Received: 09 August 2023 / Accepted: 29 December 2023 / Published online: 28 December 2023

DOI 10.34689/SH.2023.25.6.022

UDC 616.72-002.772:579.61

THE ROLE OF MICROBIOME IN RHEUMATOID ARTHRITIS DEVELOPMENT. A REVIEW.

Aigerim K. Ibrayeva[1], https://orcid.org/0000-0003-0628-9370
Natalya A. Latypova[1], https://orcid.org/0000-0003-4283-4911
Almagul R. Kushugulova[2], https://orcid.org/0000-0001-9479-0899
Assel M. Meiramova[1], https://orcid.org/0000-0002-4030-0783
Argul A. Isilbayeva[2], https://orcid.org/0000-0002-7350-6083
Samat S. Kozhahmetov[2], https://orcid.org/0000-0001-9668-0327
[1] NCJSC "Astana Medical University", Astana, Republic of Kazakhstan;
[2] AEO «Nazarbayev University», Astana, Republic of Kazakhstan.

Summary

Relevance. Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by symmetrical deforming arthritis and systemic manifestations, such as damage to the cardiovascular, respiratory systems, and skin. The prevalence of RA is high. Worldwide incidence ranges from 0.24 to 1% of the population. The disease is 2–3 times more common in women than in men. The peak incidence occurs in working age, from 35 to 64 years. Untreated RA can lead not only to patient disability, but also to death. In this connection, RA is a pressing problem of modern medicine. In recent years, the influence of epigenetic factors on the development of RA, including the influence of the microbiome, has been actively studied.

Purpose: The role of the oral and intestinal microbiome in the development of rheumatoid arthritis.

Search strategy: A search for scientific publications was carried out in the following databases of scientific publications and specialized search engines: PubMed, Google Scholar, Web of Science, Cochrane Library. A number of original publicly available publications on the research topic were analyzed. The search depth was 15 years. As a result of the search, we studied 459 foreign publications, of which 97 publications were included in this review. *Inclusion criteria:* meta-analyses, systematic reviews, cohort and cross-sectional studies. *Exclusion criteria:* short reports, newspaper articles and expert opinion in the form of short reports.

Results and conclusions: Based on the results of the review, it was revealed that in RA there is a change in the composition of the microbiome of both the oral cavity and the intestines. Experimental studies have revealed the role of the microbiome in the pathogenesis of RA development. In particular, the role of oral cavity-dwelling Porphyromonas gingivalis (P.gingivalis), Aggregatibacter actinomycetemcomitans (Aa), as well as gut microbiome representatives Prevotella copri (P. copri), Collinsella aerofaciens, Proteobacteria, Clostridium cluster XlVa and Ruminococcus genus.

Keywords: *rheumatoid arthritis, oral microbiome, intestinal microbiome, role of the microbiome, development of rheumatoid arthritis.*

Резюме

РОЛЬ МИКРОБИОМА В РАЗВИТИИ РЕВМАТОИДНОГО АРТРИТА. ОБЗОР ЛИТЕРАТУРЫ.

Айгерим К. Ибраева[1], https://orcid.org/0000-0003-0628-9370
Наталья А. Латыпова[1], https://orcid.org/0000-0003-4283-4911
Алмагуль Р. Кушугулова[2], https://orcid.org/0000-0001-9479-0899
Асель М. Мейрамова[1], https://orcid.org/0000-0002-4030-0783
Аргуль А. Исильбаева[2], https://orcid.org/0000-0002-7350-6083
Самат С. Кожахметов[2], https://orcid.org/0000-0001-9668-0327
[1] НАО «Медицинский университет Астана», г. Астана, Республика Казахстан;
[2] АОО «Назарбаев Университет» », г. Астана, Республика Казахстан.

Актуальность. Ревматоидный артрит (РА) это хроническое, аутоиммунное заболевание, характеризующееся симметричным деформирующим артритом и системными проявлениями, такими как поражение сердечно-сосудистой, дыхательной систем, кожного покрова. Распространённость РА высока. Всемирная частота встречаемости составляет от 0,24 до 1% населения. Заболевание в 2–3 раза чаще встречается у женщин, чем у мужчин. Пик заболеваемости приходится на трудоспособный возраст, от 35 до 64 лет. Своевременно нелеченый РА может приводить не только к инвалидности, но и к летальному исходу. В связи с чем, РА является актуальной проблемой современной медицины. В последние годы активно изучается влияние эпигенетических факторов на развитие РА, в том числе и влияние микробиома.

Цель: Роль микробиома ротовой полости и кишечника в развитии ревматоидного артрита.

Стратегия поиска: Проведен поиск научных публикаций в следующих базах данных научных публикаций и специализированных поисковых систем: PubMed, Google Scholar, Web of Science, Cochrane Library. Проанализирован ряд оригинальных публикаций, находящихся в открытом доступе по теме исследования. Глубина поиска составила 15 лет. В результате поиска нами было изучено 459 зарубежных публикаций, из них в данный обзор вошли 97 публикаций. *Критерии включения:* мета-анализы, систематические обзоры, когортные и поперечные исследования. *Критерии исключения:* краткие отчеты, газетные статьи и мнение экспертов в виде коротких сообщений.

Результаты и выводы: По результатам проведенного обзора литературы выявлено, что при РА отмечается изменение состава микробиома как ротовой полости, так и кишечника. В экспериментальных исследованиях выявлена роль микробиома в патогенезе развития РА. В частности, роль обитающих в ротовой полости Porphyromonas gingivalis (P.gingivalis), Aggregatibacter actinomycetemcomitans (Aa), а также представителей микробиома кишечника Prevotella copri (P. copri), Collinsella aerofaciens, Proteobacteria, Clostridium cluster XlVa и Ruminococcus genus.

Ключевые слова: *ревматоидный артрит, микробиом ротовой полости, микробиом кишечника, роль микробиома, развитие ревматоидного артрита.*

Түйіндеме

РЕВМАТОИДТЫ АРТРИТТІҢ ДАМУЫНДАҒЫ МИКРОБИОМНЫҢ РӨЛІ. ӘДЕБИЕТКЕ ШОЛУ.

Айгерим К. Ибраева[1], https://orcid.org/0000-0003-0628-9370

Наталья А. Латыпова[1], https://orcid.org/0000-0003-4283-4911

Алмагуль Р. Кушугулова[2], https://orcid.org/0000-0001-9479-0899

Әсель М. Мейрамова[1], https://orcid.org/0000-0002-4030-0783

Аргуль А. Исильбаева[2], https://orcid.org/0000-0002-7350-6083

Самат С. Кожахметов[2], https://orcid.org/0000-0001-9668-0327

[1] «Астана Медициналық университеті» КеАҚ, Астана қ., Қазахстан Республикасы;
[2] АББҰ «Назарбаев Университеті», Астана қ., Қазахстан Республикасы.

Өзектілігі. Ревматоидты артрит (РА) – бұл симметриялық деформацияланатын артрит және жүрек-тамыр, тыныс алу жүйелерінің және терінің зақымдануы сияқты жүйелі көріністермен сипатталатын созылмалы, аутоиммунды ауру. РА таралуы жоғары. Дүние жүзіндегі аурушаңдық халықтың 0,24-тен 1%-ға дейін ауытқиды. Әйелдерде ауру ерлерге қарағанда 2-3 есе жиі кездеседі. Аурудың ең жоғары деңгейі еңбекке қабілетті жаста, 35 пен 64 жас аралығында болады. Уақтылы емделмеген РА мүгедектікке ғана емес, өлімге де әкелуі мүмкін. Осыған байланысты РА қазіргі заманғы медицинаның өзекті мәселесі болып табылады. Соңғы жылдары РА дамуына эпигенетикалық факторлардың әсері, соның ішінде микробиомның әсері белсенді түрде зерттелуде.

Мақсаты: Ревматоидты артриттің дамуындағы ауыз және ішек микробиомының рөлі.

Іздеу стратегиясы: Ғылыми жарияланымдарды іздеу келесі ғылыми басылымдар мен мамандандырылған іздеу жүйелерінің дерекқорларында жүргізілді: PubMed, Google Scholar, Web of Science, Cochrane Library. Зерттеу тақырыбы бойынша көпшілікке қолжетімді бірқатар түпнұсқа басылымдар талданды. Іздеу тереңдігі 15 жыл болды. Іздестіру нәтижесінде 459 шетелдік басылымды зерттедік, оның ішінде 97 басылым осы шолуға қосылды. *Қосылу критерийлері:* мета-талдаулар, жүйелі шолулар, когорттық және секциялық зерттеулер. *Алып тастау критерийлері*: қысқаша есептер, газет мақалалары және қысқа хабарламалар түріндегі сарапшылардың пікірі.

Нәтижелер мен қорытындылар: Әдебиеттерді шолу нәтижелері бойынша РА-да ауыз қуысының да, ішектің де микробиомының құрамының өзгеретіні анықталды. Эксперименттік зерттеулерде РА дамуының патогенезіндегі микробиомның рөлін анықтады. Сонын ішінде, ауыз қуысында тіршілік ететін Porphyromonas gingivalis (P.gingivalis), Aggregatibacter actinomycetemcomitans (Aa), сондай-ақ ішек микробиомының өкілдері Prevotella copri (P. copri), Collinsella aerofaciens, Proteobacteria, ClostriocllusVcluus рөлдері анықталды.

Түйінді сөздер: *ревматоидты артрит, ауыз қуысының микробиомы, ішек микробиомы, микробиомның рөлі, ревматоидты артриттің дамуы.*

Bibliographic citation:

Ibrayeva A.K., Latypova N.A., Kushugulova A.R., Meiramova A.M., Isilbayeva A.A., Kozhahmetov S.S. The role of microbiome in Rheumatoid arthritis development. A review // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2023, (Vol.25) 6, pp. 191-198. *DOI 10.34689/SH.2023.25.6.022*

Ибраева А.К., Латыпова Н.А., Кушугулова А.Р., Мейрамова А.М., Исильбаева А.А., Кожахметов С.С. Роль микробиома в развитии ревматоидного артрита. Обзор литературы // Наука и Здравоохранение. 2023. 6 (Т.25). С. 191-198. *DOI 10.34689/SH.2023.25.6.022*

Ибраева А.К., Латыпова Н.А., Кушугулова А.Р., Мейрамова Ә.М., Исильбаева А.А., Кожахметов С.С. Ревматоидты артриттің дамуындағы микробиомның рөлі. Әдебиетке шолу // Ғылым және Денсаулық сақтау. 2023. 6 (Т.25). Б. 191-198. *DOI 10.34689/SH.2023.25.6.022*

Introduction.

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by symmetrical inflammatory arthritis with cartilage and bone deformities, production of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) and systemic manifestations including cardiovascular, pulmonary and skin disorders. [34,57] Incompletely treated RA can lead to patient disability due to irreversible joint lesions and premature mortality. [75]

The worldwide prevalence of RA ranges from 0,24 to 1%. [4–6,18] RA most frequently occurs at age 35–64, also very common among older people aged 75 years or above. Women suffer 2-3 times more often than men. [2,59,90]

Even though the exact etiology of RA is still unknown, it has become evident that RA appears based on genetic and epigenetic components. Environmental facts, such as smoking, dust inhalation, especially the microbiome changes ("internal" environment) play an important role in RA development. [71,75] Numerous studies have revealed that RA patients have different oral and gut microbiota compound compared to healthy controls. [20,55,61,63,82] Chen et al. reported about changes in β-diversity RA patients compared to healthy control. At the genus level, Bacteroides, Faecalibacterium and some probiotics were decreased, while 97 genera, including Lactobacillus, Streptococcus and Akkermansia, were increased in the RA group. [13] Surveys in animal models suggest that gut colonization of germ-free mises with specific to RA gut microbiome influence local and systemic immune response and trigger joint inflammation. [45,50]

Despite the use of disease-modifying anti-rheumatic drugs (DMARDs), biologic therapies a significant amount of patients with RA still cannot reach remission. [3,28] That is why the modulation of microbiome is an attractive therapeutic aim in RA treatment. Probiotics are live microorganisms, mainly bacteria, safe for consumption and capable of producing beneficial effects on the host's health when ingested in sufficient quantities (FAO/WHO, 2002). Published data showed that probiotics can influence systemic immune responses, gut permeability via sustaining a balance of ecosystem of gut microbiota, ensuring acceptable interactions between the gut microbiota and the mucosal immune cells. [17,87]

In this review, we endeavor to summarize the role of the microbiome in RA development.

Aim. The role of the oral and intestinal microbiome in the development of rheumatoid arthritis.

Search strategy. A search for scientific publications was carried out in the following databases of scientific publications and specialized search engines: PubMed, Google Scholar, Web of Science, Cochrane Library. A number of original publicly available publications on the research topic were analyzed. The search depth was 15 years. As a result of the search, we studied 459 foreign publications, of which 97 publications were included in this review. *Inclusion criteria*: meta-analyses, systematic reviews, cohort and cross-sectional studies. *Exclusion criteria*: short reports, newspaper articles and expert opinion in the form of short reports.

Research results

Role of microbiome in RA development.

From birth, humans are populated with commensals bacteria, especially in gastrointestinal tract, that help form the mucosal immune system and produce crucial nutrients. In the human gut the amount of microbial cells is 10 times more than in the whole human body, representing over 5000 species and consist of bacteria, viruses, fungi, and parasites. [7,73] The change of the gut microbiome to a dysbiosis condition initiate due to alteration factors, such as stress, infections, diet (excessive consumption of fat and meat), antibiotic treatment and chemotherapy. [26,74,95]

The role of microbiome in RA development has been investigated in depth. A number of animal model experiments hinted at the role of gut microbiota in the induction and progression of RA. Thus, Wu et al revealed that feeding the IL-1 receptor antagonist knockout (IL-1RA −/−) and the K/BxN mouse models with Lactobacillus and segmented filamentous bacteria (SFB) respectively induced to development of autoimmunity and inflammatory arthritis via induction of a robust TH17 response. [92] In another study, *Wu el al.* discovered that oral antigen influence combined with gut epithelial barrier dysfunction can produce RA-like inflammation in the articular joints. [91] Recently, *Evans- Martin et al.* declared that in murine models Th17 cells have a microbiota-dependent role in arthritis. [23]

The impact of the gut and oral microbiota to RA pathogenesis has been found to occur in several pathways. The first mechanism is materialized through gut microbiota diversity alteration that straightly provoke the immune response in the intestinal mucosa where afterwards local inflammatory pathways activation occurs and results to joint destruction and tissue inflammation. [10,11]

The second one is indirect way through microbes such as Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans and others that generate citrullinated proteins in the periodontal mucosa. [43,89]

In the following sections, we discuss the impact of oral and gut microbiota in RA pathogenesis.

Role of oral microbiota.

The oral microbiome is the second most diverse microbiota in the human body consists of over 700 identified germs species. Dominated bacterial phyla are Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, Spirochaetes, and Fusobacteria. [1,19,60] Numerous studies have revealed an association between Periodontal disease (PD) and RA. [5,24,27,29,56] In a Finnish cohort study where 124 early and chronic rheumatoid arthritis patients were included, Äyräväinen et al reported a robust affilation between early rheumatoid arthritis (odds ratio 5.3, 95%, P =0,044) and chronic rheumatoid arthritis (odds ratio 3.6, 95%, P =0,036) with periodontitis. [6] Recent trail made by Tar et al. studied 23 patients with RA from University of Debrecen. The authors found that the patients with RA had frightfull periodontal situation compared to healthy controls (RA: 0.68 ± 0.58; controls: 0.19 ± 0.38; p = 0.010). And that the salivary anti-CCP levels of RA positively matched up with PD staging (R = 0.464, p = 0.039). [81]

PD has been assigned to dysbiosis of oral microbiome and provocation factor of the autoimmune inflammation response in RA patients. [4] Despite PD is a commonly multibacterial infection of the gingival tissue, RA research has focused mostly on Porphyromonas gingivalis (P.gingivalis). [14] P.gingivalis has been marked as a "keystone pathogen" for PD and forms the "red complex" with Tannerella forsythia and Treponema denticola. Which were initially found by Socransky et al. in 1998. [76]

Experimental studies in animal models continuously have showed the role of P.gingivalis in PD development since 1988. [30,51] P.gingivalis can be identified in synovial fluid, proposing it's probable relationship with RA. [65,83]

McGraw et al. in 1999 first described the peptidyl-arginine deiminases (PAD or P.gingivalis PPAD) produced by P.gingivalis that catalyze the citrullination of bacterial proteins by replacing the amino acid ketamine group with the ketone group. [54] Furthermore, PPAD has a key role in activation of the human proteins citrullination. It hacks the proteinase-activated receptor 2 (PAR2), a neutrophil surface receptor that leads to an increase of the intracellular calcium concentration which activates human PADs such as PAD2 and PAD4, which are dominant in the neutrophil cells. [22,49] Generated neoepitopes induce Th17 immune response in the synovial membrane, which leads to aggregation of immune cells such as neutrophils, monocytes, and lymphocytes (T- and B-cells). This response provokes the release of a high level of pro-inflammatory cytokines such as IL-1β, IL-6, IL-22, IL-23, and tumor necrosis factor-α (TNF-α). [52,84,97] B cells separated from the synovial fluid of anti-CCP positive RA patients compose IgM antiCCP antibodies. [67] Produced anti-citrullinated autoantibodies (ACPA) are known to cause tissue damage and erosive arthritis. Courbon et al. revealed that P.gingivalis-induced periodontitis initiate seropositive anti-cyclic citrullinated peptide rheumatoid arthritis with systemic inflammation and elevated bone erosion. [16] PPAD secretion is the link between P.gingivalis and RA. Laugisch et al. reported that the PPAD enzyme is more active in RA patients, especially in the RA patients who have PD ($p = 0.038$; $p = 0.004$). [42]

Several studies showed that ACCP and P. gingivalis-specific IgG can be found long before disease onset, which sustains an aetiological role for P. gingivalis in RA occurence. [8,58] Thus, Johansson et al in case–control study investigated 251 RA patients and 198 controls. Scientists reported that elevated ACPP antibodies were detected in 5% of pre-symptomatic individuals (4.33 ± 0.59 AU/ml) compared with controls ($p < 0.001$). Additionally, concentration of both antibodies was elevated and stable in the pre-RA cases. [37] Joint MRIs and synovial biopsies of persons with circulating anti-CCP did not verify any signs of tissue damage. [85] These data suggests that autoimmunity in RA has an extra-articular beginning.

Another bacterium that strongly associated with RA development is Aggregatibacter actinomycetemcomitans (Aa). Aa secretes leukotoxin A (LtxA), a pore-forming protein that assaults all hematopoietic cells, causing cytolysis and cell death, especially neutrophils (Netosis). [65,66,67] Netosis persuades the hypercitrullination of specific proteins, including heterogeneous nuclear ribonucleoproteins, vimentin, and histone H2B. Produced proteins are accepted as an autoantigen by the immune system to produce ACPAs. [40,47] Several human studes detected correlation between Aa and RA. Laugisch et al found an escalated presence of the phylum Aa in the RA group, including the comparison between the RA/non-PD and non-RA/ non-PD groups ($p = 0.013$). [42] Whereas Reichert et al observed that infection with Aa is related with an increased creation of anti-CCP ($p=0.043$). [66] Also, anti-LtxA antibodies were strongly associated with RA (43% vs 11% positivity; $p<0.0001$). [35,40,47] However, Volkov et al. investigated that anti-LtxA antibodies could be found in a considerable relationship in RA patients, as well as in patients with other forms of arthritis (RA $p<0.05$, OA $p<0.05$, SpA $p<0.05$, PsA $p<0.001$, Sarc $p<0.0001$, Gout $p<0.0001$). [86] The role of Aa as an aetiologic periodontal pathogen is worth investigating further.

Another oral microbiota members that associated with PD and RA are shown in the table №1.

Table №1.

Another oral microbiota members that associated with PD and RA.

	Name of bacterium	Author	Year	Results
1	Anaeroglobus geminatus	Jose U. Scher et al.	2012	Was correlated with ACPA/rheumatoid factor (RF) presence in RA patients with PD [70]
2	Cryptobacterium curtum	Isabel Lopez-Oliva B.D.S, PhD	2018	capable of producing large amounts of citrulline, emerged as a robust discriminant of the microbiome in individuals with RA [48]
3	Lactobacillus salivarius	Xuan Zhang et al.	2015	was over-represented in individuals with RA at all three sites and was present in increased amounts in cases of very active RA [94]
		Yanli Tong	2020	positively correlated with ESR, C-reactive protein (CRP) [82].
4	Atopobium spp. and C. curtum			
5	Eubacterium nodatum_group	Yanli Tong	2020	ACPA concentration was positively correlated [82].
6	Peptostreptococcus	Yanli Tong	2020	ACPA concentration was positively correlated [82].
7	Tannerella	Yanli Tong	2020	ACPA concentration was positively correlated [82].
		José-Iván Martínez-Rivera	2017	is associated with RA activity [53].
8	norank_o__Absconditabacteriales_SR1	Yanli Tong	2020	ACPA concentration was positively correlated, positively correlated with ESR [82].
9	Abiotrophia	Yanli Tong	2020	RF was significantly associated [82].
10	Corynebacterium	Yanli Tong	2020	RF was significantly associated [82].
11	Fretibacterium	Yanli Tong	2020	RF was significantly associated [82].
12	Ruminococcaceae_UCG-014	Yanli Tong	2020	DAS28 positively correlated, also associated with CRP and ESR[82].

Role of gut microbiota

The gastrointestinal (GI) tract has more than 100 trillion microbes and approximately 1500 species and consist of four main phyla: the Bacteroidetes, the Firmicutes, the Actinobacteria and the Proteobacteria. The healthy gut also shelters Archaea, Eukarya, macro-parasites, viruses and bacteriophages. [38] This microbiome handle as a functional embellishment of host genomes and is appraised to harbor 50-100 folds more genes than the host. [21]

A growing body of studies has shown evidence for bacterial dysbiosis in RA. The most common findings of these studies show a significant presence of pathogenic bacteria as Prevotella copri (P. copri), Clostridium perfringens, Clostridium asparagiforme, segmented filamentous bacteria (SFB), Lactobacillus salivarius, Gordonibacter pamelaeae, Eggerthella lenta and Lachnospiraceae bacterium. And a notable decrease in the commensal bacteria such as Faecalibacteria prausnitzii, Eubacterium rectale, Clostridium coccoides, Bacteroides fragilis, certain species of Veillonellaceae family and Bifidobacteria. [12,15,31,46,50,69,79,94] On the other hand, *Zhang et al.* reviled that the global diversity and abundance did not remarkably diverge between RA and healthy samples. They studied faecal, dental and salivary samples of RA patients and healthy controls via metagenomic shotgun sequencing. [94]

Several reports related gut microbiome dysbiosis with RA pathogenesis. In a mice model of arthritis, transplantation of microbiota from RA individuals over-populated by P.copri resulted in severe arthritis. This gave a reason to authors to postulate that P.copri might carry an epitope extending cross-reactivity to arthritis-related autoantigens. [50] Pianta et al. identified that P.copri produce peptide Pc-p27 presented from peripheral blood mononuclear cells of a HLA-DRB1*0401/0101þ patient with severe chronic RA. Pc-p27 stimulated reactivity of T helper 1 (Th1) cells, RA-correlated proinflammatory T cell subset, in vitro in 42% of patients with new-onset RA. In 32% of new onset RA patients had anti-P.copri antibodies, while scarcely detected in other forms of arthritis or in healthy controls. [61,62] Another likely mechanism of involvement of P.copri in RA pathogenesis is molecular mimicry. P. copri might present an epitope that mimics the structure of 60S ribosomal protein L23a (RPL23A), an autoantigen that enhanced IL-17 responses and reacted to T cells and autoantibodies from RA patient, occurred in lymphocytes from the intestines of pre-clinical RA mice. [33,50,62] P.copri epitopes appeared high sequence homology with HLA-DR–presented T cell epitopes of N-acetylglucosamine-6-sulfatase (GNS) and filamin A (FLNA). GNS and FLNA are concentrated in RA patients' inflamed joints, that is why their autoantibody producing can be an indicator of an autoimmune process activation and joint damage in RA. [32,39] Another bacterium related to Th17/Treg imbalance in RA patients is Bifidobacterium adolescentis. Tan et al found that Bifidobacterium adolescentis, as P.copri, can induce Th17 cell production in the small intestine of murine. [80] Th17 cells is the key mediator of the inflammation and bone erosion in the synovial joints of RA patients. The activated Th17 cells discharge pro-inflammatory cytokines such as IL-17, IL-21, and IL-22. IL-17 is the dominant mediator of autoimmune tissue alteration in the arthritic synovial joints. [93,97]

There are several other microbes that also involved in RA development. The role of Collinsella aerofaciens in RA pathogenesis was dedicated in experimental arthritis. The bounty of Collinsella aerofaciens strongly corresponded with high producing of the proinflammatory cytokine IL-17A. [12] Li et al found correlation between increased number of Proteobacteria, Clostridium cluster XlVa and Ruminococcus genus with lower levels of T, B, CD4+ T, and Tregs. [44] Bacteroides fragilis, in murine colons, suppress the ability of bile acid metabolites to induce RORγt+ Treg cells via the vitamin D receptors and blacked out the bile acid metabolic pathways. [77] Wang et al reported that comparative abundance of Megamonas, Monoglobus and Prevotella was positively correlated with CD4+ T cell counts and cytokine levels. Also, the relative amount of regulatory T cells (Tregs) and T helper (Th17)/Treg ratio were negatively correlated with activity of RA. [88]

Several bacteria, such as Eubacterium, Fusobacterium, Anaerostipes, Roseburia and Faecalibacterium, have shown to support the carrying on of intestinal epithelial barrier stability by producing butyrate. Depression of Faecalibacterium level in RA patients leads to loss of gut barrier unity. This allows migration of bacterial antigens to systemic circulation and may accordingly trigger inflammatory immune reaction in extra-intestinal plats. [12,96,97]

Additionally, gut bacteria have ability to create biofilms which capable of altering the Th17/Tregs equilibrium. Unique biofilm constituents, such as amyloid fibrils, building blocks of biofilm, imply autoimmunity via TLR recognition and succeeding Th17 activation. [72,78] Gallo et al. uggested a role for chronic biofilm-producing gut infections in the pathogenesis of autoimmune diseases via demonstration that the curli, a particular type of amyloid fibrils, initiated the producing of autoantibodies in a murine model. [25] The curli also trigger NLRP3 inflammasome in mice macrophages, aimed to fabricate of inflammatory interleukin IL-1β, which assumed in the differentiation of Th17 cells. [64]

Conclusions

Based on the results of the review, it was revealed that in RA there is a change in the composition of the microbiome of both the oral cavity and the intestines. Experimental studies have revealed the role of the microbiome in the pathogenesis of RA development. In particular, the role of oral cavity-dwelling Porphyromonas gingivalis (P.gingivalis), Aggregatibacter actinomycetemcomitans (Aa), as well as gut microbiome representatives Prevotella copri (P. copri), Collinsella aerofaciens, Proteobacteria, Clostridium cluster XlVa and Ruminococcus genus.

Conflict of interest: *The authors declare that there is no conflict of interest and that no part of this article has been published in the open press. The article is not considerated by other publishers.*

Authors' contribution: *Since the article is a review, the search for materials was carried out by all authors using separate algorithms, and the decision not to include individual materials was made collectively. All authors contributed to the article and approved the submitted version.*

Funding: *This article was prepared and funded within the framework of the project of the Ministry of Education and Science of the Republic of Kazakhstan AP14869993 «Immunological*

profile and microbiome markers in evaluating the effectiveness of probiotic».

Acknowledgment: *the Ministry of Education and Science of the Republic of Kazakhstan.*

Literature:

1. *Aas J.A., Paster B.J., Stokes L.N., Olsen I., Dewhirst F.E.* Defining the Normal Bacterial Flora of the Oral Cavity // J Clin Microbiol. 2005. 43(11):5721-5732.

2. AIHW; Australian Institute of Health Welfare. Rheumatoid Arthritis. Available online: https://www.aihw.gov.au/reports/ chronic-musculoskeletal-conditions/rheumatoid-arthritis (accessed on 10 April 2021).

3. *Ajeganova S., Huizinga T.* Sustained remission in rheumatoid arthritis: latest evidence and clinical considerations // Ther Adv Musculoskelet Dis. 2017. 9(10):249-262.

4. *Alghamdi M.A., Redwan E.M.* Interplay of Microbiota and Citrullination in the Immunopathogenesis of Rheumatoid Arthritis // Probiotics Antimicrob Proteins. 2022. 14(1):99-113.

5. *Araújo V.M.A., Melo I.M., Lima V.* Relationship between Periodontitis and Rheumatoid Arthritis: Review of the Literature // Mediators Inflamm. 2015. 2015:1-15.

6. *Äyräväinen L., Leirisalo-Repo M., Kuuliala A. et al.* Periodontitis in early and chronic rheumatoid arthritis: a prospective follow-up study in Finnish population // BMJ Open. 2017. 7(1):e011916.

7. *Beam A., Clinger E., Hao L.* Effect of Diet and Dietary Components on the Composition of the Gut Microbiota // Nutrients. 2021. 13(8):2795.

8. *Bello-Gualtero J.M., Lafaurie G.I., Hoyos L.X. et al.* Periodontal Disease in Individuals With a Genetic Risk of Developing Arthritis and Early Rheumatoid Arthritis: A Cross-Sectional Study // J Periodontol. 2016. 87(4):346-356.

9. *Cai Y., Zhang J., Liang J. et al.* The Burden of Rheumatoid Arthritis: Findings from the 2019 Global Burden of Diseases Study and Forecasts for 2030 by Bayesian Age-Period-Cohort Analysis // J Clin Med. 2023. 12(4):1291.

10. *Campbell C., Kandalgaonkar M.R., Golonka R.M., Yeoh B.S., Vijay-Kumar M., Saha P.* Crosstalk between Gut Microbiota and Host Immunity: Impact on Inflammation and Immunotherapy // Biomedicines. 2023. 11(2):294.

11. *Catrina A.I., Joshua V., Klareskog L., Malmström V.* Mechanisms involved in triggering rheumatoid arthritis // Immunol Rev. 2016. 269(1):162-174.

12. *Chen J., Wright K., Davis J.M. et al.* An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis // Genome Med. 2016. 8(1):43.

13. *Chen Y., Ma C., Liu L. et al.* Analysis of gut microbiota and metabolites in patients with rheumatoid arthritis and identification of potential biomarkers // Aging. 2021.13(20):23689-23701.

14. *Cheng Z., Meade J., Mankia K., Emery P., Devine D.A.* Periodontal disease and periodontal bacteria as triggers for rheumatoid arthritis // Best Pract Res Clin Rheumatol. 2017. 31(1):19-30.

15. *Clarke J.* Disease onset goes with its gut in RA // Nat Rev Rheumatol. 2020. 16(7):350-350.

16. *Courbon G., Rinaudo-Gaujous M., Blasco-Baque V., et al.* Porphyromonas gingivalis experimentally induces periodontis and an anti-CCP2-associated arthritis in the rat // Ann Rheum Dis. 2019. 78(5):594-599.

17. *Cristofori F., Dargenio V.N., Dargenio C., Miniello V.L., Barone M., Francavilla R.* Anti-Inflammatory and Immunomodulatory Effects of Probiotics in Gut Inflammation: A Door to the Body // Front Immunol. 2021. 12:578386.

18. *Cross M., Smith E., Hoy D. et al.* The global burden of rheumatoid arthritis: estimates from the Global Burden of Disease 2010 study. // Annals of the Rheumatic Diseases, 73(7), 1316–1322. doi:10.1136/annrheumdis-2013-204627

19. *Dewhirst F.E., Chen T., Izard J. et al.* The Human Oral Microbiome // J Bacteriol. 2010. 192(19):5002-5017.

20. D*u Q., Liu X.H., Tian K., Meng S.* [Analysis of Periodontal Status and Salivary Microbial Diversity in Patients with Rheumatoid Arthritis] // Sichuan Da Xue Xue Bao Yi Xue Ban. 2019. 50(6):935-940.

21. *Eckburg P.B., Bik E.M., Bernstein C.N., et al.* Diversity of the Human Intestinal Microbial Flora // Science. 2005. 308(5728):1635-1638.

22. *Engström M., Eriksson K., Lee L. et al.* Increased citrullination and expression of peptidylarginine deiminases independently of P. gingivalis and A. actinomycetemcomitans in gingival tissue of patients with periodontitis // J Transl Med. 2018. 16(1):214.

23. *Evans-Marin H., Rogier R., Koralov S.B. et al.* Microbiota-Dependent Involvement of Th17 Cells in Murine Models of Inflammatory Arthritis // Arthritis Rheumatol. 2018. 70(12):1971-1983.

24. *Fuggle N.R., Smith T.O., Kaul A., Sofat N.* Hand to Mouth: A Systematic Review and Meta-Analysis of the Association between Rheumatoid Arthritis and Periodontitis // Front Immunol. 2016. 7. p. 80-97.

25. *Gallo P.M., Rapsinski G.J., Wilson R.P. et al.* Amyloid-DNA Composites of Bacterial Biofilms Stimulate Autoimmunity // Immunity. 2015. 42(6):1171-1184.

26. *Gautam A., Kumar R., Chakraborty N. et al.* Altered fecal microbiota composition in all male aggressor-exposed rodent model simulating features of post-traumatic stress disorder // J Neurosci Res. 2018. 96(7):1311-1323.

27. *González-Febles J., Sanz M.* Periodontitis and rheumatoid arthritis: What have we learned about their connection and their treatment? // Periodontol. 2000. 2021. 87(1):181-203.

28. G*ul H.L., Eugenio G., Rabin T. et al.* Defining remission in rheumatoid arthritis: does it matter to the patient? A comparison of multi-dimensional remission criteria and patient reported outcomes // Rheumatology. Published online August 19, 2019:kez330.

29. *Hashimoto M., Yamazaki T., Hamaguchi M. et al.* Periodontitis and Porphyromonas gingivalis in Preclinical Stage of Arthritis Patients. Heymann D, ed. // PLOS ONE. 2015. 10(4):e0122121.

30. *Holt S.C., Ebersole J., Felton J., Brunsvold M., Kornman K.S.* Implantation of Bacteroides gingivalis in Nonhuman Primates Initiates Progression of Periodontitis // Science. 1988. 239(4835):55-57.

31. H*orta-Baas G., Romero-Figueroa M.D.S., Montiel-Jarquín A.J., Pizano-Zárate M.L., García-Mena J., Ramírez-Durán N.* Intestinal Dysbiosis and Rheumatoid Arthritis: A Link between Gut Microbiota and the Pathogenesis of Rheumatoid Arthritis // J Immunol Res. 2017. 2017:1-13.

32. *Hua R., Ni Q., Eliason T.D. et al.* Biglycan and chondroitin sulfate play pivotal roles in bone toughness via

retaining bound water in bone mineral matrix // Matrix Biol. 2020. 94:95-109.

33. *Ito Y., Hashimoto M., Hirota K. et al.* Detection of T cell responses to a ubiquitous cellular protein in autoimmune disease // Science. 2014. 346(6207):363-368.

34. *Jang S., Kwon E.J., Lee J.J.* Rheumatoid Arthritis: Pathogenic Roles of Diverse Immune Cells // Int J Mol Sci. 2022. 23(2):905.

35. *Jasemi S., Erre G.L., Cadoni M.L., Bo M., Sechi L.A.* Humoral Response to Microbial Biomarkers in Rheumatoid Arthritis Patients // J Clin Med. 2021. 10(21):5153.

36. *Johansson A.* Aggregatibacter actinomycetemcomitans Leukotoxin: A Powerful Tool with Capacity to Cause Imbalance in the Host Inflammatory Response // Toxins. 2011. 3(3):242-259.

37. *Johansson L., Sherina N., Kharlamova N. et al.* Concentration of antibodies against Porphyromonas gingivalis is increased before the onset of symptoms of rheumatoid arthritis // Arthritis Res Ther. 2016. 18(1):201.

38. *Kamada N., Seo S.U., Chen G.Y., Núñez G.* Role of the gut microbiota in immunity and inflammatory disease // Nat Rev Immunol. 2013. 13(5):321-335.

39. *Kim H., McCulloch C.A.* Filamin A mediates interactions between cytoskeletal proteins that control cell adhesion // FEBS Lett. 2011. 585(1):18-22.

40. *Konig M.F., Abusleme L., Reinholdt J. et al.* Aggregatibacter actinomycetemcomitans – induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis // Sci Transl Med. 2016. 8(369).

41. Kulkarni A., Beckler M.D., Amini S.S., Kesselman MM. Oral Microbiome in Pre-Rheumatoid Arthritis: The Role of Aggregatibacter Actinomycetemcomitans in Bacterial Composition // Cureus. Published online December 5, 2022.

42. *Laugisch O., Wong A., Sroka A. et al.* Citrullination in the periodontium—a possible link between periodontitis and rheumatoid arthritis // Clin Oral Investig. 2016. 20(4):675-683.

43. *Li Y., Guo R., Oduro P.K. et al.* The Relationship Between Porphyromonas Gingivalis and Rheumatoid Arthritis: A Meta-Analysis // Front Cell Infect Microbiol. 2022. 12:956417.

44. *Li Y., Zhang S.X., Yin X.F. et al.* The Gut Microbiota and Its Relevance to Peripheral Lymphocyte Subpopulations and Cytokines in Patients with Rheumatoid Arthritis. Xu B, ed. // J Immunol Res. 2021. 2021:1-9.

45. *Liu X., Zeng B., Zhang J. et al.* Role of the Gut Microbiome in Modulating Arthritis Progression in Mice // Sci Rep. 2016. 6(1):30594.

46. *Liu X., Zou Q., Zeng B.* Analysis of Fecal Lactobacillus Community Structure in Patients with Early Rheumatoid Arthritis // Curr Microbiol. 2013. 67(2):170-176.

47. *Looh S.C., Soo Z.M.P., Wong J.J., Yam H.C., Chow S.K., Hwang J.S.* Aggregatibacter actinomycetemcomitans as the Aetiological Cause of Rheumatoid Arthritis: What Are the Unsolved Puzzles? // Toxins. 2022. 14(1):50.

48. *Lopez-Oliva I., Paropkari A.D., Saraswat S. et al.* Dysbiotic Subgingival Microbial Communities in Periodontally Healthy Patients With Rheumatoid Arthritis. Arthritis Rheumatol. 2018. 70(7):1008-1013.

49. *Lourbakos A., Chinni C., Thompson P. et al.* Cleavage and activation of proteinase-activated receptor-2 on human neutrophils by gingipain-R from Porphyromonas gingivalis // FEBS Lett. 1998. 435(1):45-48.

50. *Maeda Y., Kurakawa T., Umemoto E. et al.* Dysbiosis Contributes to Arthritis Development via Activation of Autoreactive T Cells in the Intestine: Dysbiosis contributes to arthritis development // Arthritis Rheumatol. 2016. 68(11):2646-2661.

51. *Maekawa T., Krauss J.L., Abe T. et al.* Porphyromonas gingivalis Manipulates Complement and TLR Signaling to Uncouple Bacterial Clearance from Inflammation and Promote Dysbiosis // Cell Host Microbe. 2014. 15(6):768-778.

52. *Marchesan J.T., Gerow E.A., Schaff R. et al.* Porphyromonas gingivalis oral infection exacerbates the development and severity of collagen-induced arthritis // Arthritis Res Ther. 2013. 15(6):R186.

53. *Martínez-Rivera J.I., Xibillé-Friedmann D.X. et al.* Salivary ammonia levels and Tannerella forsythia are associated with rheumatoid arthritis: A cross sectional study // Clin Exp Dent Res. 2017. 3(3):107-114.

54. *McGraw W.T., Potempa J., Farley D., Travis J.* Purification, Characterization, and Sequence Analysis of a Potential Virulence Factor from Porphyromonas gingivalis , Peptidylarginine Deiminase. Burns DL, ed. // Infect Immun. 1999. 67(7):3248-3256.

55. *Mena-Vázquez N., Ruiz-Limón P. et al., Fernández-Nebro A.* Expansion of Rare and Harmful Lineages is Associated with Established Rheumatoid Arthritis // J Clin Med. 2020. 9(4):1044.

56. *Mikuls T.R., Payne J.B., Yu F. et al.* Periodontitis and Porphyromonas gingivalis in Patients With Rheumatoid Arthritis: Periodontitis and P gingivalis in RA // Arthritis Rheumatol. 2014. 66(5):1090-1100.

57. *Nelson J., Sjöblom H., Gjertsson I., Ulven S.M., Lindqvist H.M., Bärebring L.* Do Interventions with Diet or Dietary Supplements Reduce the Disease Activity Score in Rheumatoid Arthritis? A Systematic Review of Randomized Controlled Trials // Nutrients. 2020. 12(10):2991.

58. *Nielen M.M.J.* Simultaneous development of acute phase response and autoantibodies in preclinical rheumatoid arthritis // Ann Rheum Dis. 2006. 65(4):535-537.

59. *Otón T., Carmona L.* The epidemiology of established rheumatoid arthritis // Best Pract Res Clin Rheumatol. 2019. 33(5):101477.

60. *Paster B.J., Boches S.K., Galvin J.L. et al.* Bacterial Diversity in Human Subgingival Plaque // J Bacteriol. 2001. 183(12):3770-3783.

61. *Pianta A., Arvikar S., Strle K. et al.* Evidence of the Immune Relevance of Prevotella copri , a Gut Microbe, in Patients With Rheumatoid Arthritis // Arthritis Rheumatol. 2017. 69(5):964-975.

62. *Pianta A., Arvikar S.L., Strle K. et al.* Two rheumatoid arthritis–specific autoantigens correlate microbial immunity with autoimmune responses in joints // J Clin Invest. 2017. 127(8):2946-2956.

63. *Picchianti-Diamanti A., Panebianco C., Salemi S. et al.* Analysis of Gut Microbiota in Rheumatoid Arthritis Patients: Disease-Related Dysbiosis and Modifications Induced by Etanercept // Int J Mol Sci. 2018. 19(10):2938.

64. *Rapsinski G.J., Wynosky-Dolfi M.A., Oppong G.O. et al.* Toll-Like Receptor 2 and NLRP3 Cooperate To Recognize a Functional Bacterial Amyloid, Curli. Bäumler AJ, ed. // Infect Immun. 2015. 83(2):693-701.

65. *Reichert S., Haffner M., Keyßer G. et al.* Detection of oral bacterial DNA in synovial fluid // J Clin Periodontol. 2013. 40(6):591-598.

66. *Reichert S., Jurianz E., Natalie P. et al.* Is periodontitis a prognostic factor in order to indicate antibodies against citrullinated peptides in patients with rheumatoid arthritis? // Clin Exp Rheumatol. 2020. 38(2):227-238.

67. *Reparon-Schuijt C.C. et al.* Secretion of anti-citrulline-containing peptide antibody by B lymphocytes in rheumatoid arthritis. Arthritis Rheum. 2001. 44(1):41-47.

68. *Safiri S., Kolahi A.A., Hoy D. et al.* Global, regional and national burden of rheumatoid arthritis 1990–2017: a systematic analysis of the Global Burden of Disease study 2017 // Ann Rheum Dis. 2019. 78(11):1463-1471.

69. *Scher J.U., Sczesnak A., Longman R.S. et al.* Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis. eLife. 2013. 2:e01202.

70. *Scher J.U., Ubeda C., Equinda M. et al.* Periodontal disease and the oral microbiota in new-onset rheumatoid arthritis // Arthritis Rheum. 2012. 64(10):3083-3094.

71. *Scherer H.U., Häupl T., Burmester G.R.* The etiology of rheumatoid arthritis // J Autoimmun. 2020. 110:102400.

72. *Schlafer S., Meyer R.L., Dige I., Regina V.R.* Extracellular DNA Contributes to Dental Biofilm Stability // Caries Res. 2017. 51(4):436-442.

73. *Shanahan F., Ghosh T.S., O'Toole P.W.* The Healthy Microbiome - What Is the Definition of a Healthy Gut Microbiome? // Gastroenterology. 2021. 160(2):483-494.

74. *Singh R.K., Chang H.W., Yan D. et al.* Influence of diet on the gut microbiome and implications for human health // J Transl Med. 2017. 15(1):73.

75. *Smolen J.S., Aletaha D., Barton A. et al.* Rheumatoid arthritis // Nat Rev Dis Primer. 2018. 4(1):18001.

76. *Socransky S.S., Haffajee A.D., Cugini M.A., Smith C., Kent R.L.* Microbial complexes in subgingival plaque // J Clin Periodontol. 1998. 25(2):134-144.

77. *Song X., Sun X., Oh S.F. et al.* Microbial bile acid metabolites modulate gut RORγ+ regulatory T cell homeostasis // Nature. 2020. 577(7790):410-415.

78. *Taglialegna A., Lasa I., Valle J.* Amyloid Structures as Biofilm Matrix Scaffolds. O'Toole GA, ed. // J Bacteriol. 2016. 198(19):2579-2588.

79. *Tajik N., Frech M., Schulz O. et al.* Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis // Nat Commun. 2020. 11(1):1995.

80. *Tan T.G., Sefik E. et al.* Identifying species of symbiont bacteria from the human gut that, alone, can induce intestinal Th17 cells in mice // Proc Natl Acad Sci. 2016. 113(50).

81. *Tar I., Csősz É., Végh E. et al.* Salivary citrullinated proteins in rheumatoid arthritis and associated periodontal disease. Sci Rep. 2021. 11(1):13525.

82. *Tong Y., Zheng L., Qing P. et a*l. Oral Microbiota Perturbations Are Linked to High Risk for Rheumatoid Arthritis // Front Cell Infect Microbiol. 2020. 9:475.

83. *Totaro M., Cattani P., Ria F. et al.* Porphyromonas gingivalis and the pathogenesis of rheumatoid arthritis: analysis of various compartments including the synovial tissue // Arthritis Res Ther. 2013. 15(3):R66.

84. *Trombone A.P., Claudino M., Colavite P. et al.* Periodontitis and arthritis interaction in mice involves a shared hyper-inflammatory genotype and functional immunological interferences // Genes Immun. 2010. 11(6):479-489.

85. *Van De Sande M., De Hair M. et al.* Different stages of rheumatoid arthritis: features of the synovium in the preclinical phase // Ann Rheum Dis. 2011. 70(5):772-777.

86. *Volkov M., Dekkers J. et al.* Comment on "Aggregatibacter actinomycetemcomitans – induced hypercitrullination links periodontal infection to autoimmunity in rheumatoid arthritis" // Sci Transl Med. 2018. 10(433):8349.

87. *Wang P., Tao J.H., Pan H.F.* Probiotic bacteria: a viable adjuvant therapy for relieving symptoms of rheumatoid arthritis // Inflammopharmacology. 2016. 24(5):189-196.

88. *Wang Q., Zhang S.X., Chang M.J. et al*. Characteristics of the Gut Microbiome and Its Relationship With Peripheral CD4+ T Cell Subpopulations and Cytokines in Rheumatoid Arthritis // Front Microbiol. 2022. 13:799602.

89. *Wegner N., Wait R., Sroka A. et al.* Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and α-enolase: Implications for autoimmunity in rheumatoid arthritis // Arthritis Rheum. 2010. 62(9):2662-2672.

90. v*an der Woude D., van der Helm-van Mil A.H.* Update on the epidemiology, risk factors, and disease outcomes of rheumatoid arthritis // Best Pract Res Clin Rheumatol. 2018. 32(2):174-187.

91. *Wu D., Liu X., Su H., et al.* Oral antigens induce rheumatoid arthritis-like inflammation in a rat model // Inflamm Res. 2013. 62(3):291-297.

92. *Wu H.J., Ivanov I.I., Darce J. et al.* Gut-Residing Segmented Filamentous Bacteria Drive Autoimmune Arthritis via T Helper 17 Cells // Immunity. 2010. 32(6):815-827.

93. *Wu X., He B., Liu J. et al.* Molecular Insight into Gut Microbiota and Rheumatoid Arthritis // Int J Mol Sci. 2016. 17(3):431.

94. Z*hang X., Zhang D., Jia H. et al.* The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment // Nat Med. 2015. 1(8):895-905.

95. *Zhernakova A., Kurilshikov A., Bonder M.J. et* al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity // Science. 2016. 352(6285):565-569.

96. *Zhou L., Zhang M., Wang Y. et al.* Faecalibacterium prausnitzii Produces Butyrate to Maintain Th17/Treg Balance and to Ameliorate Colorectal Colitis by Inhibiting Histone Deacetylase // Inflamm Bowel Dis. 2018. 24(9):1926-1940.

97. *Zwicky P., Unger S., Becher B.* Targeting interleukin-17 in chronic inflammatory disease: A clinical perspective // J Exp Med. 2020. 217(1):e20191123.

Coresponding Author:
Aigerim K. Ibrayeva – PhD student, gastroenterologist, NCJSC "Astana Medical University", Astana, Republic of Kazakhstan.
Mailing Address: 010000, Republic of Kazakhstan, Astana, Beibitshilik 49/A.
E-mail: ibrayeva.aigerim.k@gmail.com
Phone: 8 702 728 47 10