Received: 29 March 2022 / Accepted: 15 August 2022 / Published online: 31 August 2022

DOI 10.34689/SH.2022.24.4.018

UDC 616.34-07:616.8-071

THE ROLE OF THE INTESTINAL MICROBIOTA IN THE DEVELOPMENT OF AUTOIMMUNE RHEUMATIC DISEASES

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Abstract

Introduction: The gut microbiota plays an important role in developing rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and others rheumatic diseases. Its studies promote new opportunities for improving the early diagnosis, and possibly the prevention of severe autoimmune rheumatic diseases, as well as correcting the tactics of a personalized approach to treatment.

Aim: This review evaluates the relevant information on the relationship between changes in the microbiota and the development of rheumatic diseases in children and adults.

Search strategy: Literature search was carried out using PubMed (Medline), Scopus databases, eLibrary.ru, Google Scholar by keywords: “gut microbiome”, “microbiota”, “rheumatoid arthritis”, “rheumatic diseases”, “spondyloarthropathies”. The search depth is 20 years (2000-2021). The original language is English. *Inclusion criteria*: reports of randomized and cohort studies conducted on large populations, meta-analyses and systematic reviews. *Exclusion criteria*: articles describing single cases, series of cases, as well as experimental work on animals. Out of 113 literary sources, 78 were selected as analytical material for this article.

Summary: Analysis of the sources showed that the conducted studies revealed deviations in the diversity of intestinal microflora in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis. The main attention was paid to cataloging the microorganisms present, identifying the relationship between microbial species and diseases. Differences in the composition of the microbiota in children and adults have been established. Currently, the relationship of various factors, such as gender, age, race, living conditions, geographical location, remains not completely explored. However, there are no long-term studies with the collection of samples of the intestinal microbiome in several time intervals: before and after the appointment of basic anti-inflammatory therapy, against the background of ineffective therapy, as well as tracking the relationship with the nature of the course, the activity of the disease or the intensity of symptoms.

Key words: *gut microbiome, microbiota, rheumatoid arthritis, rheumatic diseases, spondyloarthropathies.*

Резюме

РОЛЬ КИШЕЧНОЙ МИКРОБИОТЫ В РАЗВИТИИ АУТОИММУННЫХ РЕВМАТИЧЕСКИХ ЗАБОЛЕВАНИЙ

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Введение. Микробиота кишечника играет важную роль в развитии ревматоидного артрита (РА), анкилозирующего спондилита (АС), псориатического артрита (ПсА), ювенильного идиопатического артрита (ЮИА) и других ревматических заболеваний. Исследование микробиоты открывают новые возможности для улучшения ранней диагностики, а возможно и профилактики тяжелых аутоиммунных ревматических заболеваний, а также коррекции тактики персонализированного подхода к лечению.

Цель: В этом обзоре оценивается актуальная информация о взаимосвязи между изменениями микробиоты и развитием ревматических заболеваний у детей и взрослых.

Стратегия поиска: Поиск литературы осуществлялся с использованием баз данных PubMed (Medline), Scopus, eLibrary.ru, Google Scholar, по ключевым словам, «микробиом кишечника», «микробиота», «ревматоидный артрит», «ревматические заболевания», «спондилоартропатии». Глубина поиска 20 лет (2000-2021). Язык оригинала английский. *Критерии включения*: отчеты о рандомизированных и когортных исследованиях, проведенных на больших популяциях, мета-анализы и систематические обзоры. *Критерии исключения:* статьи, описывающие единичные случаи, серии случаев, а также экспериментальные работы на животных. Из 113 литературных источников в качестве аналитического материала для данной статьи были отобраны 78.

Выводы: Анализ источников показал, что проведенные исследования выявили отклонения в разнообразии кишечной микрофлоры у больных ревматоидным артритом, анкилозирующим спондилитом, псориатическим артритом. Основное внимание уделялось каталогизации присутствующих микроорганизмов, выявлению связи между видами микробов и болезнями. Установлены различия в составе микробиоты у детей и взрослых. В настоящее время взаимосвязь различных факторов, таких как пол, возраст, раса, условия жизни, географическое положение, остается не до конца изученной. Однако отсутствуют длительные исследования со сбором образцов кишечного микробиома в несколько временных интервалов: до и после назначения базисной противовоспалительной терапии, на фоне неэффективной терапии, а также отслеживание связи с характером течения, активности заболевания или интенсивности симптомов.

Ключевые слова: *микробиом кишечника, микробиота, ревматоидный артрит, ревматические заболевания, спондилоартропатии.*

Түйіндеме

АУТОИММУНДЫ РЕВМАТИКАЛЫҚ АУРУЛАРДЫҢ ДАМУЫНДА ІШЕК МИКРОБИОТАСЫНЫҢ РӨЛІ

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Кіріспе: Ішек микробиотасы ревматоидты артрит (РА), анкилоздаушы спондилит (АС), псориатикалық артрит (ПСА), ювенильді идиопатиялық артрит (ЮИА) және басқа ревматикалық аурулардың дамуында маңызды рөл атқарады. Микробиотаны зерттеу ерте диагностиканы жақсартуға және мүмкін, ауыр аутоиммунды ревматикалық аурулардың алдын алуға, сондай-ақ емдеудің персонизирленген тактикасын жақсартуға жаңа мүмкіндіктер ашады.

Мақсаты: Бұл шолуда балалар мен ересектердегі микробиотаның өзгерістері мен ревматикалық аурулардың дамуы арасындағы байланыс туралы ағымдағы ақпарат бағаланады.

Іздеу стратегиясы: Әдебиеттерді іздеу PubMed (Medline), Scopus, eLibrary.ru, Google Scholar мәліметтер базасы арқылы «ішек микробиомы», «микробиота», «ревматоидты артрит», «ревматикалық аурулар», «спондилоартропатиялар» түйінді сөздерін қолдану арқылы жүргізілді. Іздеу тереңдігі 20 жыл (2000-2021). Түпнұсқа тілі – ағылшын тілі. Енгізу критерийлері: үлкен популяцияларда жүргізілген рандомизацияланған және когорттық зерттеулердің есептері, мета-талдаулар және жүйелі шолулар. Алып тастау критерийлері: жеке жағдайларды,

жағдайлар сериясын және жануарларға эксперименталды жұмысты сипаттайтын мақалалар. 113 әдеби дереккөздің 78-і осы мақалаға аналитикалық материал ретінде таңдалып алынды.

Қорытынды: Дереккөздерді талдау нәтижесінде, жүргізілген зерттеулер ревматоидты артритпен, анкилоздаушы спондилитпен, псориатикалық артритпен ауыратын науқастарда ішек микрофлорасының әртүрлілігінде ауытқулар анықталғанын көрсетті. Негізгі назар қазіргі микроорганизмдерді каталогтауға, микроб түрлері мен аурулар арасындағы байланысты анықтауға аударылды. Балалар мен ересектер микробиотасының құрамындағы айырмашылықтар анықталды. Қазіргі уақытта жыныс, жас, нәсіл, өмір сүру жағдайы, географиялық орны сияқты әртүрлі факторлардың өзара байланысы әлі толық зерттелмеген. Дегенмен, негізгі қабынуға қарсы терапияны тағайындағанға дейін және кейін, тиімсіз терапия фонында, сондай-ақ ішек микробиотасының байланысын бақылау, ауру ағымының сипаты, белсенділігі немесе симптомдардың қарқындылығын бірнеше уақыт аралықтарында ішек микробиотасының үлгілерін жинайтын ұзақ мерзімді зерттеулер жоқ.

Түйінді сөздер: *ішек микробиомы, микробиота, ревматоидты артрит, ревматикалық аурулар, спондилоартропатиялар.*

Bibliographic citation:

Petrova Yu.V., Ivanova R.L., Tugelbayeva A.M., Zonova E.V., Lobanov Yu. F., Goremykina M.V. The role of the intestinal microbiota in the development of autoimmune rheumatic diseases // Nauka i Zdravookhranenie [Science & Healthcare]. 2022, (Vol.24) 4, pp. 137-145. doi 10.34689/SH.2022.24.4.018

Петрова Ю.В., Иванова Р.Л., Тугелбаева А.М., Зонова Е.В., Лобанов Ю.Ф., Горемыкина М.В. Роль кишечной микробиоты в развитии аутоиммунных ревматических заболеваний // Наука и Здравоохранение. 2022. 4(Т.24). С. 137-145. *doi 10.34689/SH.2022.24.4.018*

Петрова Ю.В., Иванова Р.Л., Тугелбаева А.М., Зонова Е.В., Лобанов Ю.Ф., Горемыкина М.В. Аутоиммунды ревматикалық аурулардың дамуында ішек микробиотасының рөлі // Ғылым және Денсаулық сақтау. 2022. 4 (Т.24). Б. 137-145. doi 10.34689/SH.2022.24.4.018

Introduction

The group of autoimmune rheumatic diseases is characterized by increasing prevalence, chronic course and steady progression. They significantly reduce the overall functional status, working capacity and quality of life of sick people, which determines the great medical and socio-economic significance of this pathology [77, 66, 50]. Immunological shifts that occur under the influence of a variety of endogenous and exogenous factors play an important role in the pathogenesis of these diseases [50, 73, 27, 32]. To date, the diagnosis of autoimmune rheumatic diseases is based on the determination of various immunological indicators, which do not always provide diagnosis at preclinical and early clinical stages of the disease [23, 53, 52, 40]. At the same time, new drugs used in rheumatology have the greatest effect when they are prescribed early [43, 6]. In this regard, at the moment, there is a need for more informative, specific, and also available for everyday practice methods that allow for early diagnosis and evaluation of the effectiveness of therapy

In the last decade, a hypothesis has emerged about the connection of systemic autoimmune reactions with a violation of the regulation of immune interactions with the synanthropic intestinal microflora [27, 32, 5, 36, 38]. Using the sequencing method, deviations in the diversity of microflora were studied in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA). Most studies are descriptive in nature, and the mechanisms of interaction between the microbiome and the human body are still poorly understood. In the future, it is necessary to study more closely the components of the microbiota and not just their description. Such studies will contribute to the development of new diagnostic and possibly therapeutic interventions [49, 75, 76].

Aim: to review relevant sources on the relationship between changes in the microbiota and the development of rheumatic diseases.

Search strategy. Literature search was carried out using PubMed (Medline), Scopus databases, eLibrary.ru, Google Scholar by keywords: “gut microbiome”, “microbiota”, “rheumatoid arthritis”, “rheumatic diseases”, “spondyloarthropathies”. The search depth is 20 years (2000-2021). The original language is English. *Inclusion criteria*: reports of randomized and cohort studies conducted on large populations, meta-analyses and systematic reviews. *Exclusion criteria*: articles describing single cases, series of cases, as well as experimental work on animals. Out of 113 literary sources, 78 were selected as analytical material for this article.

Microbiome and its metabolites are normal and pathological.

Microbiota is a term that is used to characterize the microbiocenosis of individual organs and systems (intestines, skin, placenta, breast milk, etc.), genetic material and relationships within an ecological niche in a certain period of time in a certain geographical area. The human microbiota includes obligate pathogens that are constantly present in the human body and play an important role in the metabolism of the host and its protection from pathogens of infectious diseases. The second component of the normal microflora is the transient microflora (allochthonous, random). The microbiome performs many important functions in the human body, such as: creation of colonization resistance; production of enzymes involved in

the metabolism of proteins, carbohydrates, lipids; production of biologically active compounds; participation in water-salt metabolism; detoxification of exogenous and endogenous substrates and metabolites, immunogenic function and much more. In turn, the composition of microflora and reproduction of its representatives are controlled by the macroorganism and can change under the influence of endogenous and exogenous factors. [66, 50, 29, 24]. The main factors affecting the composition of the microbiome: the method of birth (natural, caesarean section) and the method of feeding (breast or artificial), living conditions, diet, age-related changes, the use of medications, in particular antibiotics [35, 39, 78, 74, 30, 46]. The state of dysbiosis leads to a violation of the functions of the microflora, which in turn contributes to the development of autoimmune disorders, most clearly manifested in inflammatory bowel diseases, systemic lupus erythematosus, multiple sclerosis and various inflammatory arthritis. [25, 34, 67, 26, 56, 9].

Rheumatoid arthritis.

Rheumatoid arthritis (RA) is the most severe form of autoimmune rheumatic diseases, which is characterized by severe erosive arthritis and multiple lesions of internal organs. The disease develops in individuals with a genetic predisposition under the influence of various environmental factors and is accompanied by a global violation in the system of humoral and cellular immunity. [11, 27, 8] It has long been known that the human intestine is the largest springboard of the immune system, changes in which can serve as a source of disorders in the human body. Currently, there is a growing body of evidence that RA patients have significant changes in the composition and function of the microbiota of the mucous membranes of the gastrointestinal tract.

Already early studies between the 1970s and 2000s have already shown quantitative changes in specific bacterial species in patients with RA who had not previously received anti-rheumatic drugs, including Clostridium perfringens (Olhagen and Månsson, 1968), genera Bacteroides, Prevotella and Porphyromonas (*Eerola et al., 1994; Toivanen et al., 2002; Vaakhtovuo et al., 2008*). With the advent of genome-wide sequencing technologies, new opportunities have emerged in the study of genetic associations with rheumatic diseases. After 2010, several studies using 16S RNA/DNA sequencing technology demonstrated a relatively increased amount of Prevotella copri in family members of patients with rheumatoid arthritis and in patients with early RA compared to healthy people in the control group [55, 37, 36, 3]. Interestingly, in patients at late stages, as well as those receiving basic methotrexate therapy, *P. Copri* increases are observed much less frequently in comparison with early stage [55, 14, 28]. *Maeda and coauthors* suggested that P. copri may carry an epitope providing cross-reactivity with autoantigens associated with arthritis [37]. Later, a group of scientists, in peripheral blood, isolated mononuclear cells from patients with newly diagnosed RA, identified HLA-DR-presented peptide from the 27-KD protein P. copri (Pc-p27). A group of patients (42%) with both newly identified and established chronic forms of RA was identified, in whom IgA against Pc-p27 was detected, the content of which positively correlated with the level of cytokines Th17 and cyclic citrullinated peptide antibodies (anti-CCP). The remaining patients synthesized IgG against P. copri, which was associated with Prevotella copri DNA in synovial fluid, a specific Th1 immune response and a lower concentration of anti-CCP. Interestingly, the production of antibodies to P. copri is rare in patients with other rheumatic diseases or in healthy people, which indicates that the immune response to P. copri is RA-specific [36, 48, 19].

Chen and co-authors in the study of feces revealed a decrease in intestinal microbial diversity in RA patients compared to healthy people, due to the duration of the disease and the level of autoantibodies. The same authors revealed the prevalence of three types of pathogens, such as Collinsella, Eggerthella and Faecalibacterium in patients with advanced, late stages of the disease. [12]. At the same time, the abundance of Collinsella had a strong correlation with high levels of alpha-aminoadipic acid and asparagine, as well as with the production of the pro-inflammatory cytokine IL17A. In addition, the Collinsella species was found in more severe forms of the disease [20].

Other studies in China found slightly different data. [33, 63, 13]. Patients with RA had more types of fecal Lactobacillus than healthy people from the control group and a decrease in the number of species of Haemophilus, Faecalibacterium. Apparently, there are differences in the composition of the microbiota due to geographical location, but reliable data confirming this assumption could not be found. [31, 51]. In addition, *Zhang X.* with co-authors using the "shotgun sequencing" method and the metagenome-wide association study (MGWAS) found that taking methotrexate in standard doses contributes to an increase in the species richness and diversity of the intestinal microbiota in patients with RA [76]. Other study, in Brazil, estimates the influence of specific DMARDs on gut microbiota composition and suggests the possible role of gut microbes and their metabolites' in response to DMARDs [51].

Spondyloarthropathies.

Spondyloarthropathies (SpA) are chronic inflammatory diseases with progressive disability, the prevalence of which ranges from 0% to 1.5-2%. [7]. This group includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), AS associated with inflammatory bowel disease (IBD) (also known as enteropathic arthritis), acute anterior uveitis and the recently studied axial non-radiographic AS

In a number of studies using the sequencing method, changes in the levels of specific organisms and the diversity of intestinal microflora were revealed in patients with AS, PsA, psoriasis and IBD with extra-intestinal manifestations [7, 22, 16, 15]. The effect of dysbiosis on the development of the disease is most clearly demonstrated in IBD, however, it is noteworthy that antibodies to the molecular component of bacterial surface membranes of flagellin (CBIR-1) are associated not only with small intestine damage in Crohn's disease [36], but also with the enteropathic variant of SpA, and are also determined in some patients with AS even in the absence of clinical intestinal damage [59]. The composition of the intestinal microflora in patients with the classical variant of AS, in contrast to a healthy population, is characterized by dysbiosis with an increase in the number of bacteria of five

families: Lachnospiraceae, Ruminococcaceae, Rikenellaceae, Porphyromonadaceae and Bacteroidaceae and a decrease in the representation of bacteria of the genus Veilonellaceae and Prevotellaceae [15]. Currently, there is no convincing evidence of the role of specific bacteria (Klebsiella pneumoniae, Bacteroides vulgatus) in the pathogenesis of AS [59, 62, 60]. The data obtained are very contradictory and call into question the classical model of studying the role of microorganisms: "one microbe is one disease." A similar situation is observed in PsA and psoriasis. Recent studies have shown that in patients with psoriasis, the biodiversity in healthy areas of the skin is greater than in the affected areas. It was found that the number of Streptococcus and Propionibacterium increased in psoriasis foci [22]. With PsA, as with cutaneous psoriasis, the intestinal microflora was less diverse than in a healthy population. However, only patients with PsA had features characteristic of patients with IBD. The revealed intestinal dysbiosis was associated with a reduced content of bacteria of three families: Akkermansia, Ruminococcus and Pseudobutyrivibrio [22].

Children.

Childhood is a crucial period of life for the development and evolution of the gut microbiota, especially for the formation and acquisition of such fundamental functions as immunotolerance to commensal microorganisms [17]. It is noteworthy that the microbiota of a 3-year-old child is 40-60% similar to the microbiota of a healthy adult and the microbial composition in adolescence is comparable to the microbiota of an adult [47].

Several studies in young children have shown that artificial feeding is associated with an increased risk of autoimmune diseases such as ankylosing spondylitis (AS) [39]. At the same time, breastfeeding, as shown by other studies involving children with juvenile idiopathic arthritis (JIA) and healthy subjects, appears to protect against JIA [30]. Reliable data indicate changes in the composition of the fecal microbiota in children with JIA in several studies [1, 70, 44].

A recent study compared the composition of the fecal microbiota of JIA patients with a healthy control group and assessed the differences in microbial profiles between the subcategories of JIA, such as enthesitis-related arthritis (ERA) and polyarticular JIA, non-enthesitis related arthritis (nERA). Indeed, taxon-level analysis has shown that changes in the components of the fecal microbiota may be involved in subclinical intestinal inflammation and contribute to joint inflammation. In the ERA group there was a decrease in the number of Clostridiaceae and Peptostreptococcaceae, and in the nERA group there was an increase in the number of Veillonellaceae compared to the control group. The abundance of Ruminococcaceae was observed in both categories compared to healthy children [18].

Stoll and colleagues studied a group of 30 patients with ERA and 19 healthy children, as well as 11 patients with spondyloarthritis (SpA) and 10 healthy adults. The only two taxa with statistically significant differences in favor of control were the genus Faecalibacterium and Lachnospiraceae, while Bifidobacterium showed a moderate but statistically significant increase. A decrease in F. prausnitzii A2-165 strain levels was confirmed in patients with ERA, and similar trends were observed in adult patients with SpA. Thus, it can be assumed that depletion of F. prausnitzii may play a role in the pathogenesis of ERA and SpA [61, 65, 72, 21]. This finding of a decrease in the number of F. prausnitzii is consistent with previous findings in both children and adults with IBD [10]. It should be noted that it is still unclear why some subjects develop ReA after an infection, while others do not [57].

Actually, Manasson with coauthors, studied the intestinal microbiota in two groups of patients undergoing infection: one group with subsequent development of ReA, and the second group infection without ReA. They found that in the first group, the number of Erwinia and Pseudomonas, as well as Salmonella, Shigella and Campylobacter were significantly higher in ReA than in the second group, who did not develop arthritis. It was also found that patients with ReA have a low content of commensals in the intestinal microbiota compared to the control group. ReA subjects had a statistically significant higher content of Erwinia and Pseudomonas, two knowns intestinal enteropathogens. This result contrasted with the control group, where the relative abundance of several genera, most of which were considered commensals, was increased, including Blautia, Coprococcus, Roseburia and Collinsella [38].

A more in-depth analysis conducted by Verma and coauthors, showed that detailed identification of the ways of interaction of the microbiota with the body can allow predicting the possible development of autoimmune pathology in individuals with ReA and IBD. The results obtained are consistent with the previous studies described above [38, 71].

It should be noted that the literature does not pay enough attention to connective tissue dysplasia (CTD) as one of the risk factors for the development of pathology of the musculoskeletal system. Despite the fact that disputes over the definition and classification of the disease still persist, few researchers have been actively studying this problem in the last decade [64, 42, 41]. It is proved that the majority of children with musculoskeletal system pathology, including arthropathies of various genesis, have symptoms of CTD, which is due to the peculiarities of the anatomical and histological structure of the musculoskeletal system, represented mainly by elements of connective tissue [54, 4, 45]. The data indicate the connection of the pathology of the musculoskeletal system with the microbiota, in particular, with yeast fungi possessing a set of enzymes (hyaluronidase, chondroitin-sulfatase) that destroy connective tissue, affecting laminin, fibronectin, fibrinogen, type 4 collagen [58, 2, 69].

Conclusion

Analysis of the sources showed that the conducted studies revealed deviations in the diversity of intestinal microflora in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis. The main attention was paid to cataloging the microorganisms present, identifying the relationship between microbial species and diseases. However, there are no long-term studies with the collection of samples of the intestinal microbiome in several time intervals: before the appointment of basic anti-inflammatory therapy, against the background of ineffective therapy, as well as tracking the relationship with the nature of the

course, the activity of the disease or the intensity of symptoms, which can help in determining the causal relationship between the characteristics of the microbiome and the course of the disease [8, 55, 14, 20, 47]. Differences in the composition of the microbiota in children and adults have been established. Currently, the relationship of various factors, such as gender, age, race, living conditions, geographical location, remains unexplored [67, 48, 12, 70, 44]. All of the above justifies the need for further study within the framework of the concept of "barrier organ disease" of the mechanisms of communication of immune disorders with the composition of synatropic microflora. Such studies open up new opportunities for improving the early diagnosis, and possibly the prevention of severe autoimmune rheumatic diseases, as well as correcting the tactics of a personalized approach to treatment.

Ethics declarations

Authors' contribution and conflict of interest: *the authors equally participated in the writing of the article and declare the absence of a conflict of interest. The authors state that none of the blocks of this article has been published in the open press and is not under consideration by other publishers.*

Human and Animal Rights and Informed Consent: *This article does not contain any studies with human or animal subjects performed by any of the authors.*

Funding: *No funding was received to assist with the preparation of this manuscript.*

References:

1. *Aggarwal A., Sarangi A. N., Gaur P., Shukla A., Aggarwal R.* Gut microbiome in children with enthesitis-related arthritis in a developing country and the effect of probiotic administration // Clinical and Experimental Immunology. - 2017. - Vol.187, № 3. - P. 480-489.

2. *Alonso R., Llopis I., Flores C., Murgui A., Timoneda J.* Different adhesins for type IV collagen on Candida albicans: identification of a lectin-like adhesin recognizing the 7S(IV) domain // Microbiology-Sgm. - 2001. - Vol.147. - P. 1971-1981.

3. *Alpizar-Rodriguez D., Lesker T.R., Gronow A., Gilbert B., Raemy E., Lamacchia C., Gabay C., Finckh A., Strowig T.* Prevotella copri in individuals at risk for rheumatoid arthritis // Annals of the Rheumatic Diseases. - 2019. - Vol.78, № 5. - P. 590-593.

4. *Bascom R., Schubart J.R., Mills S., Smith T., Zukley L.M., Francomano C.A., McDonnell N.* Heritable disorders of connective tissue: Description of a data repository and initial cohort characterization // American Journal of Medical Genetics Part A. - 2019. - Vol. 179, № 4. - P. 552-560.

5. *Belkaid Y., Hand T.W.* Role of the Microbiota in Immunity and Inflammation // Cell. - 2014. - Vol. 157, № 1. - P. 121-141.

6. *Bergstra S.A., VanDer Pol J.A., Riyazi N., Goekoop-Ruiterman Y.P., Kerstens P., Lems W., Huizinga T.W., Allaart C.F.* Earlier is better when treating rheumatoid arthritis: but can we detect a window of opportunity? // Rmd Open. - 2020. - Vol. 6, № 1. - P. 9.

7. *Breban M., Tap J., Leboime A., Said-Nahal R., Langella P., Chiocchia G., Furet J.P., Sokol H.* Faecal microbiota study reveals specific dysbiosis in spondyloarthritis // Annals of the Rheumatic Diseases. - 2017. - Vol. 76, № 9. - P 1614-1622.

8. *Brusca S.B., Abramson S.B., Scher J.U.* Microbiome and mucosal inflammation as extra-articular triggers for rheumatoid arthritis and autoimmunity // Current Opinion in Rheumatology. - 2014. - Vol. 26, № 1. - P. 101-107.

9. *Caminer A.C., Haberman R., Scher J.U.* Human microbiome, infections, and rheumatic disease // Clinical Rheumatology. - 2017. - Vol. 36, № 12. - P. 2645-2653.

10. *Cao Y., Shen J., Ran Z.H.* Association between Faecalibacterium prausnitzii Reduction and Inflammatory Bowel Disease: A Meta-Analysis and Systematic Review of the Literature // Gastroenterology Research and Practice. - 2014. - Vol. 2014. - P. 7.

11. *Catrina A.I., Joshua V., Klareskog L., Malmstrom V.* Mechanisms involved in triggering rheumatoid arthritis // Immunological Reviews. - 2016. - Vol. 269, № 1. - P. 162-174.

12. *Chen J., Wright K., Davis J. M., Jeraldo P., Marietta E.V., Murray J., Nelson H., Matteson E.L., Taneja V.* An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis // Genome Medicine. - 2016. - Vol. 8. - P. 14.

13. *Chiang H.I., Li J.R., Liu C.C., Liu P.Y., Chen H.H., Chen Y.M., Lan J.L., Chen D.Y.* An Association of Gut Microbiota with Different Phenotypes in Chinese Patients with Rheumatoid Arthritis // Journal of Clinical Medicine. - 2019. - Vol. 8, № 11. - P. 18.

14. *Chu X.J., Cao N.W., Zhou H.Y., Meng X., Guo B., Zhang H.Y., Li B.Z.* The oral and gut microbiome in rheumatoid arthritis patients: a systematic review // Rheumatology. - 2021. - Vol. 60, № 3. - P. 1054-1066.

15. *Costello M.E., Ciccia F., Willner D., Warrington N., Robinson P.C., Gardiner B., Marshall M., Kenna T.J., Triolo G., Brown M.A.* Intestinal Dysbiosis in Ankylosing Spondylitis // Arthritis & Rheumatology. - 2015. - Vol. 67, № 3. - P. 686-691.

16. *Costello M.E., Robinson P.C., Benham H., Brown M.A.* The intestinal microbiome in human disease and how it relates to arthritis and spondyloarthritis // Best Practice & Research in Clinical Rheumatology. - 2015. - Vol. 29, № 2. - P. 202-212.

17. *De Filippo C., Di Paola M., Giani T., Tirelli F., Cimaz R.* Gut microbiota in children and altered profiles in juvenile idiopathic arthritis // Journal of Autoimmunity. - 2019. - Vol. 98. - P. 1-12.

18. *Di Paola M., Cavalieri D., Albanese D., Sordo M., Pindo M., Donati C., Pagnini I., Giani T., Simonini G., Paladini A., Lionetti P., De Filippo C., Cimaz R.* Alteration of Fecal Microbiota Profiles in Juvenile Idiopathic Arthritis. Associations with HLA-B27 Allele and Disease Status // Frontiers in Microbiology. - 2016. - Vol. 7. - P. 13.

19. *Duvallet C., Gibbons S. M., Gurry T., Irizarry R.A., Alm E.J.* Meta-analysis of gut microbiome studies identifies disease-specific and shared responses // Nature Communications. - 2017. - Vol. 8. - P. 10.

20. *Forbes J.D., Van Domselaar G., Bernstein C.N.* The Gut Microbiota in Immune-Mediated Inflammatory Diseases // Frontiers in Microbiology. - 2016. - Vol. 7. - P. 18.

21. *Frank D.N., Amand A.L.S., Feldman R.A., Boedeker E.C., Harpaz N., Pace N.R.* Molecular-phylogenetic characterization of microbial community imbalances in

human inflammatory bowel diseases // Proceedings of the National Academy of Sciences of the United States of America. - 2007. - Vol. 104, № 34. - P. 13780-13785.

22. *Gao Z., Tseng C.H., Strober B.E., Pei Z.H., Blaser M.J.* Substantial Alterations of the Cutaneous Bacterial Biota in Psoriatic Lesions // Plos One. - 2008. - Vol. 3, № 7. - P. 9.

23. *Goh C.E., Kopp J., Papapanou P.N., Molitor J.A., Demmer R.T.* Association Between Serum Antibodies to Periodontal Bacteria and Rheumatoid Factor in the Third National Health and Nutrition Examination Survey // Arthritis & Rheumatology. - 2016. - Vol. 68, № 10. - P. 2384-2393.

24. *Goodrich J.K., Waters J.L., Poole A.C., Sutter J.L., Koren O., Blekhman R., Beaumont M., Van Treuren W., Knight R., Bell J.T., Spector T.D., Clark A.G., Ley R.E.* Human Genetics Shape the Gut Microbiome // Cell. - 2014. - Vol. 159, № 4. - P. 789-799.

25. *Hansen J., Gulati A., Sartor R.B.* The role of mucosal immunity and host genetics in defining intestinal commensal bacteria // Current Opinion in Gastroenterology. - 2010. - Vol. 26, № 6. - P. 564-571.

26. *Honda K., Littman D.R.* The microbiota in adaptive immune homeostasis and disease // Nature. - 2016. - Vol. 535, № 7610. - P. 75-84.

27. *Horta-Baas G., Romero-Figueroa M.D., Montiel-Jarquin A.J., Pizano-Zarate M.L., Garcia-Mena J., Ramirez-Duran N.* Intestinal Dysbiosis and Rheumatoid Arthritis: A Link between Gut Microbiota and the Pathogenesis of Rheumatoid Arthritis // Journal of Immunology Research. - 2017. - Vol. 2017. – P. 13.

28. *Jeong Y., Kim J. W., You H.J., Park S.J., Lee J., Ju J.H., Park M.S., Jin H., Cho M.L., Kwon B., Park S.H., Ji G.E.* Gut Microbial Composition and Function Are Altered in Patients with Early Rheumatoid Arthritis // Journal of Clinical Medicine. - 2019. - Vol. 8, № 5. - P. 10.

29. *Kim D., Zeng M.Y., Nunez G.* The interplay between host immune cells and gut microbiota in chronic inflammatory diseases // Experimental and Molecular Medicine. - 2017. - Vol. 49. - P. 11.

30. *Kindgren E., Fredrikson M., Ludvigsson J.* Early feeding and risk of Juvenile idiopathic arthritis: a case control study in a prospective birth cohort // Pediatric Rheumatology. - 2017. -Vol.15. - P. 9.

31. *Kishikawa T., Maeda Y., Nii T., Motooka D., Matsumoto Y., Matsushita M., Matsuoka H., Yoshimura M., Kawada S., Teshigawara S., Oguro E., Okita Y., Kawamoto K., Higa S., Hirano T., Narazaki M., Ogata A., Saeki Y., Nakamura S., Inohara H., Kumanogoh A., Takeda K., Okada Y.* Metagenome-wide association study of gut microbiome revealed novel aetiology of rheumatoid arthritis in the Japanese population // Annals of the Rheumatic Diseases. - 2020. - Vol. 79, № 1. - P. 103-111.

32. *Littman D.R., Pamer E.G.* Role of the Commensal Microbiota in Normal and Pathogenic Host Immune Responses // Cell Host & Microbe. - 2011. - Vol. 10, № 4. - P. 311-323.

33. *Liu X.F., Zou Q.H., Zeng B.H., Fang Y.F., Wei H.* Analysis of Fecal Lactobacillus Community Structure in Patients with Early Rheumatoid Arthritis // Current Microbiology. - 2013. - Vol. 67, № 2. - P. 170-176.

34. *Luckey D., Gomez A., Murray J., White B., Taneja V.* Bugs & us: The role of the gut in autoimmunity // Indian Journal of Medical Research. - 2013. - Vol. 138. - P. 732-743.

35. *MacGregor A. J., Snieder H., Rigby A. S., Koskenvuo M., Kaprio J., Aho K., Silman A. J.* Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins // Arthritis and Rheumatism. - 2000. - Vol. 43, № 1. - P. 30-37.

36. *Maeda Y., Kurakawa T., Umemoto E., Motooka D., Ito Y., Gotoh K., Hirota K., Matsushita M., Furuta Y., Narazaki M., Sakaguchi N., Kayama H., Nakamura S., Iida T., Saeki Y., Kumanogoh A., Sakaguchi S., Takeda K.* Dysbiosis Contributes to Arthritis Development via Activation of Autoreactive T Cells in the Intestine // Arthritis & Rheumatology. - 2016. - Vol. 68, № 11. - P. 2646-2661.

37. *Maeda Y., Takeda K.* Host-microbiota interactions in rheumatoid arthritis // Experimental and Molecular Medicine. - 2019. - Vol. 51. - P. 6.

38. *Manasson J., Shen N., Ferrer H.R.G., Ubeda C., Iraheta I., Heguy A., Von Feldt J. M., Espinoza L. R., Garcia Kutzbach A., Segal L. N., Ogdie A., Clemente J. C., Scher J.U.* Gut Microbiota Perturbations in Reactive Arthritis and Postinfectious Spondyloarthritis // Arthritis & Rheumatology. - 2018. - Vol. 70, № 2. - P. 242-254.

39. *Montoya J., Matta N. B., Suchon P., Guzian M. C., Lambert N. C., Mattei J. P., Guis S., Breban M., Roudier J., Balandraud N.* Patients with ankylosing spondylitis have been breast fed less often than healthy controls: a case-control retrospective study // Annals of the Rheumatic Diseases. - 2016. - Vol. 75, № 5. - P. 879-882.

40. *Moreno J.* Prevotella copri and the microbial pathogenesis of rheumatoid arthritis // Reumatologia clinica. - 2015. - Vol. 11, № 2. - P. 61-63.

41. *Mosca M., Tani C., Carli L., Bombardieri S.* Undifferentiated CTD: A wide spectrum of autoimmune diseases // Best Practice & Research in Clinical Rheumatology. - 2012. - Vol. 26, № 1. - P. 73-77.

42. *Mosca M., Tani C., Vagnani S., Carli L., Bombardieri S.* The diagnosis and classification of undifferentiated connective tissue diseases // Journal of Autoimmunity. - 2014. - Vol. 48-49. - P. 50-52.

43. *Moura C.S., Abrahamowicz M., Beauchamp M.E., Lacaille D., Wang Y. S., Boire G., Fortin P. R., Bessette L., Bombardier C., Widdifield J., Hanly J. G., Feldman D., Maksymowych W., Peschken C., Barnabe C., Edworthy S., Bernatsky S., Can A.I.M.* Early medication use in new-onset rheumatoid arthritis may delay joint replacement: results of a large population-based study // Arthritis Research & Therapy. - 2015. - Vol. 17. - P. 9.

44. *Muller P.H., de Meij T.G.J., Westedt M., de Groot E.F.J., Allaart C.F., Brinkman D.M.C., Schonenberg-Meinema D., van den Berg M., van Suijlekom-Smit L.W.A., van Rossum M., Budding A.E., ten Cate R.* Disturbance of Microbial Core Species in New-Onset Juvenile Idiopathic Arthritis // Journal of Pediatric Infectious Diseases. - 2017. - Vol. 12, № 2. - P. 131-135.

45. *Murray K.J.* Hypermobility disorders in children and adolescents // Best Practice & Research in Clinical Rheumatology. - 2006. - Vol. 20, № 2. - P. 329-351.

46. *Nakayama J., Yamamoto A., Palermo-Conde L.A., Higashi K., Sonomoto K., Tan J., Lee Y.K.* Impact of Westernized Diet on Gut Microbiota in Children on Leyte Island // Frontiers in Microbiology. - 2017. - Vol. 8. - P. 18.

47. *Palmer C., Bik E. M., DiGiulio D. B., Relman D.A., Brown P.O.* Development of the human infant intestinal microbiota // Plos Biology. - 2007. - Vol. 5, № 7. - P. 1556-1573.

48. *Pianta A., Arvikar S., Strle K., Drouin E.E., Wang Q., Costello C.E., Steere A.C.* Evidence of the Immune Relevance of Prevotella copri, a Gut Microbe, in Patients With Rheumatoid Arthritis // Arthritis & Rheumatology. - 2017. - Vol. 69, № 5. - P. 964-975.

49. *Picchianti-Diamanti A., Panebianco C., Salemi S., Sorgi M.L., Di Rosa R., Tropea A., Sgrulletti M., Salerno G., Terracciano F., D'Amelio R., Lagana B., Pazienza V.* Analysis of Gut Microbiota in Rheumatoid Arthritis Patients: Disease-Related Dysbiosis and Modifications Induced by Etanercept // International Journal of Molecular Sciences. - 2018. - Vol. 19, № 10. - P. 11.

50. *Renz H., von Mutius E., Brandtzaeg P., Cookson W.O., Autenrieth I.B., Haller D.* Gene-environment interactions in chronic inflammatory disease // Nature Immunology. - 2011. - Vol. 12, № 4. - P. 273-277.

51. *Rodrigues G.S.P., Cayres L.C.F., Goncalves F.P., Takaoka N.N.C., Lengert A.H., Tansini A., Brisotti J.L., Sasdelli C.B.G., de Oliveira G.L.V.* Detection of Increased Relative Expression Units of Bacteroides and Prevotella, and Decreased Clostridium leptum in Stool Samples from Brazilian Rheumatoid Arthritis Patients: A Pilot Study // Microorganisms. - 2019. - Vol. 7, № 10. - P. 13.

52. *Rogier R., Koenders M.I., Abdollahi-Roodsaz S.* Toll-Like Receptor Mediated Modulation of T Cell Response by Commensal Intestinal Microbiota as a Trigger for Autoimmune Arthritis // Journal of Immunology Research. - 2015. - Vol. 2015. - P. 8.

53. *Roszyk E., Puszczewicz M.* Role of human microbiome and selected bacterial infections in the pathogenesis of rheumatoid arthritis// Reumatologia. – 2017. – Vol. 55, № 5. - P. 242–250.

54. *Scheper M.C., Pacey V., Rombaut L., Adams R.D., Tofts L., Calders P., Nicholson L.L., Engelbert R.H.H.* Generalized Hyperalgesia in Children and Adults Diagnosed with Hypermobility Syndrome and Ehlers-Danlos Syndrome Hypermobility Type: A Discriminative Analysis // Arthritis Care & Research. - 2017. - Vol. 69, № 3. - P. 421-429.

55. *Scher J.U., Sczesnak A., Longman R.S., Segata N., Ubeda C., Bielski C., Rostron T., Cerundolo V., Pamer E.G., Abramson S.B., Huttenhower C., Littman D.R.* Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis // Elife. - 2013. - Vol. 2. - P. 20.

56. *Scher J.U., Ubeda C., Artacho A., Attur M., Isaac S., Reddy S.M., Marmon S., Neimann A., Brusca S., Patel T., Manasson J., Pamer E.G., Littman D.R., Abramson S.B.* Decreased Bacterial Diversity Characterizes the Altered Gut Microbiota in Patients with Psoriatic Arthritis, Resembling Dysbiosis in Inflammatory Bowel Disease // Arthritis & Rheumatology. - 2015. - Vol.67, № 1. - P. 128-139.

57. *Sieper J., Braun J., Kingsley G.H.* Report on the Fourth International Workshop on Reactive Arthritis // Arthritis and Rheumatism. - 2000. - Vol. 43, № 4. - P. 720-734.

58. *Souza-Moreira T.M., Severi J.A., Lee K., Preechasuth K., Santos E., Gow N.A.R., Munro C.A., Vilegas W., Pietro R.* Anti-Candida Targets and Cytotoxicity of Casuarinin Isolated from Plinia cauliflora Leaves in a Bioactivity-Guided Study // Molecules. - 2013. - Vol. 18, № 7. - P. 8095-8108.

59. *Stebbings S., Munro K., Simon M.A., Tannock G., Highton J., Harmsen H., Welling G., Seksik P., Dore J., Grame G., Tilsala-Timisjarvi A.* Comparison of the faecal microflora of patients with ankylosing spondylitis and controls using molecular methods of analysis // Rheumatology. - 2002. - Vol. 41, № 12. - P. 1395-1401.

60. *Stoll M.L., Kumar R., Morrow C.D., Lefkowitz E.J., Cui X.Q., Genin A., Cron R.Q., Elson C.O.* Altered microbiota associated with abnormal humoral immune responses to commensal organisms in enthesitis-related arthritis // Arthritis Research & Therapy. - 2014. - Vol. 16, № 6. – P. 486.

61. *Stoll M.L., Weiss P.F., Weiss J.E., Nigrovic P.A., Edelheit B.S., Bridges S.L., Danila M.I., Spencer C.H., Punaro M.G., Schikler K., Reiff A., Kumar R., Cron R.Q., Morrow C.D., Lefkowitz E.J.* Age and fecal microbial strain-specific differences in patients with spondyloarthritis // Arthritis Research & Therapy. - 2018. - Vol. 20. - P. 10.

62. *Stone M.A., Payne U., Schentag C., Rahman P., Pacheco-Tena C., Inman R.D.* Comparative immune responses to candidate arthritogenic bacteria do not confirm a dominant role for Klebsiella pneumonia in the pathogenesis of familial ankylosing spondylitis // Rheumatology. - 2004. - Vol. 43, № 2. - P. 148-155.

63. *Sun Y., Chen Q., Lin P., Xu R., He D.Y., Ji W.Q., Bian Y.Q., Shen Y., Li Q.T., Liu C., Dong K., Tang Y.W., Pei Z.H., Yang L.Y., Lu H.Z., Guo X.K., Xiao L.B.* Characteristics of Gut Microbiota in Patients with Rheumatoid Arthritis in Shanghai, China // Frontiers in Cellular and Infection Microbiology. - 2019. - Vol. 9. - P. 11.

64. *Tani C., Carli L., Vagnani S., Talarico R., Baldini C., Mosca M., Bombardieri S.* The diagnosis and classification of mixed connective tissue disease // Journal of Autoimmunity. - 2014. - Vol. 48-49. - P. 46-49.

65. *Thorkildsen L.T., Nwosu F.C., Avershina E., Ricanek P., Perminow G., Brackmann S., Vatn M.H., Rudi K.* Dominant Fecal Microbiota in Newly Diagnosed Untreated Inflammatory Bowel Disease Patients // Gastroenterology Research and Practice. - 2013. - Vol. 2013. - P. 13.

66. *Tobon G.J., Youinou P., Saraux A.* The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis // Autoimmunity Reviews. - 2010. - Vol. 9, № 5. - P. A288-A292.

67. *Ubeda C., Pamer E.G.* Antibiotics, microbiota, and immune defense // Trends in Immunology. - 2012. - Vol. 33, № 9. - P. 459-466.

68. *Vaahtovuo J., Munukka E., Korkeamaki M., Luukkainen R., Toivanen P.* Fecal microbiota in early rheumatoid arthritis // Journal of Rheumatology. - 2008. - Vol. 35, № 8. - P. 1500-1505.

69. *van Asbeck E.C., Clemons K.V., Stevens D.A.* Candida parapsilosis: a review of its epidemiology, pathogenesis, clinical aspects, typing and antimicrobial susceptibility // Critical Reviews in Microbiology. - 2009. - Vol. 35, № 4. - P. 283-309.

70. *van Dijkhuizen E.H.P., Del Chierico F., Malattia C., Russo A., Marafon D. P., ter Haar N.M., Magni-Manzoni S.,*

Vastert S.J., Dallapiccola B., Prakken B., Martini A., De Benedetti F., Putignani L. Model Driven Paediat E. Microbiome Analytics of the Gut Microbiota in Patients with Juvenile Idiopathic Arthritis: A Longitudinal Observational Cohort Study // Arthritis & Rheumatology. - 2019. - Vol. 71, № 6. - P. 1000-1010.

71. *Verma A., Sharda S., Rathi B., Somvanshi P., Pandey B.D.* Elucidating potential molecular signatures through host-microbe interactions for reactive arthritis and inflammatory bowel disease using combinatorial approach // Scientific Reports. - 2020. - Vol. 10, № 1. – P. 15131.

72. *Wang W., Chen L.P., Zhou R., Wang X.B., Song L., Huang S., Wang G., Xia B.* Increased Proportions of Bifidobacterium and the Lactobacillus Group and Loss of Butyrate-Producing Bacteria in Inflammatory Bowel Disease // Journal of Clinical Microbiology. - 2014. - Vol. 52, № 2. - P. 398-406.

73. *Xu H.H., Liu M.J., Cao J.F., Li X.Y., Fan D.P., Xia Y., Lu X.C., Li J.T., Ju D.H., Zhao H.Y.* The Dynamic Interplay between the Gut Microbiota and Autoimmune Diseases // Journal of Immunology Research. - 2019. - Vol. 2019. – P. 14.

74. *Yatsunenko T., Rey F.E., Manary M.J., Trehan I., Dominguez-Bello M.G., Contreras M., Magris M., Hidalgo G., Baldassano R.N., Anokhin A.P., Heath A.C., Warner B., Reeder J., Kuczynski J., Caporaso J.G., Lozupone C.A., Lauber C., Clemente J.C., Knights D., Knight R., Gordon J.I.* Human gut microbiome viewed across age and geography // Nature. - 2012. - Vol. 486, № 7402. - P. 222-+.

75. *Zamani B., Golkar H.R., Farshbaf S., Emadi-Baygi M., Tajabadi-Ebrahimi M., Jafari P., Akhavan R., Taghizadeh M., Memarzadeh M.R., Asemi Z.* Clinical and metabolic response to probiotic supplementation in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial // International Journal of Rheumatic Diseases. - 2016. - Vol. 19, № 9. - P. 869-879.

76. *Zhang X., Zhang D.Y., Jia H.J., Feng Q., Wang D.H., Liang D., Wu X.N., Li J.H. at al.* The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment // Nature Medicine. - 2015. - Vol. 21, № 8. - P. 895-905.

77. *Zhong D.L., Wu C.Y., Zeng X.F., Wang Q.* The role of gut microbiota in the pathogenesis of rheumatic diseases // Clinical Rheumatology. - 2018. - Vol. 37, № 1. - P. 25-34.

78. *Zimmer J., Lange B., Frick J.S., Sauer H., Zimmermann K., Schwiertz A., Rusch K., Klosterhalfen S., Enck P.* A vegan or vegetarian diet substantially alters the human colonic faecal microbiota // European Journal of Clinical Nutrition. - 2012. - Vol. 66, № 1. - P. 53-60.

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