PAŻYRA, Aldona, NOWAKOWSKA, Katarzyna, WIĘSYK, Piotr and OKLECIŃSKA, Łucja. A Gut microbiota and rheumatic diseases: new insights into pathogenesis. Quality in Sport. 2024;18:53972. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.18.53972
https://apcz.umk.pl/QS/article/view/53972

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 31.07.2024. Revised: 08.08.2024. Accepted: 12.08.2024. Published: 12.08.2024.

Gut microbiota and rheumatic diseases: new insights into pathogenesis

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Abstract
Background: Rheumatic diseases are a group of disorders characterised by a loss of immune tolerance, which leads to chronic inflammation, degeneration or metabolic abnormalities in various organs or tissues. Despite the lack of clarity surrounding the causes of these diseases, both environmental and genetic factors play an important role. Recent research indicates that alterations in the composition of the gut microbiota, known as gut dysbiosis, may contribute to the development of a number of rheumatic diseases, including rheumatoid arthritis, systemic lupus, ankylosing spondylitis, systemic scleroderma and Sjögren's syndrome. The gut microbiota influences the balance between pro- and anti-inflammatory immune responses, which may have important implications for the pathogenesis of these diseases.
Furthermore, studies have indicated that the composition of the gut microbiota may be associated with the response to therapies used to treat rheumatic diseases, thus opening up new avenues for the development of microbiota-targeted treatments for these conditions.

Aim of the study: The objective of this review is to investigate the impact of the gut microbiota on the pathogenesis of rheumatic diseases and to evaluate potential therapies targeting the manipulation of the gut microbiota.

Material and methods: The present study is based on literature available in scientific databases from 2019-2024, such as PubMed, Corchane Library and Google Scholar, using the following keywords: “rheumatic diseases”; “gut microbiota”; ,”rheumatoid arthritis”, “immunity”, “spondylitis”

Results and conclusions: A growing body of evidence suggests a potential link between the gut microbiota and rheumatic diseases. Patients often exhibit a reduced ratio of Firmicutes to Bacteroidetes and abnormal numbers of Bacteroides. Molecular mimicry and a potential association with short-chain fatty acids have also been observed. Further human studies are needed to more fully understand the role of the gut microbiota and potential therapeutic interventions.

Keywords: “rheumatic diseases”; “gut microbiota”; “rheumatoid arthritis”; “spondylitis” “systemic lupus erythematosus”; “ systemic scleroderma”; “Sjögren's syndrome”

Introduction

The gastrointestinal tract is populated by a vast array of prokaryotic microorganisms, including bacteria, archaea, fungi and viruses, collectively known as the gut microbiota. The microbiota comprises between 1,000 and 5,000 different species of microorganisms, with a tenfold excess of microbial cells over host cells [1], [2] . The majority of these microorganisms belong to the Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria groups. The composition of the microbiota is established during early childhood [3].

The gut microbiota is comprised of four distinct microbial groups: those that are beneficial to the host, which maintain host homeostasis in a cooperative and non-pathogenic manner; those that are sensitive to disease, which become dysregulated by disease; those that are pathogenic, which can cause disease; and those that are therapeutic, which can help reverse changes [4]. In addition to facilitating digestion and absorption of food, beneficial microbes exert a protective function by preventing pathogenic microbes from adhering to the mucosal layer [5]. Furthermore, the host can provide a suitable habitat for the survival of beneficial microbes.

The composition of the gut microbiota can be modified by a number of factors, including diet, probiotics, prebiotics, antibiotics, exogenous enzymes, faecal microbiota transplantation (FMT) and other environmental factors [6] . Additionally, the distribution of the gut microbiota is also shaped by local regional conditions in the gastrointestinal tract [7].

The gut microbiota is essential for host health, particularly for maintaining homeostasis and immune function. Components of the gut microbiota play a profound role in the modulation of the host's innate and adaptive immunity. The host immune system has the ability to induce immune tolerance to the existence of beneficial microbes and prevent the uncontrolled growth of pathogenic pathogens [2]. The development and differentiation of the local and systemic immune system, as well as non-immune components, are dependent on the presence of commensal microorganisms [8], [9]. The intestinal barrier plays a pivotal role in maintaining immune homeostasis through these microorganisms [10].

The gut microbiota is involved in immune responses, presumably by modifying intestinal barrier permeability, altering autoantigen integrity, mimicking epitopes and modulating mechanisms of cell apoptosis [11], [12]. It is essential to maintain tolerance towards the gut microbiota in order for the host to benefit from their coexistence. Conversely, colonisation with specific pathogenic microbes can be detrimental to the host, leading to disease [13]. The gut microbiota plays an important role in the pathogenesis of many intestinal and extraintestinal diseases [14], [15] . Furthermore, dysbiosis of the gut microbiota, which is closely related to the intestinal mucosal immune system, has been linked to autoimmune diseases [2]. Intestinal dysbiosis, resulting from host-microbe interactions, has been shown to disrupt the intestinal mucosal barrier and intestinal mucosal immunity, leading to increased secretion of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-17 and tumour necrosis factor alpha (TNF-α). These cytokines can in turn lead to chronic inflammation [16], [17].

Rheumatic diseases, which are defined as connective tissue disorders characterised by chronic inflammation, degeneration or metabolic disorders, are caused by a complex interaction of

environmental and genetic factors [18]. They can affect any organ or tissue without a clear cause.

Indeed, a growing body of experimental and clinical evidence indicates that the chronic inflammatory response triggered by intestinal dysbiosis is an important immunopathological mechanism leading to the development of rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic scleroderma (SSc), spondyloarthritis (AS) and Sjögren's syndrome (SS).

Molecular mechanism

The vast and diverse gut microbiota community forms a network essential for immune health and maintaining homeostasis in the body. Despite this, the influence of the microbiome on the development of autoimmune and inflammatory diseases remains unclear.

The composition of the gut microbiota is influenced by both internal and external factors. Environmental factors, such as smoking, diet, stress and medication, and genetic factors, including gender, age and susceptible genes, affect the composition of the human microbiota in various ways. Among exogenous factors, foreign microorganisms play a particular role and represent a rich source of antigenic variation [19], [20]. Certain species of gut microbes may play a protective or pathogenic role in the development of rheumatic diseases [21].

Approximately 70-80% of the body's immune cells are located in the gastrointestinal tract [22]. As a result of co-evolution, the gut microbiota and immune cells form an interdependent relationship, which is crucial for the proper functioning of the immune system.

A number of autoimmune and inflammatory diseases, including RA, psoriatic arthritis (PsA), AS, SS, SSc, polymyalgia rheumatica, giant cell vasculitis and dermatomyositis (DM), have traditionally been regarded as conditions in which T lymphocytes play a pivotal role [23].

The gut microbiota and associated metabolic signals play a pivotal role in the activation, polarization, and function of CD4+ T cells. This encompasses type 1 (Th1) T-bet+ helper T cells, Th2 GATA3+ cells, Th17 retinoid-related orphan receptor (ROR)-γt+ cells, and FOXP3+ regulatory T (Treg) cells [24]. Studies have demonstrated that segmented filamentous bacteria (SFB) are capable of inducing the differentiation of Th17 cells in the intestinal lamina propria of mice [25]. The loss of these cells from the small intestinal dermis is a characteristic feature of systemic deficiency in germ-free (GF) animals. However, the introduction of SFB into these animals resulted in the restoration of Th17 cell populations in the lamina propria and the production of autoantibodies, which rapidly led to the development of arthritis [26].

Despite the paucity of data on the prevalence of SFB in humans, they are particularly abundant in weaning animals [27]. The majority of current knowledge on SFB is derived from studies in animal models, which may not be fully translatable to humans due to differences in the gastrointestinal microbiota and immune cell profiles between species [28]. Many current studies aim to clarify these issues. Furthermore, the similarity between specific bacterial peptides and host autoantigens has long been recognised, resulting in the production of cross-reactive T cells that attack both types of antigens. This phenomenon, known as molecular mimicry, may also be a potential mechanism for the microbiome's influence on rheumatic diseases [29].

The relationship between the immune system and the gut microbiota is not fully understood due to its complexity. Short-chain fatty acids (SCFAs), including acetate, propionate and butyrate, play an important role in this relationship. Metabolites produced by intestinal bacteria, of which SCFA is the main product, have been found to regulate the differentiation of T lymphocytes and B lymphocytes [30]. SCFAs can be divided into:

- acetic acid,
- propionic acid,
- butyric acid,
- isobutyric acid,
- valeric acid
- isovaleric acid [31].

Acetic acid and propionic acid have been demonstrated to enhance the differentiation of T cells into Th1 and Th17 lymphocytes under inflammatory conditions by regulating the mammalian target of rapamycin (mTOR) protein kinase pathway [32]. Furthermore, Haghikia et al. [33] corroborated the immunomodulatory properties of propionic acid, indicating that it promotes the differentiation of regulatory cells (Tregs) and elevates IL-10 levels in the propionic acid-treated group.

Valeric acid has been demonstrated to induce IL-10 in regulatory B lymphocytes through the stimulation of glucose oxidation and increased mTOR activity [34].

Another type of SCFA, butyric acid, has been demonstrated to be responsible for Treg polarisation, as well as the downregulation of pro-inflammatory cytokines and suppression of Th cells (He et al., 2022). Additionally, butyric acid has been shown to inhibit the production of autoantibodies, probably by inhibiting the differentiation of B cells in the embryonic centre via follicular helper T cells (Tfh) [35].

Rheumatoid arthritis (RA)

Rheumatoid arthritis (RA) is a chronic systemic immune-mediated connective tissue disease characterised by non-specific symmetrical arthritis, extra-articular lesions and systemic symptoms, leading to disability and premature death. Depending on the presence or absence of serum autoantibodies (rheumatoid factor IgM class and/or anti-citrullinated peptide antibodies [ACPA]), a serologically positive or negative form of the disease can be distinguished.

The characteristic symptoms of this disease are symmetrical pain and swelling in the joints of the hands and feet, less frequently in the large joints (e.g. knee or shoulder); morning stiffness of varying duration, usually >1 h.

Metabolites produced by the intestinal microflora, including SCFAs, tryptophan derivatives, trimethylamine oxide (TMAO), bile acids, peptidoglycan and lipopolysaccharide (LPS), exhibit immunomodulatory properties that can both exacerbate and alleviate inflammation in RA. At the mechanistic level, these metabolites affect the differentiation of immune cells, cytokine production and the integrity of the intestinal barrier, which collectively shape the autoimmune environment [36].

The main periodontitis pathogens (PD) Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans have been identified as potentially involved in the onset and development of RA.

There is also a higher prevalence of PD among patients with RA, which may be due to similar risk factors or a mutual correlation between the two conditions. Furthermore, it is pertinent to note that patients with RA and PD exhibit a similar cytokine imbalance, characterised by elevated gingival fluid levels of pro-inflammatory cytokines (IL-1β, IL-6, IL-4 and TNF-α) and reduced levels of anti-inflammatory cytokines (e.g. IL-10) [37].

Airway abnormalities have been associated with the presence of rheumatoid arthritis-associated autoantibodies in patients without arthritis, suggesting that the lungs may be a potential site of RA initiation with similar autoimmunity [38]. In their study, Villis Van C. et al. [39] detected RA-associated antibodies in the sputum of patients with early RA and in a group predisposed to RA. This result indicates that the lungs may be the site of autoantibody production in early RA. Furthermore, the fact that smoking significantly increases the risk of developing RA supports the hypothesis that the lungs play a potential role in RA pathogenesis [40].

Scher et al. [41] employed 16S sequencing to demonstrate that the lung microbiota of RA patients exhibited significant divergence from that of healthy individuals, exhibiting greater resemblance to the microbiota observed in sarcoidosis. In both conditions, a reduction or absence of Actinomycetaceae, Spirochaetaceae and Burkholderiaceae, as well as the genera Actinomyces, Treponema and Porphyromonas, was observed compared to healthy individuals. These findings suggest that mucositis may be one of the factors contributing to pulmonary dysbiosis in both cases. As this dysbiosis correlates with systemic and local autoimmune changes, it may be involved in the pathogenesis of RA in some cases.

Short-chain fatty acids (SCFA) in RA

SCFAs are a group of compound with immunomodulatory potential in RA [42]. Reduced SCFA levels have been observed in patients with RA. Reduced SCFA levels were observed in both RA patients and animal models. Furthermore, reduced disease severity was observed in mouse models of RA, including CIA, antigen-induced arthritis and K/BxN serum-transmitted arthritis after SCFA supplementation

Molecular mimicry of the gut microflora in RA

Collagen XI (CXI) is a component of articular cartilage and is involved in regulating its formation. It can be used to induce arthritis in DBA/1 mice [43] . It may also exhibit molecular mimicry in conjunction with HLA-DBR1, as bacteria present in the gut, such as Citrobacter, Bacteroides, Eggerthella and Clostridium, possess epitopes that are suitable for it. HLA-DRB1 is associated with an increased risk of developing RA through the presentation of autoantigenic and self-antigenic peptides. Overall, molecular mimicry of the gut microbiome with these RA-associated antigens may lead to a breakdown of immune tolerance and the early destruction of articular cartilage [31].

Another collagen type that has been studied is collagen II (CII), the main building block of articular cartilage. This collagen was used to create a mouse model of RA [44]. Peptides

derived from Bacteroides fragilis 3_1_12, a bacterial strain in the Bacteroidaceae family, can be used to mimic those of collagen II (CII) [45]. These peptides have been shown to induce the production of autoantibodies against CII and to enhance the progression of rheumatoid arthritis[46].

It has been demonstrated that cases of cross-reactivity between Roseburia intestinalis and memory Th1 cells reactive to antibodies against β2 glycoprotein I (β2GPI) may result in the production of autoantibodies in individuals with anti-phospholipid syndrome (APS). Furthermore, the presence of β2GPI in the serum of rheumatoid arthritis patients may also be induced by cross-reactivity with R. intestinalis, which may contribute to the pathogenesis of RA [31].

In lymphocytes from the gut of mice in a preclinical model of RA, an increased interleukin-17 response to the 60s ribosomal protein L23a (RPL23A), T-cell reactive autoantigens and RA autoantibodies has been observed [47].

Prevotella copri presents an epitope that mimics the structure of RPL23A and induces pro-inflammatory Th17 cell responses [48]. Furthermore, P. copri has been demonstrated to exhibit homology with the HLA-DR-presenting T-cell epitopes N-acetylglucosamine-6-sulfatase (GNS) and filamin A (FLNA) [49]. Both GNS and FLNA are elevated in joint inflammation in RA patients. The development of autoantibodies may be a symptom of autoimmune activation and joint damage in RA patients [50].

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus (SLE) is an autoimmune disease that develops as a result of a complex dysfunction of the immune system, leading to a chronic inflammatory process in many tissues and organs.

It develops as a result of autoimmune disorders leading to chronic inflammation and dysfunction of many systems and organs: kidneys, central nervous system (CNS), haematopoietic system, joints, skin. It is characterised by a diverse clinical picture and variable disease course (exacerbations and remissions), as well as the presence of specific serum autoantibodies.

With regard to SLE, there has been a growing number of studies in mice in which significant differences in the composition of the bacterial microflora before and after the onset of lupus have been identified. Furthermore, the same study found that an increased abundance of Lactobacilli was associated with more severe clinical symptoms in NZB/WF1 mice [51].

In their study, Kim et al. [52] demonstrated that a reduced amount of the Lactobacillaceae group was present in MRL/Ipr mice. Mu et al. [53] also observed that an increase in Lactobacillales was associated with improved lupus symptoms in MRL/Ipr mice.

He et al. [54] observed an increase in Bacteroidetes abundance and a decrease in Firmicutes in the gut microbiota of MRL/lpr mice. Wang et al. [55] demonstrated that the lower Firmicutes/Bacteroidetes (F/B) ratio observed in 6-week-old MRL/lpr mice may have contributed to the early onset of disease. Abdelhamid et al. [56] investigated the relationship between Bacteroidetes and pathological glomerular outcomes and found a positive correlation between the two.

Furthermore, the investigation sought to ascertain whether the microflora of lupus patients and mice could induce the production of autoantibodies and increase the expression of lupus-related genes in germ-free mice. In a study by Choi et al. [57] , the transfer of dysbiotic gut microbiota from mice with three lupus-prone congenic mutations to germ-free C57BL/6 congenic mice was observed. This resulted in the activation of immune cells and the induction of autoantibody production in recipient mice.

Furthermore, in a study by Ma et al. [58] , the transplantation of gut microbiota from mice with SLE into germ-free mice was conducted, resulting in the induction of anti-dsDNA antibody production and an increase in SLE susceptibility gene expression in germ-free mice. Upon transplantation of faecal microbiota from SLE patients, the expression of SLE-related genes was found to be elevated, accompanied by the manifestation of lupus-like phenotypic features. These included elevated serum levels of autoantibodies, altered distribution of immune cells in mucosal and peripheral immune responses, and impaired cytokine balance [59].

A number of studies have demonstrated that the gut microbiota of patients with systemic lupus erythematosus differs significantly from that of healthy individuals. Wang et al. [60] compared lupus patients to their healthy family members, controlling for living conditions and dietary factors, and found that the gut microbiota of lupus patients still differed from that of healthy individuals.

Guo et al. [61] demonstrated that individuals with systemic lupus erythematosus exhibit intestinal dysbiosis, including a significantly lower F/B ratio, in comparison to healthy individuals. This finding corroborates a previous study conducted a year earlier [62]. It is also pertinent to note that bacteria from the Bacteroidetes and Firmicutes groups constitute the majority of the gut microbiota [63] . He et al. [64] demonstrated that Firmicutes is inversely correlated with the SLE activity index (SLEDAI). Moreover, similar findings were reported by Gerges and colleagues [65] , who observed that the F/B ratio exhibited a negative correlation with the SLEDAI-2K disease activity index.

A further significant gut dysbiosis was identified in individuals with lupus, namely a reduction in bacterial diversity [66] . Azzouz et al. [67] demonstrated that patients with elevated lupus activity indices exhibited a particularly pronounced decline in the species diversity of the gut microbiota.

In a study by Bagavant et al. [68] , it was found that higher levels of IgG antibodies against Enterococcus gallinarum in patients were significantly associated with the presence of anti-Sm, anti-ribosomal P and anti-double-stranded DNA (anti-dsDNA) antibodies.

Azzouz et al. [67] demonstrated that Ruminococcus gnavus (RG) was present at an average of 5-fold higher levels in patients with lupus nephritis compared to healthy controls. Patients with high disease activity, particularly those with lupus nephritis, exhibited the greatest expansion of this population. Furthermore, anti-RG antibodies demonstrated a direct correlation with anti-DNA antibody levels and SLEDAI results, while exhibiting a negative correlation with C3 and C4 complement protein levels. Patients with active nephritis, particularly those with class III and IV, exhibited the highest serum levels of antibodies directed against RG.

Liu et al. [69] demonstrated that the amount of Acholeplasma, Capnocytophaga and Leptotrichia exhibited a negative correlation with SLEDAI score, while the amount of Bacteroides, Ruminococcus and Akkermansia was inversely correlated with serum C3 complement levels.

A meta-analysis published in 2022 [70] provided further evidence of intestinal dysbiosis in SLE patients. This study found an increased abundance of Enterobacteriaceae and Enterococcaceae and a reduced abundance of Ruminococcaceae in the gut microbiome of lupus patients.

Systematic sclerosis (SSc)

Systemic scleroderma (SSc) is a systemic connective tissue disease characterised by progressive fibrosis of the skin and internal organs (leading to organ failure), abnormalities of blood vessel morphology and function, and abnormalities of the immune system. The disease is characterised by a highly variable clinical picture due to the different rates of progression and types of organ complications.

Recent studies, including those on rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), have confirmed the uniqueness of the bacterial microbiome in SSc patients. This is characterised by specific changes at the level of the Bacteroidetes group and genera such as Bacteroides, Faecalibacterium, Clostridium, Fusobacterium, Prevotella and Lactobacillus [71] . Another study [72] demonstrated that SSc patients exhibited a higher proportion of Lactobacillus and Streptococcus and a lower proportion of Sutterella in the formation of the bacterial microflora compared to healthy subjects.

A study by Volkmann et al. [73] evealed that patients with SSc exhibited significantly lower levels of commensal bacterial genera that have been identified as protective against inflammation, including Bacteroides, Faecalibacterium, and Clostridium, in comparison to controls. Conversely, they exhibited significantly higher levels of pathogenic bacterial genera, such as Fusobacterium. Furthermore, the study demonstrated that an elevated prevalence of the genus Clostridium was linked to a reduced severity of gastrointestinal symptoms in both cohorts.

Plichta et al. [74] observed an increased prevalence of Clostridium and Streptococcus species, accompanied by a reduction in the volume of Alistipes, Bacteroides and butyric acid-producing species, in patients with scleroderma.

In their study, Patrone et al. [75] demonstrated that elevated levels of Lactobacillus, Blautia and Coprococcus, and reduced levels of Roseburia and Faecalibacterium, were associated with an increase in gastrointestinal symptoms in scleroderma patients. These findings were compared to those of a control group.

A study by Natalello et al. [72] demonstrated that disease duration was also a significant factor in the composition of the gut microbiota. Those with long-term disease exhibited a reduction in microbial richness. Similar observations were made in patients with diffuse SSc (dsSSc) compared to those with limited SSc (lcSSc) and in patients

Ankylosing Spondylitis (AS)

Ankylosing spondylitis (AS) is a chronic, usually progressive, inflammatory process of unknown aetiology that primarily affects the sacroiliac joints, vertebral joints, fibrous rings

and ligaments of the spine, leading to their progressive stiffening. Peripheral joint involvement and extra-articular symptoms may occur.

Zhou et al. [76] demonstrated that Bacteroides coprophilus, Parabacteroides distasonis, Eubacterium siraeum, Acidaminococcus fermentans and Prevotella copri were increased in AS, while Enterococcus faecium E980 and TX0133a01 were decreased. Furthermore, they demonstrated increased oxidative phosphorylation, lipopolysaccharide biosynthesis, and glycosaminoglycan degradation in the AS gut microbiota.

Liu et al. [77] conducted 16S rRNA gene sequencing on stool samples from patients with ankylosing spondylitis (AS) and healthy controls.

Their findings indicated that the relative abundance of Bacteroidetes was diminished in AS patients, while that of Firmicutes and Verrucobacterium was augmented. Furthermore, specific gut bacteria were associated with disease activity in AS patients.

In a study published in 2019, Li and colleagues [78] demonstrated a correlation between the F/B ratio and the maintenance of intestinal homeostasis. They also found that an increase in the number of specific Firmicutes species is associated with AS.

Berland et al. [79] demonstrated a reduction in the abundance of several bacterial species in patients with SpA, with a particular focus on those belonging to the order Clostridiales. Among the bacterial species exhibiting increased abundance, Ruminococcus gnavus was identified. Additionally, significant differences in microbiota composition were observed between HLA-B27-positive and HLA-B27-negative siblings of patients with AS in control subjects.

Sjögren's syndrome

Sjögren's syndrome (pSS) is a chronic inflammatory disease of the connective tissue with an autoimmune basis, resulting in lymphocyte infiltration of the exocrine glands (salivary glands, lacrimal glands, pancreas) with subsequent dysfunction and inflammatory changes in other systems and organs.

A study by van der Meulen et al. [80] demonstrated that the composition of the intestinal microflora in patients with Sjogren's syndrome and lupus was significantly different from that of the population control group. However, no significant difference was observed between pSS and SLE. The patients exhibited a lower bacterial richness, a lower Firmicutes/Bacteroidetes ratio and a higher relative abundance of Bacteroides species in faecal samples compared with the controls. Furthermore, the composition of the oral microflora differed significantly between patients with pSS and patients with SLE. This can be partly attributed to the dryness of the mouth in patients with pSS. Moon et al. [81] additionally verified that patients with pSS exhibit a diminished F/B ratio and an augmentation in Bacteroidetes species. Moreover, they demonstrated a decline in Actinobacteria, Blautia, Dorea, and Agathobacter.

Jia et al. [82] demonstrated that patients with Sjogren's syndrome exhibited a higher abundance of Lactobacillus salivarius, Bacteroides fragilis, Ruminococcus gnavus, Clostridium bartlettii, Clostridium bolteae, Veillonella parvula and Streptococcus parasanguinis species. Furthermore, among the differential microbial pathways, the l-phenylalanine biosynthesis superpathway was also more enriched in patients with pSS

complicated interstitial lung disease (ILD). The gut microbiota of pSS patients contained more virulence genes, the majority of which encoded peritrichal cilia, fimbriae or curli fimbriae, three types of bacterial surface organelles involved in bacterial colonisation and invasion. Furthermore, five microbial peptides with the potential to mimic pSS-associated autoepitopes were also more prevalent in the gut of pSS patients.

Conclusion

A review of studies on the association of gut microbiota with rheumatic diseases, including rheumatoid arthritis, systemic lupus erythematosus, systemic scleroderma, ankylosing spondylitis and Sjögren's syndrome, indicates a significant correlation between these diseases and the status of the gut microbiota. The results of numerous studies indicate a reduced ratio of Firmicutes to Bacteroidetes in the gut microbiota of patients with the aforementioned diseases compared to controls. Furthermore, abnormalities in the abundance of bacteria of the genus Bacteroides are often reported in patients with these diseases compared to healthy individuals.

In particular, studies indicate the presence of molecular mimicry and a link to the production of short-chain fatty acids (SCFAs) in rheumatoid arthritis (RA). These phenomena may play an important role in the pathogenesis of the disease. Although numerous studies have now been carried out in mouse models, there is still a lack of sufficient studies in human populations, making it difficult to clearly identify the aetiological mechanisms and potential therapeutic interventions.

Further research, particularly on humans, is required to gain a fuller understanding of the role of the gut microbiota in the development and progression of rheumatic diseases and to develop possible therapeutic strategies based on modulation of the microbiota.

Statement of the authors‘ contribution

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References

[1] R. L. Brown, M. L. Yeung Larkinson, and T. B. Clarke, "Immunological design of commensal communities to treat intestinal infection and inflammation," PLoS Pathog, vol. 17, no. 1, p. e1009191, Jan. 2021, doi: 10.1371/JOURNAL.PPAT.1009191.

[2] H. Xu et al., "Interactions between Gut Microbiota and Immunomodulatory Cells in Rheumatoid Arthritis," Mediators Inflamm, vol. 2020, 2020, doi: 10.1155/2020/1430605.

[3] Y. Yao, X. Cai, Y. Ye, F. Wang, F. Chen, and C. Zheng, "The Role of Microbiota in Infant Health: From Early Life to Adulthood," Front Immunol, vol. 12, p. 708472, Oct. 2021, doi: 10.3389/FIMMU.2021.708472/BIBTEX.

[4] R. Yacoub, A. Jacob, J. Wlaschin, M. McGregor, R. J. Quigg, and J. J. Alexander, "Lupus: The microbiome angle," Immunobiology, vol. 223, no. 6–7, pp. 460–465, Jun. 2018, doi: 10.1016/J.IMBIO.2017.11.004.

[5] P. Paone and P. D. Cani, "Mucus barrier, mucins and gut microbiota: the expected slimy partners?," Gut, vol. 69, no. 12, pp. 2232–2243, Dec. 2020, doi: 10.1136/GUTJNL-2020-322260.

[6] Q. Guan, "A Comprehensive Review and Update on the Pathogenesis of Inflammatory Bowel Disease," J Immunol Res, vol. 2019, 2019, doi: 10.1155/2019/7247238.

[7] B. Zhou et al., "Intestinal Flora and Disease Mutually Shape the Regional Immune System in the Intestinal Tract," Front Immunol, vol. 11, p. 512969, Apr. 2020, doi: 10.3389/FIMMU.2020.00575/BIBTEX.

[8] H. Kayama, R. Okumura, and K. Takeda, "Interaction between the Microbiota, Epithelia, and Immune Cells in the Intestine," Annu Rev Immunol, vol. 38, no. Volume 38, 2020, pp. 23–48, Apr. 2020, doi: 10.1146/ANNUREV-IMMUNOL-070119-115104/CITE/REFWORKS.

[9] L. Wang, L. Zhu, and S. Qin, "Gut Microbiota Modulation on Intestinal Mucosal Adaptive Immunity," J Immunol Res, vol. 2019, no. 1, p. 4735040, Jan. 2019, doi: 10.1155/2019/4735040.

[10] S. Ghosh, C. S. Whitley, B. Haribabu, and V. R. Jala, "Regulation of Intestinal Barrier Function by Microbial Metabolites," Cell Mol Gastroenterol Hepatol, vol. 11, no. 5, pp. 1463–1482, Jan. 2021, doi: 10.1016/J.JCMGH.2021.02.007.

[11] E. Gianchecchi and A. Fierabracci, "Recent Advances on Microbiota Involvement in the Pathogenesis of Autoimmunity," International Journal of Molecular Sciences 2019, Vol. 20, Page 283, vol. 20, no. 2, p. 283, Jan. 2019, doi: 10.3390/IJMS20020283.

[12] A. Kalinkovich and G. Livshits, “A cross talk between dysbiosis and gut-associated immune system governs the development of inflammatory arthropathies,” Semin Arthritis Rheum, vol. 49, no. 3, pp. 474–484, Dec. 2019, doi: 10.1016/J.SEMARTHRIT.2019.05.007.

[13] S. Nell, S. Suerbaum, and C. Josenhans, “The impact of the microbiota on the pathogenesis of IBD: lessons from mouse infection models,” Nat Rev Microbiol, vol. 8, no. 8, pp. 564–577, Aug. 2010, doi: 10.1038/NRMICRO2403.

[14] M. Durazzo, A. Ferro, and G. Gruden, “Gastrointestinal Microbiota and Type 1 Diabetes Mellitus: The State of Art,” J Clin Med, vol. 8, no. 11, Nov. 2019, doi: 10.3390/JCM8111843.

[15] D. N. Fredricks, “The gut microbiota and graft-versus-host disease,” J Clin Invest, vol. 129, no. 5, p. 1808, May 2019, doi: 10.1172/JCI125797.

[16] C. Amoroso, F. Perillo, F. Strati, M. C. Fantini, F. Caprioli, and F. Facciotti, “The Role of Gut Microbiota Biomodulators on Mucosal Immunity and Intestinal Inflammation,” Cells 2020, Vol. 9, Page 1234, vol. 9, no. 5, p. 1234, May 2020, doi: 10.3390/CELLS9051234.

[17] F. Di Vincenzo, A. Del Gaudio, V. Petito, L. R. Lopetuso, and F. Scaldaferri, “Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review,” Intern Emerg Med, vol. 19, no. 2, pp. 275–293, Mar. 2024, doi: 10.1007/S11739-023-03374-W/FIGURES/2.

[18] G. Alsaleh, F. C. Richter, and A. K. Simon, “Age-related mechanisms in the context of rheumatic disease,” Nature Reviews Rheumatology 2022 18:12, vol. 18, no. 12, pp. 694–710, Nov. 2022, doi: 10.1038/s41584-022-00863-8.

[19] L. Zhang and C. Q. Chu, “Gut Microbiota–Medication Interaction in Rheumatic Diseases,” Front Immunol, vol. 12, p. 796865, Dec. 2021, doi: 10.3389/FIMMU.2021.796865/BIBTEX.

[20] G. Kwao-Zigah et al., “Microbiome Dysbiosis, Dietary Intake and Lifestyle-Associated Factors Involve in Epigenetic Modulations in Colorectal Cancer: A Narrative Review,” Cancer Control, vol. 31, Jan. 2024, doi: 10.1177/10732748241263650.

[21] Y. Tong, T. Marion, G. Schett, Y. Luo, and Y. Liu, “Microbiota and metabolites in rheumatic diseases,” Autoimmun Rev, vol. 19, no. 8, p. 102530, Aug. 2020, doi: 10.1016/j.autrev.2020.102530.

[22] M. Beukema, M. M. Faas, and P. de Vos, “The effects of different dietary fiber pectin structures on the gastrointestinal immune barrier: impact via gut microbiota and direct effects on immune cells,” Experimental & Molecular Medicine 2020 52:9, vol. 52, no. 9, pp. 1364–1376, Sep. 2020, doi: 10.1038/s12276-020-0449-2.

[23] Y. Li, J. Du, and W. Wei, “Emerging Roles of Mucosal-Associated Invariant T Cells in Rheumatology,” Front Immunol, vol. 13, p. 819992, Mar. 2022, doi: 10.3389/FIMMU.2022.819992/BIBTEX.

[24] E. M. Brown, D. J. Kenny, and R. J. Xavier, “Gut Microbiota Regulation of T Cells During Inflammation and Autoimmunity,” Annu Rev Immunol, vol. 37, pp. 599–624, Apr. 2019, doi: 10.1146/ANNUREV-IMMUNOL-042718-041841.

[25] U. Roy et al., “Induction of IL-22-Producing CD4+ T Cells by Segmented Filamentous Bacteria Independent of Classical Th17 Cells,” Front Immunol, vol. 12, p. 671331, Sep. 2021, doi: 10.3389/FIMMU.2021.671331/BIBTEX.

[26] D. Zhong, C. Wu, X. Zeng, and Q. Wang, “The role of gut microbiota in the pathogenesis of rheumatic diseases,” Clin Rheumatol, vol. 37, no. 1, pp. 25–34, Jan. 2018, doi: 10.1007/S10067-017-3821-4.

[27] H. Chen, L. Wang, X. Wang, X. Wang, H. Liu, and Y. Yin, “Distribution and Strain Diversity of Immunoregulating Segmented Filamentous Bacteria in Human Intestinal Lavage Samples,” Microb Ecol, vol. 79, no. 4, pp. 1021–1033, May 2020, doi: 10.1007/S00248-019-01441-4/METRICS.

[28] L. A. Oemcke, R. C. Anderson, E. Altermann, N. C. Roy, and W. C. McNabb, “The Role of Segmented Filamentous Bacteria in Immune Barrier Maturation of the Small Intestine at Weaning,” Front Nutr, vol. 8, p. 759137, Nov. 2021, doi: 10.3389/FNUT.2021.759137/BIBTEX.

[29] S. Topi et al., “Biomolecular Mechanisms of Autoimmune Diseases and Their Relationship with the Resident Microbiota: Friend or Foe?,” Pathophysiology 2022, Vol. 29, Pages 507-536, vol. 29, no. 3, pp. 507–536, Sep. 2022, doi: 10.3390/PATHOPHYSIOLOGY29030041.

[30] C. H. Kim, “Control of lymphocyte functions by gut microbiota-derived short-chain fatty acids,” Cellular & Molecular Immunology 2021 18:5, vol. 18, no. 5, pp. 1161–1171, Apr. 2021, doi: 10.1038/s41423-020-00625-0.

[31] L. Lin et al., “Gut microbiota in pre-clinical rheumatoid arthritis: From pathogenesis to preventing progression,” J Autoimmun, vol. 141, p. 103001, Dec. 2023, doi: 10.1016/J.JAUT.2023.103001.

[32] F. Golpour et al., “Short chain fatty acids, a possible treatment option for autoimmune diseases,” Biomedicine & Pharmacotherapy, vol. 163, p. 114763, Jul. 2023, doi: 10.1016/J.BIOPHA.2023.114763.

[33] A. Haghikia et al., “Propionate attenuates atherosclerosis by immune-dependent regulation of intestinal cholesterol metabolism,” Eur Heart J, vol. 43, no. 6, pp. 518–533, Feb. 2022, doi: 10.1093/EURHEARTJ/EHAB644.

[34] M. Luu et al., “The short-chain fatty acid pentanoate suppresses autoimmunity by modulating the metabolic-epigenetic crosstalk in lymphocytes,” Nature Communications 2019 10:1, vol. 10, no. 1, pp. 1–12, Feb. 2019, doi: 10.1038/s41467-019-08711-2.

[35] E. Rosser, C. Piper, D. Matei, P. B.-C. metabolism, and undefined 2020, “Microbiota-derived metabolites suppress arthritis by amplifying aryl-hydrocarbon receptor activation in regulatory B cells,” cell.comEC Rosser, CJM Piper, DE Matei, PA Blair, AF Rendeiro, M Orford, DG Alber, T KrausgruberCell metabolism, 2020•cell.com, Accessed: Jun. 20, 2024. [Online]. Available: https://www.cell.com/cell-metabolism/pdf/S1550-4131(20)30118-2.pdf

[36] Z. feng Lu et al., “Exploring the significance of microbiota metabolites in rheumatoid arthritis: uncovering their contribution from disease development to biomarker potential,” APMIS, vol. 132, no. 6, pp. 382–415, Jun. 2024, doi: 10.1111/APM.13401.

[37] A. Korzeniowska and E. Bryl, “Infectious and Commensal Bacteria in Rheumatoid Arthritis—Role in the Outset and Progression of the Disease,” International Journal of Molecular Sciences 2024, Vol. 25, Page 3386, vol. 25, no. 6, p. 3386, Mar. 2024, doi: 10.3390/IJMS25063386.

[38] M. K. Demoruelle, T. M. Wilson, and K. D. Deane, “Lung inflammation in the pathogenesis of rheumatoid arthritis,” Immunol Rev, vol. 294, no. 1, pp. 124–132, Mar. 2020, doi: 10.1111/IMR.12842.

[39] V. C. Willis et al., “Sputum Autoantibodies in Patients With Established Rheumatoid Arthritis and Subjects at Risk of Future Clinically Apparent Disease,” Arthritis Rheum, vol. 65, no. 10, pp. 2545–2554, Oct. 2013, doi: 10.1002/ART.38066.

[40] S. Kadura and G. Raghu, “Rheumatoid arthritis-interstitial lung disease: manifestations and current concepts in pathogenesis and management,” European Respiratory Review, vol. 30, no. 160, Jun. 2021, doi: 10.1183/16000617.0011-2021.

[41] J. U. Scher et al., “The lung microbiota in early rheumatoid arthritis and autoimmunity,” Microbiome, vol. 4, no. 1, p. 60, Nov. 2016, doi: 10.1186/S40168-016-0206-X/FIGURES/4.

[42] W. Ratajczak, A. Rył, A. Mizerski, K. Walczakiewicz, O. Sipak, and M. Laszczyńska, “Immunomodulatory potential of gut microbiome-derived shortchain fatty acids (SCFAs),” Acta Biochimica Polonica, vol. 66, no. 1. Acta Biochimica Polonica, pp. 1–12, 2019. doi: 10.18388/abp.2018_2648.

[43] L. Alcaide-Ruggiero, V. Molina-Hernández, M. M. Granados, and J. M. Domínguez, “Main and Minor Types of Collagens in the Articular Cartilage: The Role of Collagens in Repair Tissue Evaluation in Chondral Defects,” International Journal of Molecular Sciences 2021, Vol. 22, Page 13329, vol. 22, no. 24, p. 13329, Dec. 2021, doi: 10.3390/IJMS222413329.

[44] M. Miyoshi and S. Liu, “Collagen-Induced Arthritis Models,” Methods in Molecular Biology, vol. 2766, pp. 3–7, 2024, doi: 10.1007/978-1-0716-3682-4_1.

[45] C. Zhou et al., “Metagenomic profiling of the pro-inflammatory gut microbiota in ankylosing spondylitis,” J Autoimmun, vol. 107, p. 102360, Feb. 2020, doi: 10.1016/J.JAUT.2019.102360.

[46] B. Liang et al., “The autoantibody response to cyclic citrullinated collagen type II peptides in rheumatoid arthritis,” Rheumatology, vol. 58, no. 9, pp. 1623–1633, Sep. 2019, doi: 10.1093/RHEUMATOLOGY/KEZ073.

[47] Y. Ito et al., “Detection of T cell responses to a ubiquitous cellular protein in autoimmune disease,” Science (1979), vol. 346, no. 6207, pp. 363–368, Oct. 2014, doi: 10.1126/SCIENCE.1259077/SUPPL_FILE/ITO.SM.PDF.

[48] N. Garabatos and P. Santamaria, “Gut Microbial Antigenic Mimicry in Autoimmunity,” Front Immunol, vol. 13, p. 873607, Apr. 2022, doi: 10.3389/FIMMU.2022.873607/BIBTEX.

[49] A. Pianta et al., “Two rheumatoid arthritis–specific autoantigens correlate microbial immunity with autoimmune responses in joints,” J Clin Invest, vol. 127, no. 8, pp. 2946–2956, Aug. 2017, doi: 10.1172/JCI93450.

[50] B. Lucchino, F. R. Spinelli, C. Iannuccelli, M. P. Guzzo, F. Conti, and M. Di Franco, “Mucosa–Environment Interactions in the Pathogenesis of Rheumatoid Arthritis,” Cells 2019, Vol. 8, Page 700, vol. 8, no. 7, p. 700, Jul. 2019, doi: 10.3390/CELLS8070700.

[51] X. M. Luo et al., “Gut Microbiota in Human Systemic Lupus Erythematosus and a Mouse Model of Lupus,” Appl Environ Microbiol, vol. 84, no. 4, Feb. 2018, doi: 10.1128/AEM.02288-17.

[52] D. S. Kim, Y. Park, J. W. Choi, S. H. Park, M. La Cho, and S. K. Kwok, “Lactobacillus acidophilus Supplementation Exerts a Synergistic Effect on Tacrolimus Efficacy by Modulating Th17/Treg Balance in Lupus-Prone Mice via the SIGNR3 Pathway,” Front Immunol, vol. 12, Dec. 2021, doi: 10.3389/FIMMU.2021.696074.

[53] Q. Mu et al., “Control of lupus nephritis by changes of gut microbiota,” Microbiome, vol. 5, no. 1, p. 73, Jul. 2017, doi: 10.1186/S40168-017-0300-8.
[54] H. He et al., “Sodium Butyrate Ameliorates Gut Microbiota Dysbiosis in Lupus-Like Mice,” Front Nutr, vol. 7, Nov. 2020, doi: 10.3389/FNUT.2020.604283.
[55] H. Wang et al., “Aberrant Gut Microbiome Contributes to Intestinal Oxidative Stress, Barrier Dysfunction, Inflammation and Systemic Autoimmune Responses in MRL/lpr Mice,” Front Immunol, vol. 12, Apr. 2021, doi: 10.3389/FIMMU.2021.651191.
[56] L. Abdelhamid et al., “Retinoic Acid Exerts Disease Stage-Dependent Effects on Pristane-Induced Lupus,” Front Immunol, vol. 11, Mar. 2020, doi: 10.3389/FIMMU.2020.00408.
[57] S. C. Choi et al., “Gut microbiota dysbiosis and altered tryptophan catabolism contribute to autoimmunity in lupus-susceptible mice,” Sci Transl Med, vol. 12, no. 551, Jul. 2020, doi: 10.1126/SCITRANSLMED.AAX2220.
[58] Y. Ma, X. Xu, M. Li, J. Cai, Q. Wei, and H. Niu, “Gut microbiota promote the inflammatory response in the pathogenesis of systemic lupus erythematosus,” Mol Med, vol. 25, no. 1, Aug. 2019, doi: 10.1186/S10020-019-0102-5.
[59] Y. Ma et al., “Lupus gut microbiota transplants cause autoimmunity and inflammation,” Clin Immunol, vol. 233, Dec. 2021, doi: 10.1016/J.CLIM.2021.108892.
[60] X. Wang, Q. Shu, L. Song, Q. Liu, X. Qu, and M. Li, “Gut Microbiota in Systemic Lupus Erythematosus and Correlation With Diet and Clinical Manifestations,” Front Med (Lausanne), vol. 9, Jun. 2022, doi: 10.3389/FMED.2022.915179.
[61] M. Guo et al., “Alteration in gut microbiota is associated with dysregulation of cytokines and glucocorticoid therapy in systemic lupus erythematosus,” Gut Microbes, vol. 11, no. 6, pp. 1758–1773, Nov. 2020, doi: 10.1080/19490976.2020.1768644.
[62] Y. Li et al., “Disordered intestinal microbes are associated with the activity of Systemic Lupus Erythematosus,” Clin Sci (Lond), vol. 133, no. 7, pp. 821–838, Apr. 2019, doi: 10.1042/CS20180841.
[63] J. Qin et al., “A human gut microbial gene catalogue established by metagenomic sequencing,” Nature, vol. 464, no. 7285, pp. 59–65, 2010, doi: 10.1038/NATURE08821.
[64] J. He et al., “Microbiome and Metabolome Analyses Reveal the Disruption of Lipid Metabolism in Systemic Lupus Erythematosus,” Front Immunol, vol. 11, Jul. 2020, doi: 10.3389/FIMMU.2020.01703.
[65] M. A. Gerges, N. E. Esmaeel, W. K. Makram, D. M. Sharaf, and M. G. Gebriel, “Altered Profile of Fecal Microbiota in Newly Diagnosed Systemic Lupus Erythematosus Egyptian Patients,” Int J Microbiol, vol. 2021, 2021, doi: 10.1155/2021/9934533.
[66] T. A. van der Meulen et al., “Shared gut, but distinct oral microbiota composition in primary Sjögren’s syndrome and systemic lupus erythematosus,” J Autoimmun, vol. 97, pp. 77–87, Feb. 2019, doi: 10.1016/J.JAUT.2018.10.009.
[67] D. Azzouz et al., “Lupus nephritis is linked to disease-activity associated expansions and immunity to a gut commensal,” Ann Rheum Dis, vol. 78, no. 7, pp. 947–956, Jul. 2019, doi: 10.1136/ANNRHEUMDIS-2018-214856.
[68] H. Bagavant et al., “Immune Response to Enterococcus gallinarum in Lupus Patients Is Associated With a Subset of Lupus-Associated Autoantibodies,” Front Immunol, vol. 12, May 2021, doi: 10.3389/FIMMU.2021.635072.

[69] F. Liu et al., “Distinct Microbiomes of Gut and Saliva in Patients With Systemic Lupus Erythematous and Clinical Associations,” Front Immunol, vol. 12, Jul. 2021, doi: 10.3389/FIMMU.2021.626217.

[70] S. Xiang et al., “Association between systemic lupus erythematosus and disruption of gut microbiota: a meta-analysis,” Lupus Sci Med, vol. 9, no. 1, Mar. 2022, doi: 10.1136/LUPUS-2021-000599.

[71] C. Bellocchi et al., “Microbial and metabolic multi-omic correlations in systemic sclerosis patients,” Ann N Y Acad Sci, vol. 1421, no. 1, pp. 97–109, Jun. 2018, doi: 10.1111/NYAS.13736.

[72] G. Natalello et al., “Gut microbiota analysis in systemic sclerosis according to disease characteristics and nutritional status,” Clin Exp Rheumatol, vol. 38, pp. S73–S84, 2020, Accessed: Jun. 21, 2024. [Online]. Available: https://www.clinexprheumatol.org/abstract.asp?a=15489

[73] E. R. Volkmann et al., “Systemic sclerosis is associated with specific alterations in gastrointestinal microbiota in two independent cohorts,” BMJ Open Gastroenterol, vol. 4, no. 1, p. e000134, Apr. 2017, doi: 10.1136/BMJGAST-2017-000134.

[74] D. R. Plichta et al., “Congruent microbiome signatures in fibrosis-prone autoimmune diseases: IgG4-related disease and systemic sclerosis,” Genome Med, vol. 13, no. 1, Dec. 2021, doi: 10.1186/S13073-021-00853-7.

[75] V. Patrone et al., “Gut microbiota profile in systemic sclerosis patients with and without clinical evidence of gastrointestinal involvement,” Sci Rep, vol. 7, no. 1, Dec. 2017, doi: 10.1038/S41598-017-14889-6.

[76] C. Zhou et al., “Metagenomic profiling of the pro-inflammatory gut microbiota in ankylosing spondylitis,” J Autoimmun, vol. 107, Feb. 2020, doi: 10.1016/J.JAUT.2019.102360.

[77] G. Liu, Y. Hao, Q. Yang, and S. Deng, “The Association of Fecal Microbiota in Ankylosing Spondylitis Cases with C-Reactive Protein and Erythrocyte Sedimentation Rate,” Mediators Inflamm, vol. 2020, 2020, doi: 10.1155/2020/8884324.

[78] M. Li et al., “Altered Bacterial-Fungal Interkingdom Networks in the Guts of Ankylosing Spondylitis Patients,” mSystems, vol. 4, no. 2, Apr. 2019, doi: 10.1128/MSYSTEMS.00176-18.

[79] M. Berland et al., “Both Disease Activity and HLA–B27 Status Are Associated With Gut Microbiome Dysbiosis in Spondyloarthritis Patients,” Arthritis and Rheumatology, vol. 75, no. 1, pp. 41–52, Jan. 2023, doi: 10.1002/ART.42289/ABSTRACT.

[80] T. A. van der Meulen et al., “Shared gut, but distinct oral microbiota composition in primary Sjögren’s syndrome and systemic lupus erythematosus,” J Autoimmun, vol. 97, pp. 77–87, Feb. 2019, doi: 10.1016/J.JAUT.2018.10.009.

[81] J. Moon, S. H. Choi, C. H. Yoon, and M. K. Kim, “Gut dysbiosis is prevailing in Sjögren’s syndrome and is related to dry eye severity,” PLoS One, vol. 15, no. 2, p. e0229029, Feb. 2020, doi: 10.1371/JOURNAL.PONE.0229029.

[82] X. miao Jia et al., “Compositional and functional aberrance of the gut microbiota in treatment-naïve patients with primary Sjögren’s syndrome,” J Autoimmun, vol. 141, p. 103050, Dec. 2023, doi: 10.1016/J.JAUT.2023.103050.