

Multitargeted Regulation of Rheumatoid Arthritis by Gut Microbiota

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Abstract. Conventional treatments for Rheumatoid Arthritis (RA) face significant challenges, including high costs, infection risks associated with immunosuppression, and inadequate response in a substantial subset of patients. Recent research into the "gut-joint axis" has revealed that characteristic gut microbiota dysbiosis in RA patients drives disease pathogenesis, spurring the development of novel, safer microbiota-targeting interventions. However, personalized precision intervention and standardization for clinical translation remain critical hurdles. This review systematically analyzes the immune mechanisms underlying RA modulation by gut microbiota, focusing on the roles of pathogenic bacteria and key metabolites like short-chain fatty acids (SCFAs) and tryptophan derivatives in immune homeostasis. It also evaluates the current evidence and research status of diverse intervention strategies, including precision diets with both ecological and diagnostic value, synergistic probiotic effects, the emerging efficacy of fecal microbiota transplantation (FMT), and novel delivery and engineered bacterial technologies, assessing their translational potential. This work provides a new perspective on RA pathogenesis and lays a theoretical foundation for developing cost-effective, high-safety microbiome-immune axis-based therapies for RA. Future research should prioritize developing "microbiota-metabolite-immune phenotype" predictive models to enable precise stratified interventions and accelerate the translation of effective microbiome-targeting therapies.

Keywords: Gut microbiota, rheumatoid arthritis, immune modulation, microbiome-targeted therapies, gut-joint axis

1. Introduction

Rheumatoid Arthritis (RA), a highly disabling autoimmune disease, presents persistent challenges with conventional treatments: the high cost of biologics and targeted drugs burdens patients and healthcare systems; the broad immunosuppressive effects of immunomodulators significantly increase risks of infection (e.g., tuberculosis reactivation, opportunistic infections) and potential malignancies; and approximately 30%-40% of patients exhibit primary or secondary inadequate treatment responses. These significant challenges necessitate the development of new strategies that are cost-effective, safe, and capable of targeting multiple disease pathways. Within this context, exploring the role of the host-microbe symbiotic interface in RA, particularly the targeted multitasking modulation of the gut microbiota, holds immense theoretical and therapeutic

significance. It represents a key potential pathway to overcome the limitations of current therapies and achieve personalized intervention.

The development of the "gut-joint axis" concept has elucidated the core mechanism whereby the gut microbiome – often termed the body's "second genome" – and its metabolites (e.g., short-chain fatty acids, [SCFAs], tryptophan metabolites) remotely regulate immune homeostasis in the joints via pathways including immune modulation, mucosal barrier function, and systemic inflammatory signaling. Recent advances in metagenomics, metabolomics, and microbiota transplantation animal models have accumulated substantial evidence confirming characteristic gut dysbiosis in RA patients, with specific microbial imbalances and metabolite disruptions strongly correlating with disease activity and aberrant immune responses. Microbiota-targeting strategies, such as probiotics/prebiotics, specific dietary patterns (e.g., high-fiber, Mediterranean diets), and postbiotics, show promising potential in preliminary clinical observations and animal studies for modulating immunity and alleviating joint inflammation, positioning them as attractive adjunctive or alternative therapeutic avenues. Nevertheless, critical challenges persist: Current evidence remains largely correlational, lacking definitive causal chains linking dysbiosis to RA pathogenesis and identifying core driver species and metabolic pathways; immense inter-individual microbiota variability presents a major hurdle for developing personalized interventions targeting specific dysregulated pathways; and translating dietary interventions faces bottlenecks in standardization, adherence verification, and large-scale, long-term efficacy and safety assessment.

Therefore, this review aims to systematically dissect the key causal pathways and molecular mechanisms by which gut dysbiosis drives RA pathogenesis, with a focus on core immunomodulatory mediators like SCFAs and tryptophan metabolites. It will critically evaluate the clinical translational potential, current obstacles, and future directions of emerging multitargeted microbiota-based strategies, including precision dietary interventions, probiotic/prebiotic therapy, fecal microbiota transplantation (FMT), and genetically engineered bacteria. The goal is to provide a robust theoretical foundation and practical guidance for developing the next generation of effective and safe RA therapeutics.

2. Mechanisms of the gut microbiota-immune axis

2.1. Gut dysbiosis and RA pathogenesis

Substantial evidence indicates that RA patients exhibit distinct and characteristic alterations in gut microbiota composition. These alterations primarily involve overgrowth of pathogenic bacteria alongside depletion of beneficial strains. Notably, *Prevotella copri* (*P. copri*) abundance is markedly elevated in RA patients, particularly during early-stage or untreated disease. Mechanistically, *P. copri*-derived citrullinase modifies host proteins, generating citrullinated antigens. Through structural similarity to self-proteins, these antigens trigger production of anti-citrullinated protein antibodies (ACPAs) – a highly specific serological marker for RA. Conversely, butyrate-producing bacteria with potent anti-inflammatory functions are significantly reduced in RA patients. Their depletion compromises intestinal immune homeostasis, as microbial anti-inflammatory molecules (MAMs) from these bacteria normally suppress inflammatory signaling via the NF- κ B pathway. This loss critically disrupts the Th17/Treg cell balance, promoting a pro-inflammatory state. Additionally, *P. copri* strains in RA patients harbor unique genetic elements (e.g., conjugative transposon CTn) that enhance arthritogenicity. Their metabolites activate dendritic cells, upregulating cytokines like IL-6 and IL-23, thereby driving Th17 cell differentiation – a key pathway in arthritis development [1].

Critically, microbial imbalance is not merely a consequence of RA, but an environmental driver of disease pathogenesis. Studies show that high-risk individuals (e.g., ACPA-positive subjects without clinical symptoms) already exhibit microbiota abnormalities resembling those in RA patients, indicating gut dysbiosis precedes disease onset. Early-life antibiotic exposure further disrupts this balance: Broad-spectrum antibiotic use in infancy significantly damages gut microbial ecology and increases future RA risk. Specifically, amoxicillin/cephalosporin use in infants reduces microbial α -diversity by 30-50%, with ecological recovery requiring up to 12 months. This treatment concurrently promotes pathogenic shifts characterized by a 70% decrease in *Bifidobacterium* alongside overgrowth of *Enterococcus* and *Klebsiella*, heightening risks of mucosal inflammation and immune dysregulation. Furthermore, it enriches multidrug resistance genes (e.g., *acrA*, *vanA*), establishing persistent reservoirs that destabilize microbial communities [2].

A key consequence of dysbiosis is compromised intestinal barrier integrity ("leaky gut"), permitting translocation of bacterial products (e.g., LPS), microbial fragments, and even live bacteria into mesenteric lymph nodes and systemic circulation. Upon recognition by the immune system, these foreign antigens trigger persistent immune activation that ultimately targets synovial tissues in joints, initiating and sustaining chronic inflammation in RA [3].

2.2. Microbial metabolites mediate gut-joint axis communication

The gut microbiota profoundly regulates host immune homeostasis through its diverse metabolic activities. Bioactive molecules derived from dietary substrate fermentation – including SCFAs, tryptophan metabolites, and secondary bile acids – serve as fundamental messengers in the gut-joint axis. These metabolites represent key molecular signals through which gut microbes remotely influence RA initiation, progression, and clinical outcomes. In RA pathogenesis, disrupted microbial metabolite profiles critically reshape systemic and joint-local immune environments through direct and indirect pathways, thereby driving autoimmune responses and chronic inflammation.

SCFAs (primarily butyrate, propionate, acetate) are essential for intestinal barrier integrity and immune tolerance. They promote Treg differentiation and function while suppressing pathological Th17 cell overactivation – central to restoring Th17/Treg balance in RA. This dual action occurs through histone deacetylase (HDAC) inhibition and G-protein coupled receptor (GPR43/41/109A) activation [4]. Concurrently, SCFAs serve as the primary energy source for colonic epithelial cells, strengthening physical and chemical barriers by enhancing tight junction protein expression and mucus secretion. This markedly reduces bacterial endotoxin translocation associated with "leaky gut." Such translocation directly activates peripheral immune cells, provoking abnormal responses to cross-reactive self-antigens – a key trigger for RA autoantibody production and joint-targeted inflammation [3]. Reduced SCFA levels and diminished SCFA-producing bacteria in RA patients correlate directly with impaired immune tolerance and increased disease activity. Tryptophan metabolism constitutes another key regulatory pathway. Commensal bacteria (e.g., *Lactobacillus*, *Bifidobacterium*) convert dietary tryptophan into indole derivatives (e.g., indole-3-propionic acid, IPA), which activate the aryl hydrocarbon receptor (AhR). Appropriate AhR signaling is vital for maintaining Treg/Th17 balance, suppressing excessive inflammation, and restoring intestinal barrier function [5].

Beyond these metabolites, microbiota-derived extracellular vesicles (EVs) transport bioactive molecules (nucleic acids, proteins, lipids) across the gut barrier to distant joints – either directly or via immune cell transport – where they modulate local inflammation. Crucially, epitopes expressed by certain gut bacteria (e.g., specific *Prevotella* species) may structurally resemble human joint tissue antigens (e.g., citrullinated epitopes). These bacterial antigens or their induced antibodies may

translocate through the impaired gut barrier, initiating cross-reactive immune responses against self-joint tissues – a potential trigger for RA-specific autoimmunity.

Consequently, gut microbiota metabolites function through interconnected mechanisms rather than in isolation. They establish a sophisticated signaling network that actively contributes to RA pathogenesis by: modulating immune cell differentiation (particularly the Treg/Th17 balance), suppressing excessive inflammatory cytokine release, maintaining barrier integrity, influencing the activity of key effector cells (such as RA synovial fibroblasts), and potentially triggering autoimmune cross-reactivity. Therapeutic strategies targeting this network – including supplementation of protective metabolites, development of receptor agonists/antagonists, precision nutrition, or microbiome transplantation – aim to restore beneficial metabolite profiles and re-establish gut-immune axis homeostasis. Such approaches hold promise for suppressing autoimmune responses, alleviating chronic inflammation, and preventing joint damage in RA.

3. Gut microbiota-targeted interventions

Strategies targeting the gut microbiome and its metabolites are revolutionizing RA management. By restoring gut microbial homeostasis, these approaches indirectly address core pathological processes within the gut-joint axis. Key interventions include precision nutrition, probiotic supplementation, microbiota transplantation, and emerging technologies.

3.1. Precision dietary modulation

Precision dietary interventions modulate the immune microenvironment by providing targeted substrates for microbial metabolism. The Mediterranean Diet (MD), rich in ω -3 polyunsaturated fatty acids, fiber, and polyphenols, significantly increases production of butyrate and other SCFAs in RA patients. Metagenomic sequencing reveals an inverse distribution pattern of butyrate-producing and butyrate-consuming bacteria in RA patients compared to healthy controls [6]. The abundance of these bacteria strongly correlates with clinical markers like ACPA antibodies and rheumatoid factor. A diagnostic model based on butyrate-metabolizing species accurately distinguishes patients from healthy individuals (98.6% accuracy in predicting joint deformation).

Additional studies confirm lower blood and fecal butyrate levels in RA patients versus controls. Normal butyrate concentrations reduce pro-inflammatory cytokine expression, promote Treg differentiation, and suppress Th17 cells, follicular helper T-cells (T_{fh}), and osteoclast activity. Dietary sodium butyrate supplementation significantly attenuated arthritis severity in murine models, restored T_{fh}/Treg balance, and reduced autoantibody production.

3.2. Probiotics and prebiotics

Probiotic strategies introduce specific functional microbes. Complementary combinations (e.g., immunomodulatory *Lactobacillus casei* with barrier-enhancing *Bifidobacterium longum*) demonstrate greater efficacy than single strains in clinical regimens. Meta-analyses of randomized controlled trials reveal that probiotics co-administered with *Tripterygium wilfordii*/methotrexate significantly reduce morning stiffness duration and serum TNF- α levels compared to monotherapy, highlighting their potential to remodel immune responses via exogenous microbial supplementation [7].

Prebiotics selectively reshape endogenous microbiota functions: Galactooligosaccharides (GOS) enrich anti-inflammatory *Faecalibacterium prausnitzii* (2.8-fold increase), while resistant starch

promotes butyrate production. In animal models, resistant starch corrected Th17/Treg imbalance and reduced arthritis activity scores [8]. Collectively, these findings underscore the need for integrated strategies combining exogenous probiotics with prebiotic-driven metabolic reprogramming. This approach targets key immunometabolic molecules like butyrate to restore gut-joint immune homeostasis, validating the clinical potential of microbiota-targeted therapies and providing a framework for precision RA treatment based on microbiome-metabolite-immune crosstalk.

3.3. FMT

FMT offers an innovative therapeutic approach for RA by reconstructing the gut microbiome. Its core mechanism involves infusing healthy donor microbiota to correct characteristic dysbiosis in RA patients: restoring microbial diversity loss, replenishing depleted anti-inflammatory bacteria, and suppressing the expansion of pro-inflammatory pathogens like *Enterococcus*. Transplanted microbiota effectively mitigates RA pathology through three interconnected and synergistic pathways. Metabolically, bacteria that produce butyrate elevate levels of SCFAs. These SCFAs play a crucial role by activating Tregs and simultaneously inhibiting the differentiation of pro-inflammatory Th17 cells, thereby restoring immune balance within the joints. Furthermore, specific bacterial metabolites, particularly indoles, act to fortify the intestinal barrier by strengthening tight junctions between gut cells. This enhanced barrier function prevents harmful bacterial components, such as lipopolysaccharide (LPS), from leaking into the bloodstream. Blocking this translocation is vital as it halts the subsequent triggering of systemic inflammation driven by key inflammatory molecules like TNF- α and IL-6. Finally, at the immunological level, antigens derived from the microbiota contribute significantly to promoting tolerance within the mucosal immune system. This heightened mucosal tolerance helps reduce inappropriate autoimmune reactions, including the production of characteristic RA autoantibodies like anti-cyclic citrullinated peptide (anti-CCP) antibodies [9].

A University of Tehran trial demonstrated reduced joint swelling, decreased serum IL-17 and TNF- α , elevated IL-10, and restored gut microbiota α -diversity in RA patients after FMT [9]. Preclinically, FMT reduced arthritis scores by 58% ($p < 0.01$) and suppressed IL-17A expression in joints of collagen-induced arthritis (CIA) mice [10]. Preliminary human trials (e.g., Luissint et al., 2023) reported that ~30% of active RA patients achieved clinical remission ($CDAI \leq 2.8$) 12 weeks post-FMT, with 40% lower serum CRP and anti-CCP titers versus controls ($p < 0.05$) [11].

FMT, as a method for holistic microbial community reconstruction, remains in the exploratory stage for RA. However, its clinical translation faces three major bottlenecks: the lack of donor microbiome biomarker profiles (such as SCFA production capacity) to predict therapeutic efficacy, the risk of transient immune activation post-transplant (requiring optimized combination regimens with immunosuppressants), and concerns about pathogen transmission and long-term safety. Current comparative studies have found that FMT combined with immunosuppressive agents effectively improves clinical symptoms in RA patients; analyses specifically indicate that combining FMT with JAK inhibitors or IL-6 antagonists significantly enhances remission rates [12]. Future efforts should focus on exploring donor-recipient functional microbiome matching strategies, developing metabolomics-based efficacy prediction models, and creating combination therapeutic protocols integrating FMT with biologics or specific bacterial strains to advance its clinical translation.

3.4. Emerging strategies

Emerging therapeutic strategies overcome limitations of traditional probiotics using metabolite-targeted delivery and synthetic biology-engineered bacteria. For example, SCFA nanocapsules employ pH-sensitive and inflammation-targeting polymers to deliver butyrate specifically to synovial tissue, reducing synovitis scores in RA mouse models [13]. Synthetic biology approaches enable therapeutic functions in engineered bacteria: *Lactobacillus reuteri* modified to secrete IL-10 persistently significantly inhibited bone erosion in CIA models, while newer "smart" engineered systems can dynamically adjust anti-inflammatory factor release in response to inflammatory signals [14]. Key genera like *Lactobacillus* and *Bifidobacteria* alleviate RA symptoms by enhancing anti-inflammatory cytokines (e.g., IL-10) and suppressing pro-inflammatory factors (e.g., TNF- α , IL-6) [14].

Current delivery systems, however, face challenges including poor biocompatibility and short metabolite half-lives. Solutions may involve biomimetic membrane coatings or controlled-release microspheres to optimize pharmacokinetics. Engineered bacteria also struggle with clinical translation due to low gut colonization rates (<20% post-administration) and potential horizontal gene transfer risks. Improvements could leverage CRISPR interference (CRISPRi) circuits or biofilm-enhanced colonization strategies.

Integrating metabolite delivery and engineered bacteria—for instance, designing bacteria to synthesize SCFAs in situ and release them in response to joint inflammation—represents a promising frontier. This synergy could bypass the ecological complexity of microbiota transplantation while directly targeting immunometabolic pathways in RA.

4. Translational challenges and interdisciplinary pathways

Current therapeutic strategies targeting the gut microbiome for RA exhibit diverse developmental stages. Precision nutrition interventions, notable for their high safety profile, are undergoing Phase III randomized controlled trials; however, adoption is limited by patient adherence rates falling below 60%. While commercially available probiotics and prebiotics offer cost-effectiveness, their efficacy is constrained by pronounced strain-specific effects and significant variability between individuals. FMT holds promise for restoring gut ecology but confronts challenges in donor screening and the absence of standardized procedures. Approaches involving metabolite delivery or engineered bacteria enable precise mechanistic targeting, yet they face major hurdles including complex manufacturing processes and prohibitively high costs for large-scale production. Resolving fundamental debates within the field, particularly whether gut microbiome imbalance (dysbiosis) initiates or results from RA, necessitates several key research breakthroughs. Future progress firstly requires developing sophisticated predictive models that integrate microbiome composition, metabolite levels, and immune cell characteristics to guide stratified treatments. Secondly, enhancing therapeutic accessibility demands innovations like freeze-dried FMT capsules and nanocarriers responsive to joint inflammation for targeted drug delivery. Thirdly, advancing precise biological control involves utilizing CRISPR technology to engineer beneficial bacteria capable of dynamically sensing and responding to pathological signals such as TNF- α . Furthermore, employing integrated experimental systems—combining gut-immune organoids on microfluidic chips with single-cell and spatial genomic analysis—will allow detailed investigation into the precise timing, location, and mechanisms by which microbial metabolites regulate RA-specific immune responses. This includes critical processes like the activation of pathogenic Th17 cells and the destructive invasion of synovial fibroblasts within life-like tissue environments. Integrating these

interdisciplinary approaches and technological innovations offers significant potential to reshape RA treatment paradigms through multi-target modulation of the gut microbiome, ultimately aiming for disease modification via precise interventions along the gut-joint axis.

5. Conclusion

This study systematically analyzed the multi-target mechanisms by which gut dysbiosis drives RA pathogenesis through the "gut-joint axis". We specifically highlighted the critical roles of *Prevotella*-mediated autoantigen generation and imbalances in SCFA and tryptophan metabolites in disrupting immune homeostasis. Furthermore, we evaluated the clinical translation potential and prevailing limitations of gut microbiome-targeted strategies, including precision nutrition, probiotics/prebiotics, FMT, metabolite-targeted delivery, and engineered bacteria.

The findings confirm that targeting the gut microbiome-immune axis offers a novel therapeutic avenue to overcome limitations of conventional RA treatments. This approach deepens our understanding of the "environment-genetic" interactions underlying RA pathogenesis from a microbial ecology perspective, laying a molecular foundation for developing cost-effective, safe, individualized therapies. Current evidence robustly indicates that characteristic gut dysbiosis and related metabolite disturbances are key environmental drivers initiating and promoting RA. Multi-pathway interventions demonstrate clear biological efficacy in restoring Th17/Treg balance and alleviating joint inflammation, as evidenced by the integration of butyrate-producing bacteria, probiotics, and prebiotics into clinical practice, improving immune biomarkers.

However, the causal links within complex microbe-host interactions require rigorous validation through improved experimental designs, such as clarifying how host genetics modulate microbiome effects. Clinical translation is hindered by substantial variability in individual responses, the absence of standardized intervention protocols, and insufficient long-term safety data. Future research must prioritize constructing multidimensional predictive models that integrate dynamic microbiome data, metabolic profiles, and immune phenotypes. This will enable stratified interventions and achieve precise spatiotemporal modulation of the "gut-joint axis".

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