Review Article

Gut Microbiota in Rheumatoid Arthritis: Pathogenic Mechanisms and Therapeutic Potential

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and systemic complications. Although genetic susceptibility and environmental factors contribute to disease development, the precise mechanisms underlying RA pathogenesis remain incompletely understood. Increasing evidence suggests that the gut microbiota plays a critical role in regulating host immune responses and maintaining immune homeostasis. Alterations in the composition and function of gut microbial communities (dysbiosis) have been associated with immune dysregulation and the development of autoimmune diseases, including RA. Recent studies indicate that modulation of the gut microbiome through probiotics, prebiotics, dietary interventions, and microbiota-targeted therapies may alleviate inflammation and improve clinical outcomes in RA patients. This review summarizes the current understanding of RA pathogenesis, highlights the role of gut microbiota in immune regulation, and discusses the therapeutic potential of microbiome-based interventions in the management of RA.

Keywords: Rheumatoid Arthritis, Gut Microbiota, Dysbiosis, Probiotics, Immune Regulation, Inflammation

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Introduction

Rheumatoid arthritis (RA) is considered as one of the most common chronic inflammatory diseases. Between 0.4% to 1.3% of the population is affected by RA with a two to three times higher prevalence in women than in men. Both environmental factors (smoking, pollution, life style) and genetic factors such as genetic polymorphisms such as leukocyte antigen (HLA)-DRB1, tumor necrosis factor receptor superfamily member 14 (TNFRSF14), protein tyrosine phosphatase non-receptor type 22 (PTPN22), signal transducer and activator of transcription (STAT4), peptidyl arginine deiminase type 4 (PADI4), and CC chemokine receptor (CCR6) can contribute to RA incidence (1).

Rheumatoid arthritis development process can be divided into preclinical and clinical periods. Preclinical phase, happening before clinical symptoms occurrence, is crucial for early intervention and can be diagnosed through the evaluation of serum biomarkers like anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) (2). RA clinical symptoms are linked to local and systemic inflammation, leading to swelling, pain, stiffness of the joints and cartilage and bone destruction; as well as fever, muscle pain, and fatigue. In addition, RA-related systemic inflammation can increase the risk of cardiovascular disease, atherosclerosis, pulmonary disorders, glomerulonephritis, and gastrointestinal complications (3).

The treatment of RA, as recommended by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR), aims to reduce inflammation and control disease progression (3). Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in relieving pain, reducing inflammation, and improving joint function; however, they do not prevent disease progression and may cause adverse effects such as renal, hepatic, gastrointestinal, and cardiovascular complications when used at high doses (4). The primary treatment strategy for RA currently involves disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, which can slow disease progression with relatively fewer side effects (2, 5). In addition, biological therapies including tumor necrosis factor (TNF)-α inhibitors, anti-interleukin (IL)-6 antibodies, and β-cell–targeted therapies are used when conventional DMARDs are insufficient (6). Recently, increasing attention has been given to the role of the gut microbiota in the pathogenesis of RA. Alterations in gut microbial composition (dysbiosis) have been associated with immune dysregulation and chronic systemic inflammation. Emerging evidence suggests that the gut microbiome may influence host immune responses and contribute to either the initiation or progression of autoimmune processes in RA. Therefore, modulation of the gut microbiota through dietary strategies, probiotics, and other microbiome-targeted interventions is being investigated as a potential adjunctive therapeutic approach in RA management.

Pathogenesis of rheumatoid arthritis

Rheumatoid arthritis (RA) is a systemic inflammatory disease involving both innate and adaptive immunity (Figure 1). The inflammatory cascade promotes autoimmunity in synovial joints and other organs. Autoreactive β cells differentiate in lymph nodes and generate plasma cells that secrete two key RAassociated autoantibodies: (RF and ACPA). RF (IgM/IgA) binds the Fc region of selfIgG, though its pathogenic role remains unclear. ACPA (IgG) targets citrullinated proteins and forms immune complexes (7). While most complexes are cleared by macrophages, smaller ones persist and accumulate in capillaries, especially of joints, kidneys, and lungs, causing tissue injury, release of selfantigens, and production of damage-associated molecular patterns (DAMPs). These antigens promote the activation of autoreactive T cells and their differentiation into T helper 1 (Th1) and T helper 17 (Th17) subsets within regional lymph nodes. Th1 cells, driven by interleukin-12 (IL-12), secrete interferon-γ (IFN-γ), which promotes the polarization of pro-inflammatory M1 macrophages. Th17 cells differentiate in response to IL-1, IL-6, and transforming growth factor-β (TGF-β) and produce cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-17 (IL-17), which enhance neutrophil recruitment and activation, as well as interleukin-23 (IL-23), which contributes to the activation and proliferation of fibroblast-like synoviocytes (FLS) and chondrocytes (8).

In addition, anti-citrullinated protein antibody (ACPA)-containing immune complexes activate Fcγ receptors on macrophages and neutrophils, leading to production of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α. Activated neutrophils, which are unable to efficiently clear immune complexes and matrix-bound antigens, undergo enhanced degranulation, increased reactive oxygen species (ROS) production, and neutrophil extracellular trap (NET) formation, thereby amplifying local inflammation (9).

Damage-associated molecular patterns (DAMPs) and inflammatory mediators further sustain the activation of macrophages and neutrophils. Meanwhile, FLS and chondrocytes acquire an aggressive, invasive phenotype and produce matrix metalloproteinases (MMPs), leading to extracellular matrix degradation and progressive tissue damage (10). Osteoclast activation, driven by receptor activator of nuclear factor kappa-B ligand (RANKL) produced by macrophages and FLS, is further enhanced by inflammatory cytokines and immune complexes, resulting in bone resorption and joint destruction (11). If uncontrolled, these processes may extend beyond the joints and contribute to systemic manifestations of RA.

RARelated Signaling Pathways

Immune system activity is largely regulated by receptor–ligand interactions that initiate intracellular signaling cascades controlling cell survival, differentiation, and inflammatory responses. Key signaling pathways involved in inflammation and immunity include Janus kinase/signal transducer and activator of transcription (JAK–STAT), mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), spleen tyrosine kinase (SYK), Wnt, Notch, and NF-κB, most of which play important roles in RA pathogenesis.

JAKSTAT Signaling Pathway

The JAK–STAT pathway mediates signaling from type I and type II cytokine receptors, particularly those activated by IL-6 and IFN-γ, which are central mediators of RA-associated inflammation. This pathway consists of four Janus kinases (JAK1–3 and TYK2) and seven signal transducers and activators of transcription (STAT1–4, STAT5a/b, and STAT6). Following ligand-induced receptor dimerization, JAKs become activated and phosphorylate STAT proteins, which then form dimers and translocate to the nucleus to regulate cytokine-responsive gene expression. Dysregulation of this pathway contributes significantly to RA progression (12).

JAK1, TYK2, and STAT1 are involved in transmitting IL-6 and IFN-γ signaling, while STAT1 also participates in IL-10 signaling, reflecting its dual pro- and anti-inflammatory roles. STAT1 and STAT4 are associated with Th1 differentiation through IFN-γ and IL-12 signaling, promoting M1 macrophage polarization and production of nitric oxide (NO), ROS, IL-1, IL-12, and TNF. STAT4 polymorphisms have also been associated with increased susceptibility to RA.

STAT3, activated mainly by IL-6 and IL-21, promotes Th17 differentiation and T follicular helper (Tfh)-mediated β cell activation, leading to immunoglobulin G (IgG) class switching and autoantibody production (13). Overactivation of JAK2/STAT3 signaling in chondrocytes enhances MMP expression and RANKL production, contributing to cartilage degradation and osteoclast activation (14). In addition, STAT3 promotes the hyperproliferation and invasive behavior of FLS. In contrast, STAT5 and STAT6 support regulatory T (Treg) and Th2 cell differentiation, and their suppression has been associated with increased RA severity (3).

NF-κB Signaling Pathway

The NF-κB family is activated downstream of multiple receptors, including those for IL-1, TNF, IL-17, Toll-like receptors (TLRs), NOD-like receptors (NLRs), and lymphocyte antigen receptors. The core components of this pathway include NF-κB transcription factors, inhibitor of κB (IκB) proteins, and IκB kinase (IKK) complexes. This pathway plays a central role in inflammation, immune cell activation and maturation, and lymphoid organ development. In RA, NF-κB expression is significantly increased in synovial tissues,

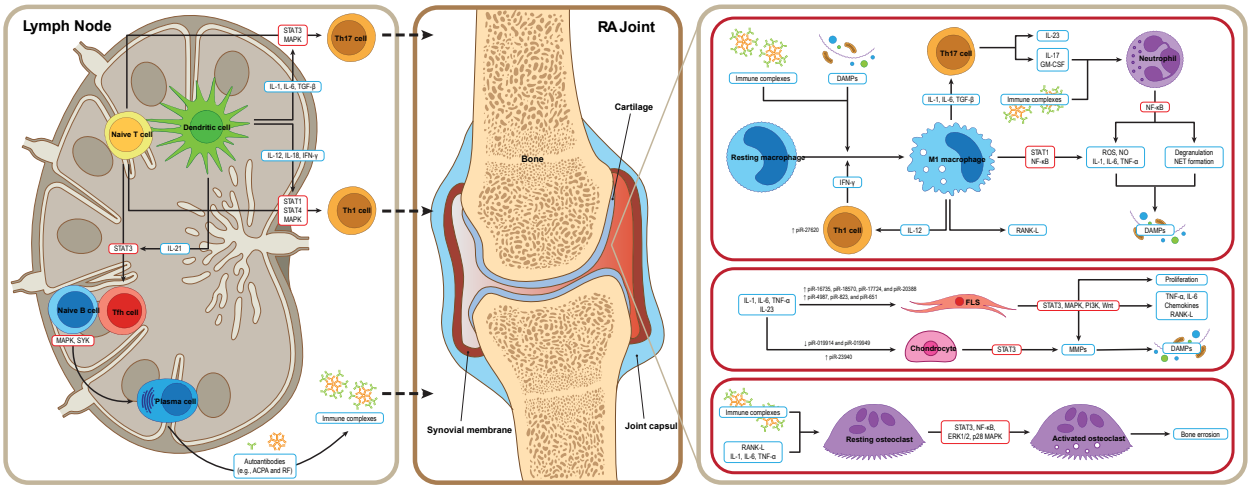


Figure 1. Cellular and Molecular Mechanisms Driving RA Pathogenesis. The primary activation of potentially autoreactive T cells occurs in the lymph nodes. The differentiated Th1 and Th17 cells then migrate into the joint and stimulate the inflammation and tissue destruction cascades by activating macrophages and neutrophils. Activated M1 macrophages and neutrophils as well as FLS, chondrocytes, and osteoclasts take part in the pathogenesis of RA by secreting different mediators, cytokines, and enzymes. Moreover, M1 macrophages can produce cytokines to further stimulate the differentiation of Th1 and Th17. Autoreactive B cells also activate in lymph nodes and differentiate into autoantibody-producing plasma cells. Autoantibodies can bind self-antigens to form immune complexes which accumulate in the joint. Immune complexes activate macrophages, neutrophils, and osteoclasts through interaction with Fc receptors. The important signaling pathways are presented in red-frame boxes and the possible miss-regulations of piRNAs are included as well. DAMPs: Damage-associated molecular patterns; FLS: Fibroblast-like synoviocyte; Th cell: Helper T cell; Tfh cell: Follicular helper T cell.

and its inhibition has been shown to reduce angiogenesis and osteoclast differentiation (3). Activation of NF-κB enhances the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in response to PAMPs and DAMPs, thereby establishing a self-amplifying inflammatory loop. Dysregulated NF-κB signaling in RA synovium contributes to synovial hyperplasia and abnormal FLS behavior, ultimately promoting cartilage and bone destruction (15). In chondrocytes, NF-κB activation induces metabolic reprogramming toward glycolysis and upregulates lactate dehydrogenase A (LDHA), which contributes to oxidative stress, extracellular matrix degradation, increased proliferation, and enhanced cell migration (16).

MAPK Signaling Pathway

Mitogen-activated protein kinase (MAPK) signaling pathways are activated by a wide range of extracellular stimuli and play an important role in the pathogenesis of RA. The major mammalian MAPK subfamilies include p38 MAPK, extracellular signal-regulated kinases (ERK1/2), and c-Jun N-terminal kinases (JNK). Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α activate ERK1/2 signaling. MAPK members, particularly JNK and ERK1/2, contribute to RA pathogenesis through activation of MMPs, leading to tissue degradation (17). In addition, p38 MAPK is highly activated in RA tissues and inhibits Fas-mediated T cell apoptosis, thereby sustaining inflammatory cell survival (3). MAPK signaling also plays a critical role in T and B cell activation and activator protein-1 (AP-1) transcription factor formation. Furthermore, ERK1/2 and p38 MAPK act downstream of RANKL signaling, promoting osteoclast differentiation and the expression of genes involved in bone resorption (18).

PI3K/AKT Signaling Pathway

The phosphatidylinositol 3-kinase (PI3K)–AKT signaling pathway is associated with the development and progression of RA (3). This pathway mediates growth factor signaling and regulates key cellular processes, including metabolism, survival, and proliferation. Activation of PI3K/AKT promotes FLS proliferation in response to inflammatory cytokines and stimulates the mechanistic target of rapamycin (mTOR) pathway, thereby inhibiting autophagy (3). In addition, the PI3K–AKT–mTOR axis contributes to angiogenesis through upregulation of hypoxia-inducible factors (HIF-α) and vascular endothelial growth factor (VEGF) (19).

SYK Signaling Pathway

Spleen tyrosine kinase (SYK) and ζ-chain-associated protein kinase 70 (ZAP70) are key non-receptor tyrosine kinases involved in B cell receptor (BCR) and T cell receptor (TCR) signaling. Following antigen receptor engagement, these kinases phosphorylate immunoreceptor tyrosine-based activation motifs (ITAMs), leading to SYK activation. Activated SYK triggers downstream signaling cascades involving MAPK, NF-κB, and calcium mobilization.

In RA, B cells produce autoantibodies such as RF and ACPA, and increased levels of phosphorylated SYK have been reported in patients with elevated RF/ACPA titers (3, 15). Bruton's tyrosine kinase (BTK), a member of the TEC family of non-receptor tyrosine kinases, plays a central role in B cell differentiation, activation, and proliferation. BTK can be activated downstream of SYK and PI3K signaling pathways and contributes to antibody production, cytokine release, and cell migration. In addition, BTK functions downstream of RANK signaling and is involved in osteoclast-mediated bone resorption (20).

Notch Signaling Pathway

The Notch signaling pathway is a highly conserved regulatory system that controls cell fate determination. It consists of four Notch receptors and five ligands, including Delta-like ligands (DLL1, DLL3, DLL4) and Jagged ligands (Jagged1 and Jagged2). Ligand binding induces sequential proteolytic cleavages, resulting in the release of the Notch intracellular domain, which translocate to the nucleus and functions as a transcriptional regulator.

Notch signaling is essential for T cell development and differentiation. Notch-3 has been implicated in the regulation of Th1 and Th17 responses, with increased expression observed in synovial fibroblasts. Interaction between Jagged-1 on dendritic cells and Notch-4 on T cells promotes Th2 and Th17 differentiation through interactions with Hippo and Wnt signaling pathways (21). In RA, Notch signaling also enhances the production of pro-inflammatory cytokines by synoviocytes, macrophages, and FLS (3).

Wnt Signaling Pathway

Wnt proteins bind to cell surface receptors such as Frizzled (Fz) to activate either the canonical Wnt/β-catenin pathway or non-canonical signaling cascades. β-catenin plays a central role in the canonical pathway, functioning as both a transcriptional co-activator and a regulator of cytoskeletal organization (22).

The Wnt/β-catenin pathway is dysregulated in RA and contributes to FLS activation and angiogenesis (3, 22, 23). Conversely, suppression of Wnt signaling is associated with bone loss and osteoporosis in RA. Elevated levels of Dickkopf-1 (Dkk-1), an inhibitor of Wnt signaling, have been detected in the serum of RA patients compared with healthy individuals. Therapeutic interventions such as TNF-α inhibitors, IL-1 receptor antagonists, and anti-IL-6 antibodies have been shown to reduce Dkk-1 levels (22).

PiRNAs

PIWI-interacting RNAs (piRNAs) are small non-

coding RNAs of 24–32 nucleotides that maintain genomic stability mainly by silencing transposable elements in germline cells. Recent studies show that they are also expressed in somatic tissues and may regulate key cellular processes such as proliferation, differentiation, and metabolism (24). piRNAs are transcribed by RNA polymerase II and processed into mature molecules that bind PIWI proteins (PIWIL1–4) to form PIWI–piRNA complexes. These complexes regulate gene expression through epigenetic silencing, post-transcriptional RNA regulation, and modulation of signaling pathways (25). More than 23,000 piRNA loci have been identified in the human genome, often organized in clusters. Overall, piRNAs are important regulators of gene expression and genome stability, and their dysregulation has been linked to human diseases, although their exact roles remain unclear (24, 26).

The dysregulation of PIWI-piRNA in the context of RA and osteoarthritis (OA) has been reported in several studies (Table 1). In one study, it was identified 24 differentially expressed piRNAs (9 downregulated and 15 upregulated piRNAs) in RA patients compared to healthy controls. Gene ontology enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of these piRNAs revealed their association with many cellular functions and signaling pathways related to RA, including PI3K/AKT and MAPK signaling, Th17, and osteoclast differentiation, as well as transcriptional regulation of STAT3, FcγR2A, and CXCL12. Expression of DDX39B, MYBL1, and HENMT1, all of which are required for the expression of the piRNA gene cluster, have been reported in the peripheral blood of RA patients. Elevation of piR-27620 in the peripheral blood of RA patients is also correlated positively with IgA concentrations and negatively with IgM. and piR-27124 positively correlated with neutrophil count and CRP levels. In addition, a significant upregulation of C4B, the potential target of piRhsa-25672, was observed in the peripheral blood of RA patients (27). In another study, PlesÏtilova L. et al. found up to 300 piRNAs expressed in RA and OA patients' synovial fibroblasts. Out of these piRNAs, the most expression belonged to piR-16735, which covered 20% of piRNA reads, followed by piR-18570, piR-17724, and piR-20388, each covered about 5% of total piRNA reads (28). In addition, higher expression of piR-4987, piR-823, and piR-651 was observed in peripheral blood mononuclear cells (PBMCs) and synovial fibroblasts of RA patients compared to healthy controls. A study identified about 10 piRNA downregulations in human chondrocyte cell line C28/I2 treated with IL-1, TNF-α, or LPS. Among these, piR-019914 and piR-019949 were shown to promote chondrocyte proliferation and survival when overexpressed. Has-pir-019914 also inhibits the LDHA-dependent ROS production in chondrocytes (29). This can represent the adverse effect of an inflammatory microenvironment on chondrocyte viability. In the case of PIWI proteins, no significant increase in PIWIL2 and PIWIL4 was reported in RA patients compared to healthy controls with no detectable amounts of PIWIL1 and PIWIL3. Although, in vitro stimulation of synovial fibroblasts with TLR-ligands LPS and Poly(I:C) or with the IL-1β in combination with TNFα caused an increase in PIWIL2 and PIWIL4 mRNA suggesting their potential involvement in inflammatory signaling pathways (28). Altogether, the fact that piRNAs take part in the regulation of many inflammatory and immune cells depended processes that are essential for RA pathogenesis and progression seems undeniable; but whether piRNA dysregulations have a causative role in RA pathogenesis or is a consequence of inflammatory environment is still unclear and needs further investigation.

Probiotics and Immunomodulation

Probiotics, primarily consisting of the *Lactobacillus* and *Bifidobacterium* genera, are microorganisms that offer significant health benefits when ingested in appropriate amounts. Beyond their role in modulating the gut microbiome and alleviating dysbiosis, these bacteria exert profound antioxidant, immunomodulatory, and anti-inflammatory effects (30).

A central feature of probiotic function is immunomodulation, facilitated by interactions with

Table 1. PiRNA studies involving in the pathogenesis of RA

PiRNA	Study Model	Cellular Effect	Reference
piR-019914	Human chondrocyte	Promotes proliferation and survival. Reduces the production of MMP-3 and MMP-13.	(16)
piR-019949	Human chondrocyte	Promotes proliferation and survival. Decreases MMP-13 expression.	(29)
piR-36,741	Human bone marrow stem cell	Promotes osteogenic differentiation.	(48)
piR_037459	Mouse chondrocyte	Decreases the expression of collagen II. Promotes the apoptosis of chondrocytes.	(49)
piR-25672	RA	Inhibits KLRD1 gene expression	(50)
piR-27620	RA	Inhibits TBX21 gene expression. Positive correlation with IgA and negative correlation with IgM in serum.	(50)
piR-23940	RA	Inhibits IL23R gene expression.	(50)
piR-27124	RA	Positively correlated with neutrophil count and CRP levels.	(50)

intestinal epithelial cells and various immune cells, including lymphocytes, monocytes, macrophages, and dendritic cells (DCs). A key mechanism involves enhancing intestinal immune function by stimulating B cells to produce IgA. Research indicates that oral administration of various *Lactobacillus* species and *Streptococcus thermophilus* increases intestinal IgA-producing cells in a dose-dependent manner. Specifically, studies using *Lactobacillus casei* CRL 431 and *Lactobacillus helveticus* R389 demonstrate that this IgA increase occurs via IL-6 secretion in a TLR2-dependent manner, promoting B cell clonal expansion without necessarily increasing CD4+ T cell counts. This suggests that Lactobacilli effectively trigger B cell expansion through IL-6 signaling pathways (31). Probiotics also regulate the expression of inflammatory and anti-inflammatory cytokines, thereby modulating host immune cell activation. In vitro evidence shows that *L. casei* and *L. crispatus* upregulate IL-10 and TGF-β, while *L. rhamnosus* reduces INF-γ levels and inhibits T cell and NK cell activation. Similarly, *B. lactis* and *B. longum* can suppress IL-6 and IL-1β expression. These changes favor anti-inflammatory outcomes through signaling pathways such as JAK/STAT, MAPK, TGF-β, and NF-κB, which collectively shape the immune response and provide potential therapeutic targets for inflammatory and immune-related disorders (32).

The immunomodulatory mechanisms of probiotics are broadly categorized into direct and indirect pathways. Direct pathways involve physical interactions between probiotics and intestinal epithelial cells or immune cells via pattern recognition receptors (PRRs), most notably TLRs (33). Through this direct pathway, probiotics can downregulate PRRs across various immune and epithelial cells. This modulation influences the interaction between antigen-presenting cells (APCs) and T helper cells. Furthermore, the secretion of anti-inflammatory cytokines like IL-10 and TGF-β by APCs inhibits pro-inflammatory mediators including IL-1β, TNF-α, IL-6, IL-17, and IL-23 effectively shifting T cell differentiation toward a Treg phenotype. By balancing these signaling cascades, probiotics serve as powerful agents in maintaining immune homeostasis and preventing autoimmune-like inflammatory reactions (33).

Probiotics exert indirect anti-inflammatory effects by promoting the production of beneficial microbial metabolites, such as short-chain fatty acids (SCFAs), tryptophan, adenosine, and histamine. These metabolites help inhibit pathogenic bacteria, thus reducing invasion risks. Probiotics also bolster intestinal barrier integrity by increasing mucosal secretions and enhancing the expression of tight junction proteins, which collectively restore a normal intestinal microbiome and decrease systemic inflammation (34).

SCFAs, produced from dietary fiber fermentation, are key regulators of immune responses. They influence peripheral immunity and systemic inflammation by controlling immune cell functions. For example, SCFAs can inhibit dendritic cell differentiation and alter their cytokine profiles. Butyrate and propionate induce neutrophil apoptosis and modulate their phagocytic activity, while butyrate, acetate, and propionate suppress pro-inflammatory mediators in activated macrophages. Butyrate, in particular, suppresses inflammatory cytokine secretion and has shown promise in ameliorating RA by influencing regulatory T cells (Tregs) (35). Evidence from *in vitro* studies and animal models also suggests that SCFAs have systemic anti-inflammatory effects. Butyrate has been shown to suppress antigen-induced arthritis in mice by affecting B and T cell development, specifically inhibiting germinal center B cell differentiation and cytokine production from invariant natural killer T cells involved in joint inflammation (34).

Probiotics' effect on RA

Probiotics, have been reported as a treatment agent in alleviating RA symptoms. The precise pathways through which probiotics exert their anti-inflammatory and immunomodulatory effects in RA are not entirely understood. However, research indicates that probiotics can regulate systemic inflammation through both direct and indirect pathways, leading to a reduction of pathologic activity in RA (Figure 2).

Along with SCFAs, there are other mechanisms capable of explaining the beneficial effects of probiotics in rheumatic diseases. The regulation of T helper cell functions and induction of immune tolerance are among the most important. For example, it has been shown that *L. casei* Shirota can prevent autoimmune diseases by regulating cytokine release from APCs, affecting T lymphocyte differentiation. This is exceptionally important considering the crucial role of Th1 and Th17 responses in the development of autoimmune disorders. Probiotic bacteria have also been reported to induce Treg immune responses in experimental models of immune disorders such as RA. For instance, they promote the differentiation of T cells into Tregs that express the transcription factor FoxP3 while enhancing the suppressive activity of naturally occurring Tregs (34).

Several studies have established a compelling link between gut microbiota (GM) and the onset of collagen-induced arthritis (CIA) through the administration of various bacterial strains in animal models, particularly mice and rats. For instance, research conducted by Fan *et al.* highlighted that preventive treatment with *Bifidobacterium adolescentis* in CIA rats. This intervention was associated with a significant reduction in clinical symptoms, rebalanced pro- and anti-inflammatory responses, and the reversal of gut dysbiosis. These findings suggest that early exposure to *B. adolescentis* increases production of SCFAs, enhances Treg frequency, and reduces TNF levels, indicating that early probiotic intervention may strongly influence the

onset of arthritic inflammation (36). In a separate study, Kato et al. examined the effects of *L. casei* Shirota (LcS) on CIA in mice. The LcS administration to CIA mice during the induction phase hindered the abnormal production of anti-type II collagen antibodies and delayed the onset of the disease (37). Similarly, oral administration of *Lactobacillus helveticus* SBT2171 strongly ameliorated joint swelling and weight loss while downregulating the abundance of immune cells and reducing IL-6 production, suggesting its possible role in RA prevention (38). Amdekar *et al.* screened LcS for its therapeutic potential in CIA models and demonstrated significant reductions in arthritis scores, with pro-inflammatory cytokines such as TNF and IL-6 being lowered, and a corresponding increase in the anti-inflammatory cytokine IL-10 detected. The authors attributed the beneficial effects to inactivation of the COX-2 and NF-κB pathways (39). Further studies concerning LcS and *Lactobacillus acidophilus* concluded that both probiotics downregulated pro-inflammatory cytokines while upregulating IL-10 and IL-4 levels. They also showed a reduction in the levels of lipid peroxidation and an increase in the levels of antioxidant enzymes, demonstrating the dual role of these probiotics in anti-inflammatory and antioxidant action (40). These studies together illustrate how gut microbiota can influence immune responses and, therefore, the course of collagen-induced arthritis, pointing to promising perspectives for probiotic intervention in the management of this autoimmune disease.

Adjuvant-induced arthritis (AIA) is another RA model used in some studies. In a study, Pan *et al.* focused on the management of AIA through the administration of *L. casei*. Significant changes in gut microbial composition, with altered clinical manifestations, were found during the induction and progression of arthritis. Accordingly, joint swelling and arthritis scores were reduced, and bone degradation was hindered. Indeed, after a 30-day prophylactic treatment with *L. casei*, pro-inflammatory cytokine levels were significantly lowered. The relative abundance of various *Lactobacillus* species such as *L. acidophilus, L. hominis, L. reuteri, and L. vaginalis* was improved, which thus suggests that *L. casei* may alleviate arthritis mainly by rectifying *Lactobacillus* populations (41). Certain *Lactobacillus* species have been reported to promote the differentiation of intraepithelial CD4+ T cells toward Treg cells, and their metabolic products, including SCFAs, have been implicated in maintaining colonic Treg cell homeostasis. In another study the prophylactic effects of three strains of *Bifidobacteria*; namely, *Bifidobacterium breve* NCIM 5671, *Bifidobacterium longum* NCIM 5672, and *Bifidobacterium bifidum* NCIM 5697 were examined using an AIA model. The results indicated that *Bifidobacteria* decrease the severity and progression of arthritis. Astonishingly, among all tested strains, *B.*

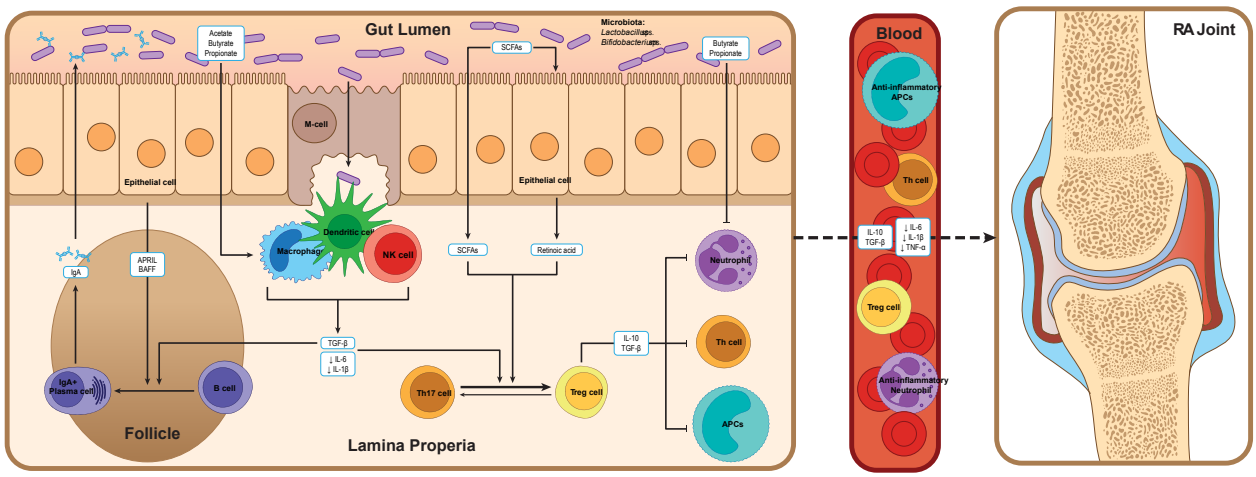


Figure 2. The Immunosuppressive Effect of Gut Microbiota. The normal flora colonizing the lumen of the intestine can affect the immune cells underlying the lamina propria layer. The gut microbiome manages to regulate the activation of the immune system to set the microenvironment towards an anti-inflammatory profile through different mechanisms. The gut microbiome can modulate immune function indirectly through the secretion of SCFAs and their metabolites such as butyrate, acetate, and propionate. The SCFAs can stimulate the differentiation of Treg cells. They also increase the secretion of retinoic acid from epithelial cells, contributing to Treg cell differentiation. The microbiota may directly alter the function of lamina propria DCs, macrophages, and natural killer cells to an anti-inflammatory profile as they can pass through M-cells. An increase in TGF-β and a decrease in IL-1β and IL-6 shifts the differentiation of T cells towards Treg cells rather than Th17 cells. Treg cells inhibit the pro-inflammatory function of a variety of immune cells. The anti-inflammatory cytokines and immune cells may recirculate in blood and enter the inflammatory sites like RA joints where they can alleviate the inflammation. In addition, the anti-inflammatory milieu of the lamina propria, alongside cytokines such as APRIL and BAFF contributes to the differentiation of B cells into IgA+ plasma cells. APCs: Antigen-presenting cells; NK cell: Natural killer cell; SCFAs: Short-chain fatty acids; Treg cell: Regulatory T cell; Th cell: Helper T cell.

breve NCIM 5671 exhibited the best anti-arthritic effects. These results indicate that their efficacies depend on strains, and thus further investigation into their use for RA treatment is warranted (42).

The effectiveness of probiotics in combination with other drugs and supplements in alleviating RA has been shown by some investigations. Rovensky *et al.* investigated the efficacy of *Escherichia coli* O83 (Colinfant) in combination with methotrexate (MTX) in the management of AIA. The study demonstrated that there is a significant reduction in inflammation and arthritis-related changes with the treatments of MTX and combined MTX and Colinfant. In addition, combination therapy was associated with a greater increase in arthritis scores than MTX given as monotherapy (43). Another research focused on the impact of *Bacillus coagulans* and inulin, administered individually and in combination, on the course of arthritis in AIA rat models. The observations demonstrated that *B. coagulans* and/or inulin reduced paw swelling and levels of pro-inflammatory markers such as fibrinogen and TNF-α (44).

On the other hand, the therapeutic effect of probiotics on RA in human studies lacks strong evidence and needs further investigation. For instance, the effect of probiotic supplementation on stable RA in a randomized controlled trial using *L. rhamnosus* GG versus a placebo revealed no differences in clinical parameters and biochemical variables. Also, no significant reductions in inflammatory markers occurred. Importantly, although no statistical differences in disease activity were observed, more improvement in subject well-being in intervention group than recipients of placebo was observed (45). The combination of *Lactobacillus rhamnosus* with *Lactobacillus reuteri* was also studied as an adjunctive therapy in patients with active RA. The results demonstrated that there is no significant difference between probiotics and placebo in terms of anti-inflammatory activity and clinical improvement of RA (46). However, a systematic review and meta-analysis on the therapeutic effect of probiotics on RA demonstrated that probiotics can decrease the production of pro-inflammatory cytokines in RA even though heir direct impact on clinical outcomes is still uncertain (47). Overall, looking through the literature available on the effectiveness of probiotics in model animals and in humans with RA disorders, the evidence shows probiotics can be a promising treatment for alleviation of RA symptoms through restoration of gut microbiome, reduction of inflammation, and modulation of immune responses.

Conclusion and Future Perspectives

RA is a complex autoimmune disease driven by the interplay of genetic susceptibility, environmental factors, and immune dysregulation. Growing evidence indicates that the gut microbiota plays an important role in maintaining immune homeostasis and that microbial dysbiosis may contribute to the initiation and progression of RA through modulation of inflammatory and immune signaling pathways. Alterations in gut microbial composition have been associated with enhanced Th1/Th17 responses, autoantibody production, and persistent activation of pro-inflammatory mediators involved in joint damage. Recent studies have highlighted the potential of microbiota-targeted interventions, particularly probiotics, as adjunctive strategies for RA management. Experimental evidence suggests that probiotics can restore microbial balance, strengthen intestinal barrier function, promote regulatory immune responses, and reduce systemic inflammation. However, clinical findings in RA patients remain inconsistent, and further large-scale, well-designed clinical trials are needed to establish their therapeutic efficacy and optimal use.

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Competing interest

The authors declare that they have no conflict.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used chatgpt in order to paraphrasing and editing. After using this service, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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