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Г.В. Порядин[1], А.Н. Захватов*[2], И.А. Захаркин[2], А.Ю. Паршина[2], А.А. Шаев[2]

[1] — Федеральное государственное автономное образовательное учреждение высшего образования «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова», Москва, Россия
[2] — Федеральное государственное бюджетное образовательное учреждение высшего образования «Национальный исследовательский Мордовский государственный университет им. Н.П. Огарёва», Медицинский институт, Саранск, Россия

ПАТОГЕНЕТИЧЕСКИЕ МЕХАНИЗМЫ ВЗАИМОСВЯЗИ ОСТЕОАРТРИТА И ДИСБИОЗА КИШЕЧНИКА

G.V. Poryadin[1], A.N. Zakhvatov*[2], I.A. Zakharkin[2], A.Yu. Parshina[2], A.A. Shaev[2]

[1] — Pirogov Russian National Research Medical University, Moscow, Russia
[2] — National Research Ogarev Mordovia State University, Medical institute, Saransk, Russia

Pathogenetic Mechanisms of the Relationship Between Osteoarthritis and Intestinal Dysbiosis

Резюме

Потенциальная взаимосвязь между дисбиозом кишечной микробиоты и остеоартритом подтверждается всё большим количеством исследований. Учитывая высокую социальную значимость и распространённость остеоартрита, а также доказательства того, что количественные и качественные изменения кишечной микробиоты оказывают влияние на его прогрессирование, представляется важным прояснить механизмы, лежащие в основе данной ассоциации.

Остеоартрит является многофакторным заболеванием суставов, в основе которого лежит, в первую очередь, прогрессирующее разрушение суставного хряща. Нарушенная метаболическая активность хондроцитов, проявляющаяся дисбалансом процессов синтеза и деградации внеклеточного матрикса, способствует персистирующему высвобождению молекулярных паттернов, связанных с повреждением. Это приводит к активации широкого спектра рецепторов врожденных иммунных клеток и является основой развития воспалительной реакции в суставе. Привлечение макрофагов в синовиальную оболочку и их активация, приводит к выработке провоспалительных цитокинов, приводя к развитию воспалительного состояния низкой степени активности в суставе, поддерживая синтез катаболических ферментов хондроцитам и усугубляя дегенерацию хряща.

Микробный дисбиоз, определяемый как неблагоприятное изменение разнообразия, структуры или метаболической активности кишечной микробиоты, является скрытым фактором риска, сопровождающимся метаболической эндотоксемией и, как следствие, повышенной выработкой провоспалительных цитокинов, поддерживающих системное воспалительное состояние низкой степени активности и патофизиологические механизмы остеоартрита. Показано, что дисбиоз кишечника принимает участие в формировании других факторов риска остеоартрита, например, ожирения и метаболических нарушений.

Определение важных взаимосвязанных патофизиологических механизмов данных патологий будет способствовать разработке новых способов лечения патогенетической направленности с последующим их активным внедрением в клиническую практику.

Ключевые слова: *кишечная микробиота, дисбиоз, остеоартрит, метаболическая эндотоксемия, цитокины, воспаление*

*Контакты: Алексей Николаевич Захватов, e-mail: zachvatan78@mail.ru
*Contacts: Eugenia S. Mykhailichenko, e-mail: zachvatan78@mail.ru
ORCID ID: https://orcid.org/0000-0003-1433-0337

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Abstract

The potential association between dysbiosis of the gut microbiota and osteoarthritis is confirming by a growing number of studies. Given the social significance, the high prevalence of osteoarthritis, and evidences that quantitative and qualitative modification of the gut microbiota affects its progression, it seems important to clarify the underlying mechanisms of this association.

Osteoarthritis is a multifactorial joint disease, which is based primarily on the progressive degeneration of articular cartilage. Impaired metabolic activity of chondrocytes, consisting in an imbalance in the extracellular matrix synthesis and degradation processes, causes the persistent release of molecular patterns associated with damage. This leads to the activation of a wide range of innate immune cells receptors and is the basis for the development of an inflammatory reaction in the joint. The involvement of macrophages in the synovial membrane and their activation leads to the production of pro-inflammatory cytokines, leading to the development of chronic low-grade inflammation in the joint, supporting the synthesis of catabolic enzymes by chondrocytes and escalating the cartilage degeneration.

Microbial dysbiosis, defined as an adverse modification in the diversity, structure, or metabolic activity of the gut microbiota, is a hidden risk factor, accompanied by metabolic endotoxemia and, consequently, by increased production of pro-inflammatory cytokines, that support the systematic low-grade inflammation and pathophysiological mechanisms of osteoarthritis. It has been shown that dysbiosis of the gut microbiota intestinal takes part in the formation of other osteoarthritis risk factors for, for example, obesity and metabolic disorders.

The identification of important interrelated pathophysiological mechanisms of these pathologies will contribute to the development of new pathogenetic treatment methods with their subsequent active introduction into clinical practice.

Key words: *gut microbiota, dysbiosis, osteoarthritis, metabolic endotoxemia, cytokines, inflammation*

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IL-1β — interleukin-1β, DAMPs — damage-associated molecular patterns, MMP — matrix metalloproteinase, TNF — tumor necrosis factor, OA — osteoarthritis

Introduction

Osteoarthritis (OA) is one of the most common musculoskeletal system disorders associated with arthrodial cartilage degeneration, subchondral bone remodelling, synovial membrane inflammation resulting in restricted joint movement; this disease in one of the leading causes of disability and poorer quality of life [1]. OA affects around 303 million people all over the world; and, since the population is ageing and there are more and more obese people, there is an upward trend in the number of cases. The incidence of this pathology has grown by 8–10 % vs. 1990 [2].

Risk factors for OA are ageing, sex, joint traumas, obesity, genetic predisposition [3]. Currently, the trigger of OA is unknown. Recent studies which confirmed the association between type 2 diabetes mellitus, obesity and OA, were dedicated to the role of metabolic syndrome in joint damage induction or worsening. The link between metabolic disorders and OA is probably a chronic, mildly active systemic inflammation. Available data from numerous studies demonstrate that this inflammatory condition is facilitated by gastrointestinal microbiota translocation [4]. It was demonstrated that blood and synovial fluid lipopolyssacharide (LPS) levels in gastrointestinal microbiota representatives had close association with joint inflammation severity and activity. Also, data presented by Zhao, et al. (2018) confirm the presence of bacterial nucleic acids in synovial fluid of patients with OA [5]. Dunn, et al. (2020) found nucleic acids of gram-negative bacteria in cartilage of patients susceptible to OA vs. controls who have certain resistance to degenerative joint damages [6].

Thus, these results evidence the significance of bacteria translocation from gastrointestinal microbiota due to marked impairment of the barrier function of gastrointestinal epithelium for the development of inflammatory degenerative processes in joints. A systematic analysis of studies allows assuming that there are cause-effect relationships between the qualitative and quantitative composition of gastrointestinal microbiota and the probability of osteoarthritis; assessing the pathogenic role in the activation of system and local joint inflammation, bacteria-associated molecular patterns, as well as their direct and indirect impact on synovial environment in the joint [7-9].

This review presents the results of literature analysis for 2010–2023 in RSCI, PubMed, Scopus. The analysis includes data from authors who conducted clinical and experimental studies to explain possible mechanisms of the role of intestinal dysbiosis in onset and progression of osteoarthritis in various locations.

Pathogenic Aspects of Osteoarthritis Development

Osteoarthritis (OA) is a heterogeneous degenerative joint disease of various origin associated with articular cartilage destruction and united by common biological, morphological and clinical presentation and outcome [10]. OA progression is affected by metabolic, epigenetic, genetic and cellular disorders. Risk factors of OA development and progression are elderly age, traumas, sex, obesity, nutrition, sedentary lifestyle [11-14].

The key components of a healthy joint are cartilage, synovial membrane, synovial fluid as well as a subchondral bone, ligaments, capsule and periarticular muscles. OA is caused by involvement of all joint components: subchondral bone thickening, periosteophytes, synovial membrane inflammation (synovitis), ligaments and menisci degeneration, joint capsule hypertrophy, but first and foremost — progressive articular cartilage destruction. Cartilaginous cells are a cellular component of the cartilage and play an important role in maintaining tissue homeostasisa, acting as sensors of mechanic, ionic and osmotic signals in cartilage microenvironment. In physiological conditions, cartilaginous cells produce extracellular matrix (ECM) components including type II collagen, glycoproteins, proteoglycans and hyaluronic acid that are essential for maintaining cartilage structure and functions [15].

Such factors as excessive loads, hypermobility, impaired congruence result in excessive mechanic stress and chronic cartilage damage. Cellular and tissue cartilage pathology is characterised by mismatch in synthesis and extracellular matrix degradation processes caused by changes in metabolic activity of cartilaginous cells. Cartilaginous cells reduce ECM component production, increase secretion of enzymes that destroy ECM, including collagenases and aggrecanase. Collagenases, namely matrix metalloproteinases (MMPs) 1 and 13, are the leading factors resulting in general degradation of collagen lattice, whereas aggrecanases, namely A Disintegrin and Metalloproteinase with Thrombospondin motifs (ADAMTS 4 and 5), are proteolytic enzyms that destroy proteoglycans [16]. Cartilage damage impairs normal joint functioning and causes poor congruence and reduced mechanical load absorbance.

Macrophages are a main source of inflammation mediators in OA. Production of pro-inflammatory cytokines, IL-1β (interleukin-1β), IL-6 (interleukin-6), IL-8 (interleukin-8), TNF (tumour necrosis factor) by activated macrophages is believed to be the main factor of continued joint damage. Persistent destruction of cartilage and adjacent tissues ensures steady supply of endogenous stimuli that maintain low-activity local chronic inflammation [17]. Extracellular and intracellular damage-associated molecular patterns (DAMPs) are released into synovial fluid following tissue damage or cellular stress and initiate inflammatory reaction. DAMPs activate pattern recognising receptors (PRR), including Toll-like receptors (TLR), nucleotide binding domain-like oligomerization receptors or NOD-like receptors (NLR) and receptors for advanced glycation end (RAGEs), that are expressed on macrophages present in a joint, on synoviocytes and cartilaginous cells, and initiate signal cascades resulting in activation of transcription factors participating in production of inflammatory mediators and enzymes that destroy extracellular matrix. Activation of PRR cartilaginous cells is associated with catabolic factor production [18]. TLR2/TLR4 receptor stimulation results in recruitment of adaptor proteins such as MyD88, TICAM-1, TICAM-2, that activate signal paths for NF-κB, MAPK and PI3K, causing production of pro-inflammatory cytokines, NO, synthesis of PGE2 and MMPs. NLRs mediate activation of inflammasomes that trigger pore formation in cellular membrane associated with release of IL-1α, β and IL-18 [19]. The complement system also contributes to the development of joint inflammation, since DAMPs can bind and activate complement molecule cascade resulting in formation of a membrane attack complex that triggers cytolysis.

Extracellular DAMPs originate from extracellular matrix and are released as a result of mechanical or proteolytic cartilage damage: fibronectin, hyaluronan, biglycan, tenastin-C, syndecan-4, fragments of type II collagen and aggrecan, the concentration of which in synovial fluid in OA increases drastically and forms a vicious circle of cartilage destruction. For instance, fibronectin facilitates an inflammatory reaction of macrophages by activation of TLR and JNK2 (JAK 2) and p38 MAPK signal path causing production of TNF, IL-1β and IL-8 [20]. Also, fibronectins trigger catabolic processes in cartilage by cartilaginous cell activation for production of pro-inflammatory cytokines and MMP-1 and 3. Crystals of calcium pyrophosphate dihydrate (CPPD) and basic calcium phosphate (BCP) can react both with TLR and NLR of macrophages, resulting in inflammasome activation and release of pro-inflammatory cytokines IL-1β and IL-18 and can also induce production of NO and MMPs by cartilaginous cells by means of activation of TLR2-NF-κB signal path [21].

Intracellular DAMPs are endogenous molecules acting as alert molecules and participating in various inflammatory diseases: HMGB1, s100 proteins, heat shock proteins, IL-1α, IL-33 and other [22]. Passive release of these molecules can result from necrosis and cell death, whereas active release is mediated by secreted extracellular vesicles [23]. Vascular exudation is another sources of DAMPs. Fibrinogen, Gc-globulin, α1-microglobulin and α2-macroglobulin levels in synovial fluid in OA increase and correlate with disease severity. These molecules activate macrophages and other innate cells in TLR4-dependent way causing IL-1β, IL-6 and TNF production.

Ageing is the main factor contributing to OA development. Senescence-associated secretory phenotype (SASP) is developed which is characterised by increased production of pro-inflammatory agents, catabolic mediators and DAMP in tissue microenvironment. Long-term release of these predictors results in low-activity pro-inflammatory system condition (inflammaging) that facilitates degenerative processes in tissues. Cartilaginous cells undergo cellular senescence due to mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, damaged cellular protein accumulation and damage to cellular DNA. Accumulation of ageing cartilaginous cells jeopardises the ability of cartilaginous cells to maintain cartilaginous homeostasis and contributes to production of inflammatory cytokines, DAMPs and enzymes that destroy extracellular matrix [24].

Association Between Disbacteriosis and Osteoarthritis

The affinity of pathogenic mechanisms in OA and intestinal dysbiosis manifests itself through similar risk factors: age, sex, physical inactivity, diet with excessive fats and carbohydrates, obesity that participate in OA progression wither directly or via intestinal microbiota modulation. Microbial dysbiosis can be one of the key triggers of OA, and microbial patterns can stimulate existing mechanisms of OA development [25].

The most recognised link between dysbiosis and OA onset is a low-grade chronic inflammation. Dysbiosis affects OA pathogenesis both at the system and local levels via mechanisms of inborn immunity activation [26]. Through activation of innate receptors and stimulation of pro-inflammatory cytokines synthesis, existing intestinal dysbiosis causes dysregulation of production of transmembrane (occludins, claudins) and intracellular (ZO-1, ZO-2, ZO-3) tight proteins that are main components of tight junctions of apical part of enterocytes. In particular, γ-IFN inhibits expression both of ZO-1 and occludin. Besides, dysregulation of tight junction assembly can be associated with increased activity of zonulin, a physiological regulator of intestinal permeability, which is pathologically stimulated by pro-inflammatory cytokines and bacterial pathogens in case of dysbiotic microbiome [27]. Impaired integrity of enterocyte tight junctions results in increased intestinal barrier permeability, thus creating conditions for excessive permeation of bacteria-associated molecular patterns (lipopolyssacharide, peptidoglycane, flagellin, bacterial DNA) to the blood flow. Resulting endotoxemia causes pro-inflammatory reaction of residential immunocytes, also in cartilage and synovial membrane [28].

Macrophages are an important component of the innate immune system and play an important role in OA onset and progression. Macrophage-associated inflammation is a driving factor for structural damage and OA progression. For instance, when metabolites produced by Streptococcus spp. pass the intestinal barrier, they either activate macrophages in synovial membrane, causing inflammation and joint damage, or get into the blood flow and activate macrophages so that they become pro-inflammatory macrophages, thereby causing system inflammation which triggers and worsens joint damage [29]. M1/M2 macrophage ratio defines disease severity. The former induces cartilaginous cell apoptosis and inhibits synthesis of extracellular matrix components,

while the latter stimulates chondrogenesis and formation of collagen II and proteoglycans via expression of transforming growth factor-β (TGF-β) [30].

Joint tissue macrophages are activated upon stimulation of pattern recognition receptors by molecular patterns associated with the damage, not only as a result structural joint damage, but also due to endotoxemia from dysbiosis. Lipopolyssacharide activates innate immune response by binding CD14–LPS–LBP (CD14–lipopolyssacharide–lipopolyssacharide-binding protein) complex to TLR4, and also co-receptor myeloid differentiation protein-2 (MD-2), expressed on the cell surface of various types of cells, especially macrophages [31]. It results in higher levels of NF-κB transcriptional factor, production of pro-inflammatory cytokines and chemokines, such as TNF, IL-1β, IL-6, receptor activator of nuclear factor kappa-B ligand (RANKL) and IL-8, that enhance MMPs production, reduce synthesis of collagen and proteoglycan and enhance activation of NF-κB transcription factor even more, causing secondary joint tissue inflammation.

Besides, bacterial cell wall lipopolyssacharide (LPS) activates cartilaginous cells and induces production of complement C1r sub-component, complement B factor, complement C3, mimecan and PTX3-bound protein. It results in activation of a complement cascade and production of active complement proteins which can bind to receptors or accumulate on synovial cells, thus causing an increase in pro-inflammatory cytokine production [32]. Therefore, LPS not only induce innate immunity via TLR4 activation, but also aggravate existing low-activity chronic inflammation and make OA a chronic disease.

Bacterial peptidoglycane stimulates intraarticular synovial fibroblasts and induces expression of matrix metalloproteinases (MMPs), pro-inflammatory cytokines via TLR2 receptor activation. Peptidoglycane also initiates system innate immunity via NLRs recognition, causing inflammasome activation and increased production of pro-inflammatory cytokines [33].

Intestinal microbiota participates in OA progression and impacts adaptive immunity. T-cells play a biological role in inflammation control and recovery. They produce catabolic cytokines that stimulate proteases to destroy cartilage matrix, modulate pro-inflammatory cytokine secretion and cytokine receptor expression, i.e., they can impact OA progression. Via TLR4 activation, LPS triggers an inflammatory cascade, where interferons and inflammatory cytokines are released, which act as transcription factors and induce maturation of naive immune cells [34]. Dysbiosis can determine the predominant lineage for primitive CD4+ T-cells to become effector T-cells. The balance between Treg-cells and effector T-cells of subsets Th1, Th2 и Th17 is essential for immune homeostasis, the imbalance of which can result in chronic inflammation, including joint inflammation. Biologically active substances, biosynthesis of which depends on microbiota, affect T-cell biology. For example, butyrate produced by intestinal microbiota helps in maintaining immune homeostasis of intestines by inducing Treg-cell differentiation. Moreover, butyrate inhibits collagen-induced arthritis via Treg-cells/ IL-10/ Th17-cells axis [35].

Another well-known risk factor for OA is obesity, which usually is associated with intestinal dysbiosis development. In terms of the mechanistic theory, the association between obesity and OA is due to excessive joint stress resulting from higher body weight. Changes in intestinal microbiota are closely related to development of obesity and insulin resistance. Endotoxemia in dysbiosis facilitates transformation of adipose tissue macrophages from phenotype M2 to phenotype M1 and their activation, resulting in increased secretion of pro-inflammatory cytokines and adipokines and aggravating low-activity system inflammation what makes joint inflammation even worse [36]. Hyperglycemia promotes inflammatory reaction and oxidative stress in articular tissue, thus aggravating OA. Besides, pro-inflammatory hyperproduction and resulting endotoxemia can be caused by excessive adipose tissue associated with hyperproduction of adipokines, such as leptin, resistin, visfatin and adiponectin [37]. Leptin, secreted both by adipose tissue and by additional secretion stimulation due to endotoxin translocation to blood flow, via binding with leptine receptors (Ob-Rb), promotes IL-6 expression via signal paths of JAK2/signal protein and transcription activator 3 (JAK2/STAT3), p38 MAPK [38]. Also, leptin can enhance expression of other factors, such as IL-1, matrix metalloproteinases-9 and 13 (MMP-9, MMP-13).

Dysbiosis is associated with significantly increased expression of genes related to synthesis of free fatty acids (FFAs) and FFAs transport in liver. FFAs metabolite levels in synovial fluid, such as myristic acid, oleinic acid and lanosterol, demonstrate positive correlation with OA progression [39]. Lipotoxic effects aggravate synovitis in patients with OA. Hypercholesterolemia facilitates system inflammatory response, and accumulation of low density lipoprotein (LDLP) in synovial fluid and cartilaginous cells (observed in patients with OA) promotes local inflammation reactions and cartilage degeneration [40].

The structure and functions of intestinal microbial community are closely associated with the diet. OA pathophysiology is also depends on various dietary factors, such as saturated fatty acids, polyunsaturated fatty acids (PSFAs), antioxidants and aminoacids. Some microbial metabolites interact with inflammatory signal paths and affect host immunity, which can speed up OA progression. For instance, choline and carnitine can be metabolised by intestinal microbiota to form trimethylamine N-oxide (TMAO) [41]. TMAO increases TNF-α and IL-1β levels, reduces IL-10 levels and can cause oxidative stress which plays an important role in OA pathogenesis [42].

Intestinal microbiota has direct and indirect impact on bone tissue metabolism, affecting absorption of vitamins, calcium and sex hormone levels. Short-chain fatty acids (SCFAs) promote IGF-1 (insulin growth factor-1) levels in serum and brain, therefore, intestinal microbiota has anabolic action for bone tissue [43]. Intestinal microbiota significantly affects bone mass via signal paths NOD1 and NOD2. MAMPs distributed in bone tissue have direct impact on bone remodelling via stimulation of innate immune osteocyte receptors [44].

The bidirectional communication between the brain and intestine is considerably dependent on intestine microbiota [45]. Intestine microbiota impacts CNS functions via stimulation of enteroendocrine cells which produce neuropeptides and bacterial neurotransmitters, especially serotonin (5-HT) and tryptophane metabolites. Imbalance between the CNS and intestinal nervous system participates in development of the above metabolic mechanisms and, therefore, facilitates OA progression. Hyperactivity of dorsal horn microglia underlies central pain sensibilization mechanisms in OA [46]. It is possible that SCFAs that stimulate microglia maturation and regulate homeostatic metabolic status participate in regulation of OA-associated pain [47].

The role of intestinal dysbiosis in osteoarthritis pathogenesis is supported by studies of the microbial profile of articular tissue of OA patients. In a study by Dunn et al. (2020), gene 16s of ribosomal RNA was sequenced to identify microbial nucleic acids in affected and intact articular cartilage samples of patients with knee and hip OA as well as of controls. Significant differences in microbial profile of knee and hip joints were reported. Articular cartilage samples from patients with knee OA demonstrated abundance of Firmicutes spp., whereas articular cartilage samples from patients with hip OA had Proteobacteria spp., specifically Beta- and Gammaproteobacteria. The results were compared to a similar study of articular cartilage samples from OA-sensitive C57BL6 mice and OA-resistant MRL-mice. MRL-mice that were protected against OA demonstrated a microbial profile similar to the results of the study of articular cartilage samples from controls, whereas OA-sensitive B6-mice had microbial patterns similar to those in patients with OA [46]. Therefore, it can be assumed that a number of bacterial OA-associated species can induce and maintain OA.

The route of articular cartilage contamination is still unknown. In this connection, it is interesting to find out that these sequencing results differ for one and the same joint. It might be explained by the fact that eroded cartilage areas are exposed to blood flow products to a greater extent, therefore, microbial profile changes take place significantly faster that in intact areas.

In their study, Zhao et al. (2018) also used sequencing of gene 16s of ribosomal RNA to identify bacterial nucleic acids in synovial tissue and synovial fluid of patients with OA and rheumatoid arthritis. Significant differences were identified in the flora: Agrobacterium, Comamonas, Kocuria, Meiothermus and Rhodoplanes are typical of synovial tissue of patients with rheumatoid arthritis, whereas Atopobium, Rhodotorula mucilaginosa, Bacteroides uniformis, Turicibacter, Leptotrichia, Haemophilus parainfluenzae, Bacteroides fragilis, Porphyromonas and Streptococcus are a characteristic of synovial tissue of patients with OA [47].

Nevertheless, these studies do not provide a clear opportunity to draw any conclusions on the direct role of bacteria or any species in the development or progression of OA. Further studies are required to analyse bacterial metabolites for better understanding of potential changes in cartilage microbiome as a new factor of OA pathogenesis. Also, it is essential to analyse when and how cartilage is contaminated with its own microbiome, to assess its changes with age and, hence, age-related increase in susceptibility to OA.

Explanation of the possible pathogenic role of certain bacteria species in OA development will make it possible to develop new therapies. For instance, O-Sullivan et al. (2022) present data demonstrating that Lactobacillus acidophilus significantly modify the intestine microbiota structure in an experimental model, promoting accumulation of Akkermansia spp. and Lachnospiraceae app. with favourable antiiflammatory effects. A systemic effect was identified which is manifested via reduced levels of pro-inflammatory cytokines and mediators of pain. A histological examination confirmed that Lactobacillus acidophilus also have favourable effect on cartilage integrity as a result of RUNX2/

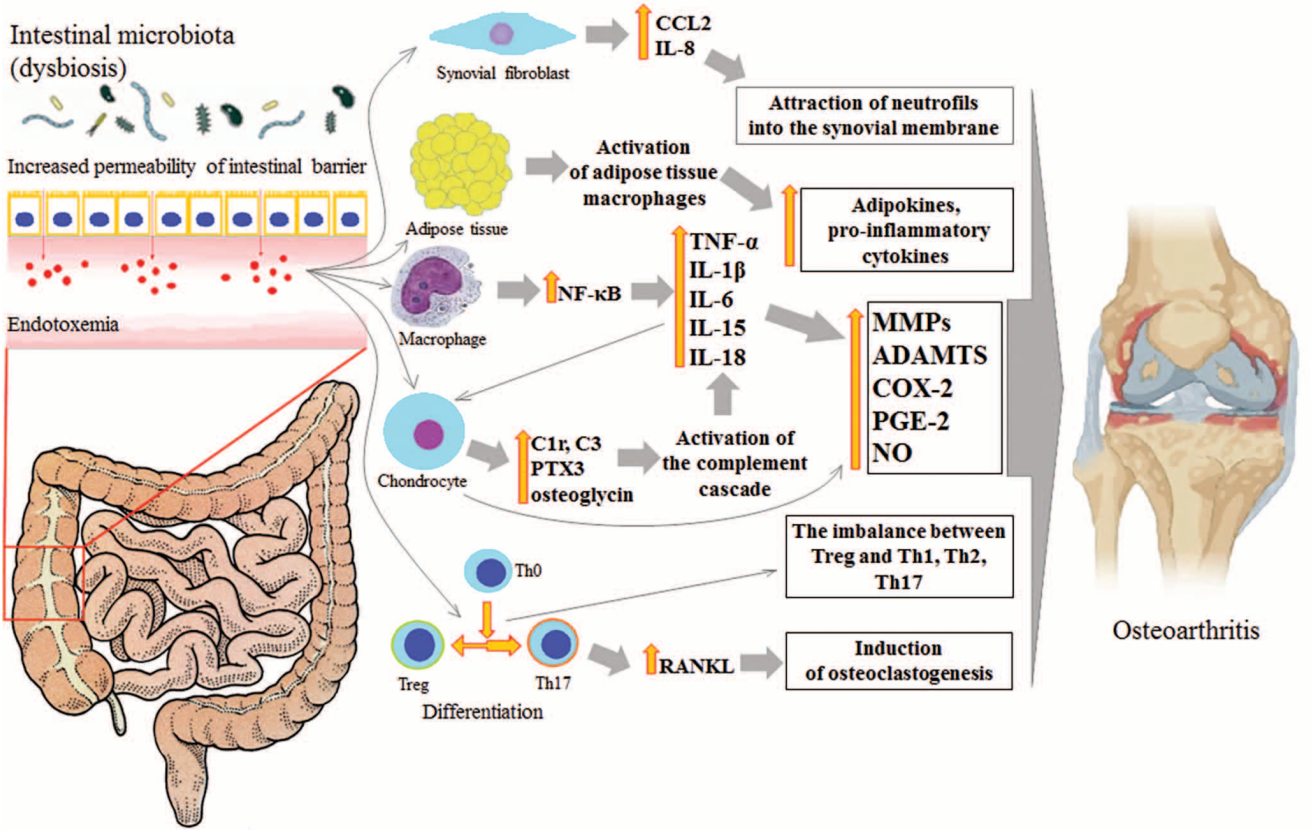

Figure 1. *Pathogenetic relationship of intestinal dysbiosis and osteoarthritis*

Notes. TNF — tumor necrosis factor; IL-1β — interleukin-1β; IL-6 — interleukin-6; IL-8 — interleukin-8; CCL2 — C-C motif ligand 2; NF-kB — nuclear factor kappa light-chain-enhancer of activated B cells; C1r — complement C1r subcomponent; C3 — complement C3 component; PTX3 — pentraxin 3; MMPs — matrix metalloproteinases; ADAMTS — a disintegrin and metalloprotease with thrombospondin motif; COX-2 — cyclooxygenase-2; PGE-2 — prostaglandin E2; NO — nitric oxide; RANKL — receptor activator of NF-κB ligand; Th0 — undifferentiated T-helper cell; Th1 — T-helper cell type 1; Th2 — T-helper cell type 2; Th17 — T-helper cell type 17; Treg — regulatory T cell

MMP13 inhibition [48]. Future studies may provide additional evidence of the substantial potential of the strategies for OA diagnostics and management, including the use of probiotics.

Conclusion

Thus, despite the limitations in available studies, all the data consistently evidence involvement of intestinal dysbiosis in OA initiation and progression. Dysbiosis contributes to OA development, aggravates existing risk factors, such as obesity, metabolic syndrome and joint traumas, activates immune system, affects T-cells differentiation and system metabolism, and impairs normal interaction of the CNS and intestinal vegetative nervous system. The most probable linking mechanism between these two disorders is a common low-activity chronic inflammation. Although not specific for OA, a chronic systemic inflammatory reaction has an important role to play in disease development via persistent local inflammation in synovial membrane and catabolic reactions of cartilaginous cells resulting in articular cartilage degeneration (Fig. 1).

Healthy intestinal microbiota is fundamental for prevention of initiation and progression of a number of diseases, including OA. Intestinal microbiome profile may be used as a tool for forecasting and identification of potential disorders. Moreover, it can be expected that in the near future targeted manipulations with intestinal microbiome will become an integral part of osteoarthritis management. However, detailed mechanisms of the association between dysbiosis and OA are still unknown and require further exploration.

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Порядин Г.В. (ORCID ID: https://orcid.org/0000-0003-2010-3296): разработка концепции и дизайна, сбор, анализ и интерпретация данных, проверка критически важного интеллектуального содержания, утверждение окончательного варианта рукописи, автор согласен быть ответственным за все аспекты работы

Захватов А.Н. (ORCID ID: https://orcid.org/0000-0003-1433-0337): разработка концепции и дизайна, сбор, анализ и интерпретация данных, написание и редактирование текста рукописи, утверждение окончательного варианта рукописи, автор согласен быть ответственным за все аспекты работы

Захаркин И.А. (ORCID ID: https://orcid.org/0000-0001-7132-4887): сбор, анализ и интерпретация данных, написание и редактирование текста рукописи, утверждение окончательного варианта рукописи, автор согласен быть ответственным за все аспекты работы

Паршина А.Ю. (ORCID ID: https://orcid.org/0000-0003-0415-1132): сбор, анализ и интерпретация данных, написание и редактирование текста рукописи, утверждение окончательного варианта рукописи, автор согласен быть ответственным за все аспекты работы

Шаев А.А. (ORCID ID: https://orcid.org/0009-0007-5151-123X): сбор, анализ и интерпретация данных, написание и редактирование текста рукописи, утверждение окончательного варианта рукописи, автор согласен быть ответственным за все аспекты работы

Author Contribution:

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

Poryadin G.V. (ORCID ID: https://orcid.org/0000-0003-2010-3296): conception and design; verification of critical intellectual content, collection, analysis and interpretation of the data, edit of the submitted article, approval of the final version of the submitted article, the author agrees to be responsible for all aspects of the work

Zakhvatov A.N. (ORCID ID: https://orcid.org/0000-0003-1433-0337): conception and design; collection, analysis and interpretation of the data, edit of the submitted article, approval of the final version of the submitted article, the author agrees to be responsible for all aspects of the work

Zakharkin I.A. (ORCID ID: https://orcid.org/0000-0001-7132-4887): collection, analysis and interpretation of data, writing and editing of the text of the submitted article, approval of the final version of the submitted article, the author agrees to be responsible for all aspects of the work

Parshina A.Yu. (ORCID ID: https://orcid.org/0000-0003-0415-1132): collection, analysis and interpretation of data, writing and editing of the text of the submitted article, approval of the final version of the submitted article, the author agrees to be responsible for all aspects of the work.

Shaev A.A. (ORCID ID: https://orcid.org/0009-0007-5151-123X): collection, analysis and interpretation of data, writing and editing of the text of the submitted article, approval of the final version of the submitted article, the author agrees to be responsible for all aspects of the work

Список литература/References:

1. Safiri S, Kolahi AA, Smith E, et al. Global, Regional and National Burden of Osteoarthritis 1990-2017: A Systematic Analysis of the Global Burden of Disease Study 2017. Ann. Rheum. Dis. 2020; 79(6): 819–828. DOI: 10.1136/annrheumdis-2019-216515.
2. Zhao X., Shah D., Gandhi K., et al. Clinical, humanistic, and economic burden of osteoarthritis among noninstitutionalized adults in the United States. Osteoarthr Cartil. 2019; 27(11): 1618–1626. DOI: 10.1016/j.joca.2019.07.002.
3. Berenbaum F., Wallace I.J., Lieberman D.E., et al. Modern-day environmental factors in the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2018; 14(11): 674–681. DOI: 10.1038/s41584-018-0073-x.
4. Adak A, Khan MR. An insight into gut microbiota and its functionalities. Cell Mol Life Sci. 2019; 76(3): 473–493. DOI: 10.1007/s00018-018-2943-4.
5. Zhao Y, Chen B, Li S, et al. Detection and Characterization of Bacterial Nucleic Acids in Culture-Negative Synovial Tissue and Fluid Samples From Rheumatoid Arthritis or Osteoarthritis Patients. Sci. Rep. 2018; 8(1): 14305. DOI: 10.1038/s41598-018-32675-w.
6. Dunn CM, Velasco C, Rivas A, et al. Identification of Cartilage Microbial DNA Signatures and Associations With Knee and Hip Osteoarthritis. Arthritis Rheumatol. 2020; 72(7): 1111–1122. DOI: 10.1002/art.41210.
7. Rios JL, Bomhof MR, Reimer RA, et al. Protective effect of prebiotic and exercise intervention on knee health in a rat model of diet-induced obesity. Sci Rep. 2019;9(1):3893. DOI: 10.1038/s41598-019-40601-x.
8. Contartese D, Tschon M, De Mattei M, et al. Sex specific determinants in osteoarthritis: a systematic review of preclinical studies. Int J Mol Sci. 2020; 21(10): 3696. DOI: 10.3390/ijms21103696.
9. de Sire A, de Sire R, Petito V, et al. Gut-Joint Axis: The Role of Physical Exercise on Gut Microbiota Modulation in Older People With Osteoarthritis. Nutrients. 2020; 12(2): 574. DOI: 10.3390/nu12020574.
10. Урясьев О.М., Заигрова Н.К. Остеоартрит: патогенез, диагностика, лечение. Земский врач. 2016;1-2(29-30):27-35. Uryas'ev O.M., Zaigrova N.K. Osteoarthritis: pathogenesis, diagnosis, treatment. Zemsky doctor. 2016;1-2(29-30):27-35 [In Russian].
11. Mills S, Stanton C, Lane JA, et al. Precision Nutrition and the Microbiome, Part I: Current State of the Science. Nutrients. 2019; 11(4): 923. DOI: 10.3390/nu11040923.
12. Guss JD, Ziemian SN, Luna M, et al. The effects of metabolic syndrome, obesity, and the gut microbiome on load-induced osteoarthritis. Osteoarthr Cartil. 2019; 27(1): 129–139. DOI: 10.1016/j.joca.2018.07.020.
13. Terkawi M.A., Matsumae G., Shimizu T., et al. Interplay between Inflammation and Pathological Bone Resorption: Insights into Recent Mechanisms and Pathways in Related Diseases for Future Perspectives. Int. J. Mol. Sci. 2022; 23(3): 1786. DOI: 10.3390/ijms23031786.

14. Thomson A., Hilkens C.M.U. Synovial Macrophages in Osteoarthritis: The Key to Understanding Pathogenesis? Front. Immunol. 2021; 12: 678757. DOI: 10.3389/fimmu.2021.678757.
15. Lambert C., Zappia J., Sanchez C., et al. The Damage-Associated Molecular Patterns (DAMPs) as Potential Targets to Treat Osteoarthritis: Perspectives From a Review of the Literature. Front. Med. 2020; 7: 607186. DOI: 10.3389/fmed.2020.607186.
16. Larkin DJ, Kartchner JZ, Doxey AS, et al. Inflammatory markers associated with osteoarthritis after destabilization surgery in young mice with and without Receptor for Advanced Glycation End-products (RAGE). Front. Physiol. 2013; 4: 121. DOI: 10.3389/fphys.2013.00121.
17. Bosch M.H.J. Inflammation in osteoarthritis: Is it time to dampen the alarm(in) in this debilitating disease? Clin. Exp. Immunol. 2019; 195(2): 153–166. DOI: 10.1111/cei.13237.
18. Hwang H.S., Park S.J., Cheon E.J., et al. Fibronectin fragment-induced expression of matrix metalloproteinases is mediated by MyD88-dependent TLR-2 signaling pathway in human chondrocytes. Arthritis Res. Ther. 2015; 17: 320. DOI: 10.1186/s13075-015-0833-9.
19. Zhou Q., Zhu Z., Hu X., et al. HMGB1: A critical mediator for oxidized-low density lipoproteins induced atherosclerosis. Int. J. Cardiol. 2016; 202: 956–957. DOI: 10.1016/j.ijcard.2015.08.203.
20. Aulin C., Lassacher T., Palmblad K., et al. Early stage blockade of the alarmin HMGB1 reduces cartilage destruction in experimental OA. Osteoarthr. Cartil. 2020; 28 (5): 698–707. DOI: 10.1016/j.joca.2020.01.003.
21. Chen K., Jiao Y., Liu L., et al. Communications Between Bone Marrow Macrophages and Bone Cells in Bone Remodeling. Front. Cell Dev. Biol. 2020; 8: 598263. DOI: 10.3389/fcell.2020.598263.
22. Toh W.S., Brittberg M., Farr J., et al. Cellular senescence in aging and osteoarthritis. Acta Orthop. 2016; 87(363): 6–14. DOI: 10.1080/17453674.2016.1235087.
23. Biver E, Berenbaum F, Valdes AM, et al. Gut microbiota and osteoarthritis management: An expert consensus of the European society for clinical and economic aspects of osteoporosis, osteoarthritis and musculoskeletal diseases (ESCEO). Ageing Res Rev. 2019; 55: 100946. DOI: 10.1016/j.arr.2019.100946.
24. Liu Y, Ding W, Wang HL, et al. Gut Microbiota and Obesity-Associated Osteoarthritis. Osteoarthr. Cartil. 2019; 27(9): 1257–1265. DOI: 10.1016/j.joca.2019.05.009.
25. Ulici V, Kelley KL, Azcarate-Peril MA, et al. Osteoarthritis Induced by Destabilization of the Medial Meniscus Is Reduced in Germ-Free Mice. Osteoarthr. Cartil. 2018; 26(8): 1098–1109. DOI: 10.1016/j.joca.2018.05.016.
26. McAllister M.J., Chemaly M., Eakin A.J., et al. NLRP3 as a Potentially Novel Biomarker for the Management of Osteoarthritis. Osteoarthr. Cartil. 2018; 26(5): 612–619. DOI: 10.1016/j.joca.2018.02.901.
27. Rosenberg J.H., Rai V., Dilisio M.F., et al. Damage-associated molecular patterns in the pathogenesis of osteoarthritis: Potentially novel therapeutic targets. Mol. Cell. Biochem. 2017; 434: 171–179. DOI: 10.1007/s11010-017-3047-4.
28. Zhang H, Cai D, Bai X. Macrophages regulate the progression of osteoarthritis. Osteoarthr Cartil. 2020; 28(5): 555-561. DOI: 10.1016/j.joca.2020.01.007.
29. Lorenz W., Buhrmann C., Mobasheri A., et al. Bacterial Lipopolysaccharides Form Procollagen-Endotoxin Complexes That Trigger Cartilage Inflammation and Degeneration: Implications for the Development of Rheumatoid Arthritis. Arthritis Res. Ther. 2013; 15(5): 111. DOI: 10.1186/ar4291.
30. Huang Z., Kraus V.B. Does Lipopolysaccharide-Mediated Inflammation Have a Role in OA? Nat. Rev. Rheumatol. 2016; 12(2): 123–129. DOI: 10.1038/nrrheum.2015.158.
31. Zhao LR, Xing RL, Wang PM, et al. NLRP1 and NLRP3 Inflammasomes Mediate LPS/ATP–induced Pyroptosis in Knee Osteoarthritis. Mol. Med. Rep. 2018; 17(4): 5463–5469. DOI: 10.3892/mmr.2018.8520.
32. Woodell-May J.E., Sommerfeld S.D. Role of Inflammation and the Immune System in the Progression of Osteoarthritis. J. Orthop Res. 2020; 38(2): 253–257. DOI: 10.1002/jor.24457.
33. Hao F, Tian M, Zhang X, et al. Butyrate Enhances CPT1A Activity to Promote Fatty Acid Oxidation and iTreg Differentiation. Proc. Natl. Acad. Sci. USA 2021; 118(22): 2014681118. DOI: 10.1073/pnas.2014681118.
34. Murugesan S., Nirmalkar K., Hoyo-Vadillo C., et al. Gut microbiome production of short-chain fatty acids and obesity in children. Eur. J. Clin. Microbiol. Infect. Dis. 2018; 37: 621-625. DOI: 10.1007/s10096-017-3143-0.
35. Zeddou M. Osteoarthritis Is a Low-Grade Inflammatory Disease: Obesity's Involvement and Herbal Treatment. Evid Based Complement Alternat Med. 2019: 2037484. DOI: 10.1155/2019/2037484.
36. Xiong H., Li W., Ke J., et al. Leptin Levels in the Synovial Fluid of Patients With Temporomandibular Disorders. J. Oral. Maxillofac. Surg. 2019; 77(3): 493–498. DOI: 10.1016/j.joms.2018.09.012.
37. Rodríguez-Carrio J, Salazar N, Margolles A, et al. Free Fatty Acids Profiles Are Related to Gut Microbiota Signatures and Short-Chain Fatty Acids. Front. Immunol. 2017; 8: 823. DOI: 10.3389/fimmu.2017.00823.
38. Kim S., Hwang J., Kim J., et al. Metabolite Profiles of Synovial Fluid Change With the Radiographic Severity of Knee Osteoarthritis. Joint Bone Spine. 2017; 84(5): 605–610. DOI: 10.1016/j.jbspin.2016.05.018.

39. Koeth RA, Lam-Galvez BR, Kirsop J, et al. L-Carnitine in Omnivorous Diets Induces an Atherogenic Gut Microbial Pathway in Humans. J. Clin. Invest. 2019; 129(1): 373–387. DOI: 10.1172/jci94601.
40. Canyelles M., Tondo M., Cedó L., et al. Trimethylamine N-Oxide: A Link Among Diet, Gut Microbiota, Gene Regulation of Liver and Intestine Cholesterol Homeostasis and HDL Function. Int. J. Mol. Sci. 2018; 19(10): 3228. DOI: 10.3390/ijms19103228.
41. Ohlsson C., Nigro G., Boneca I.G., et al. Regulation of Bone Mass by the Gut Microbiota Is Dependent on NOD1 and NOD2 Signaling. Cell Immunol. 2017; 317: 55–58. DOI: 10.1016/j.cellimm.2017.05.003.
42. Caputi V., Giron M.C. Microbiome-Gut-Brain Axis and Toll-Like Receptors in Parkinson's Disease. Int. J. Mol. Sci. 2018; 19(6): 1689. DOI: 10.3390/ijms19061689.
43. Morris JL, Letson HL, Gillman R, et al. The CNS Theory of Osteoarthritis: Opportunities Beyond the Joint. Semin. Arthritis Rheum. 2019; 49(3): 331–336. DOI: 10.1016/j.semarthrit.2019.03.008.
44. Pan T.T., Pan F., Gao W., et al. Involvement of Macrophages and Spinal Microglia in Osteoarthritis Pain. Curr. Rheumatol. Rep. 2021; 23(5): 29. DOI: 10.1007/s11926-021-00997-w.
45. Erny D, Dokalis N, Mezö C, et al. Microbiota-Derived Acetate Enables the Metabolic Fitness of the Brain Innate Immune System During Health and Disease. Cell Metab. 2021; 33(11): 2260–2276. DOI: 10.1016/j.cmet.2021.10.010.
46. Lorenzo D, GianVincenzo Z, Carlo Luca R, et al. Oral-Gut Microbiota and Arthritis: Is There an Evidence-Based Axis? J. Clin. Med. 2019; 8(10): 0. DOI: 10.3390/jcm8101753.
47. Kalinkovich A., Livshits G. A Cross Talk Between Dysbiosis and Gut-Associated Immune System Governs the Development of Inflammatory Arthropathies. Semin. Arthritis Rheum. 2019; 49(3): 474–484. DOI: 10.1016/j.semarthrit.2019.05.007.
48. O-Sullivan I, Natarajan Anbazhagan A, Singh G, et al. Lactobacillus acidophilus Mitigates Osteoarthritis-Associated Pain, Cartilage Disintegration and Gut Microbiota Dysbiosis in an Experimental Murine OA Model. Biomedicines. 2022; 10(6): 1298. DOI: 10.3390/biomedicines10061298.