevent apoptosis and *TP53* is a tumor suppressor gene [56]. RA like OA, is associated with HLA genes, primarily *HLA-DRB1* [57]; haplotypes DRB1*01, DRB1*04, DRB1*08 and DRB1*011 are also considered significant for the risk of developing RA [58].

3. Mechanisms of epigenetic control of gene expression in OA

The main mechanisms of epigenetic regulation include DNA methylation, histone modification and non-coding RNAs (ncRNAs). OA is characterized by demethylation of genes that activate the inflammatory response. Methylation of CpG sites (regions of genes consisting of repeating CG sequences) in the region of promoters of metalloproteinases *MMP2* (-635 position relative to the transcription initiation site), *MMP9* (-36), *MMP13* (-110), *ADAMTS4* (-753) is reduced in OA [59]. Methylation of genes for pro-inflammatory cytokines IL1α and TNF also decreases, which correlates with increased expression of these genes in OA [60, 61]. Demethylation of promoter or enhancer sites in the IL8 gene is associated with increased expression of the genes in cartilage affected by OA [62]. Decreased methylation of NF-κB (nuclear factor kappa-B) sensitive iNOS (inducible nitric oxide synthase) enhancer regions was more common in OA-affected cartilage than in normal cartilage. It is assumed that the loss of methylation leads to the induction of iNOS synthesis by NF-κB, which forms reactive nitrogen species causing local inflammation [63].

Post-translational histone modifications through acetylation, methylation, and other reversible chemical modulations regulate gene expression by controlling chromatin compaction interacting with transcription factors and providing signals to chromatin code readers. Increased histone acetylation in the *IL-6* promoter region is observed in OA [64] which leads to an increase in the activity of this interleukin; inhibition of histone deacetylases (HDAC) I and II leads to the same effect [65]. Histone demethylases H3 *KDM6A* and JMJD3 (*KDM6B*) effecting trimethylate lysine at position 27 (H3K27me3) regulate chondrocyte activity by inhibiting TGFβ (transforming growth factor beta)-induced anti-inflammatory cytokine gene expression. Sirtuin deacetylase SIRT1 (NAD+-dependent HDAC) provides chondroprotective functions, however, *SIRT1* expression in cartilage is reduced in OA and leads to increased chondrocyte apoptosis; in addition to that, *SIRT1* initiates a reduction in the inflammatory response by deacetylation of the p65 NF-κB subunit and blocking NF-κB binding to DNA in chondrocytes. Conversely, overexpression of *SIRT1* may inhibit the pro-inflammatory effect of IL1β induction in human chondrocytes. In mice, a decrease in *SIRT1* expression in chondrocytes contributed to the accelerated progression of OA and intra-articular injection of the natural phenol resveratrol attenuated the progression of OA by activating *SIRT1* [61].

MicroRNAs (miRNAs) are non-coding RNAs that provide RNA interference, one of the ways to suppress gene overexpression [66]. Some microRNAs can influence the activity of inflammatory processes in OA and contribute to the pathogenesis of the disease [67]. The miRNAs are able to modulate inflammation by participating in the regulation of NF-κB1 (miR-9) [68] and SDF1/CXCR4 pathways (miR-221-3p) [69]. The miRNA-9 suppresses overexpression of matrix metalloproteinase 13 (MMP-13) and inhibits collagen destruction [70]. Downregulation of MMP-13 expression by RNA interference can be mediated by downregulation of leptin which induces MMP-13 synthesis [71].

DISCUSSION

Our findings indicate to the role of genetic (Table 1) and epigenetic (Table 2) changes in the immune system in OA, since there is an association of mutations in the genes of pro-inflammatory cytokines, HLA, and metalloproteases with clinical manifestations of OA. This indicates the need for a more thorough examination of OA patients and introduction of new methods of treatment for the aggressive course of the disease aimed at reducing the pathological response of the immune system.

Table 1

Genetic changes in the immune system associated with osteoarthritis

Gene	Alteration pattern	Author
IL-1b	Increased expression of pro-inflammatory cytokines (IL-1)	Smith A.J.P. et al. [12]
IL1R	Increased expression of receptors for pro-inflammatory cytokines (IL-1)	Moxley G., Meulenbelt I., Chapman K. [16]
IL-6	Increased expression of pro-inflammatory cytokines (IL-6)	Singh M., Mastana S., Singh S. [22]
IL-17A, IL-17F	Increased expression of pro-inflammatory cytokines (IL-17A, IL-17F)	Hartupee, J., Liu, C., Novotny, M. [25]
TNFR2	Increased expression of receptors for pro-inflammatory cytokines (TNFα)	Kou S., Wu Y. [39]
ADAMTS-7	Increased binding of metalloproteases	Lai Y. et al. [40]
HLA-DRB1	Increased expression of MHC II receptors on APC	Ramonda R. [42]
HLA-DQ2	Increased expression of MHC II receptors on APC	Shi D., Zheng Q., Chen D. [46]
IL4	Reduced expression of anti-inflammatory cytokines (IL-4)	Yigit S., Inanir A., Tekcan A. [48]
IL4R	Decreased activity of the receptor for anti-inflammatory cytokines (IL-4)	Vargiolu M., Silvestri T., Bonora E. [49]
IL2	Increased expression of pro-inflammatory cytokines (IL-2)	Zhu N. et al. [56]
PLCH2	Increased expression of phospholipase C	Li H. et al. [55]
PLCB1	Increased expression of phospholipase C	Li H. et al. [70]
AKT1	Increased expression of serine-threonine protein kinase	Zhu N. et al. [56]
TP53	Increased expression of the oncosuppressor protein p53	Zhu N. et al. [56]

Table 2

Changes in epigenetic regulation of immune system genes in osteoarthritis

Gene	The nature of the change in epigenetic regulation	Author
MMP2	Demethylation, increased expression	Roach H.I., Yamada N., Cheung K.S. [59]
MMP9	Demethylation, increased expression	Roach H.I., Yamada N., Cheung K.S. [59]
MMP13	Demethylation, increased expression	Iliopoulos D., Malizos K.N., Tsezou A. [60]
ADAMTS4	Demethylation, increased expression	Shen J. et al. [61]
iNOS	Demethylation, increased expression	de Andrés M.C., Imagawa K., Hashimoto K. [63]
IL-6	Hyperacetylation, demethylation, increased expression	Yang F., Zhou S., Wang C. [64]
NF-κB	Hyperacetylation, demethylation, increased expression	Chen K., Rajewsky N. [66]

CONCLUSION

OA is a multifactorial polygenic disease. Both genetic risk factors and the features of epigenetic regulation being characteristic of OA patients have been described in the development of OA. Changes in the nucleotide sequence in the genes associated with the regulation of inflammation including mutations in the genes of pro-inflammatory cytokines (*IL-1, IL-6, IL-17, TNF*) and receptors for them, in the genes of metalloproteases, the HLA genes and the anti-inflammatory cytokine (IL-4) gene reducing the regulatory activity are more common for OA patients than for healthy people. There are reports about polymorphisms in the genes associated with the regulation of the inflammatory process which are characteristic of both OA and rheumatoid arthritis in the PLCH2 and PLCB1 phospholipase genes and IL-2 genes, in particular. The epigenetic regulation in OA include a decrease in methylation of promoters of genes for pro-inflammatory cytokines and metalloproteases (*MMP2, MMP9, MMP13, ADAMTS4, TNF, IL1*) and iNOS enhancer regions sensitive to NF-κB. OA patients showed enhanced activity of histone acetylases in the IL-6 promoter zone. Expression of anti-inflammatory cytokines, on the contrary, is reduced due to reduced activity of SIRT1 deacetylase.

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The article was submitted 12.04.2021; approved after reviewing 29.06.2021; accepted for publication 26.01.2022.

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