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# Bidirectional Regulation of the Gut Microbiota-Immune Axis in Autoimmune Diseases

## Abstract

This review focuses on the dual regulatory gut microbiota-immune interactions in the context of autoimmune diseases. Autoimmune disorders affect 5-10% of the global population, imposing substantial individual and societal burdens. Emerging studies suggest that there is a gut microbiota-immune system crosstalk which tends to be disrupted in the context of many autoimmune diseases and their pathogenesis. Microbial products, especially short-chain fatty acids (SCFAs), influence the Th17/Treg balance along with G protein-coupled receptor signalling and histone deacetylation which is important for maintaining immune homeostasis. This review describes the dysbiosis of gut microbiota in rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis and other autoimmune diseases, including the potential of microbiome-based therapies. The exploration of such complex controlling systems stimulates the search for new therapeutic approaches to restore immunity homeostasis and alleviate autoimmune damage.

**Keywords**: Gut microbiota; Autoimmune diseases; Short-chain fatty acids; Th17/Treg balance; Dysbiosis

## 1. Introduction

Autoimmune diseases show a sharp increase in prevalence, particularly in industrialised countries, affecting around 5-10% of the global population [1]. These disorders arise from an impairment in immune system self-regulation which results in a failure to maintain self-tolerance, giving rise to various diverse conditions like rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and inflammatory bowel disease [2]. Regardless of the different ways in which they clinically present, there is growing evidence pointing to one shared autoimmune mechanism: the imbalance of the gut microbiota-immune axis [3].

The human gastrointestinal tract contains a diverse ecosystem of microorganisms, which are referred to as the gut microbiota, consisting of trillions of microorganisms. The gut microbiota is critical in nutrient metabolism, pathogen defence, and the development of the immune system [4]. The close relationship between the gut microbiota and the immunity of the host has co-evolved for thousands of years, resulting in a fragile balance of homeostasis which, when disturbed, can incite inflammatory and autoimmune responses [5]. Dysbiosis reflects diversity and compositional changes of the microbiota. It has been documented in numerous autoimmune diseases, albeit with specific signatures for each condition [6].

The two-way relationship of the gut microbiota-immune axis shifts our understanding of autoimmune diseases. As with every set of organisms, the immune system modulates the microbial consortia via antimicrobial peptides as well as secretory IgA:

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the microbiome, however, reciprocally spares immune ontogeny and function through the production of metabolites and direct contacts at the cellular level [7]. At the core of this complexity is the carefully regulated homeostasis of pro-inflammatory T helper 17 (Th17) cells and the immunosuppressive regulatory T (Treg) cells, which is fundamental for modulation of inflammation and immune tolerance [8].

Of microbial metabolites, especially SCFAs like butyrate, propionate, and acetate, are produced from the fermentation of dietary fibres and have gained consideration as key mediators in the immunoregulatory process [9]. In addition, they exert multiple effects on the Th17/Treg cell equilibrium via G protein-coupled receptors, as well as through the inhibition of specific histone deacetylases [10]. Ultimately, this modulation impacts the development and progression of autoimmune diseases, thus presenting interesting opportunities for therapeutic engagement [11].

Exploring the gut microbiota-immune axis in autoimmune diseases integrates potential clinical developments with an understanding of the underlying disease mechanisms. The personalised medicine revolution made possible by recent breakthroughs in multi-omics methods and high-throughput sequencing has furthered our capabilities in microbiome characterisation and metabolism, thus creating new opportunities for tailored intervention approaches. This review integrates existing information on the reciprocal modulation of the gut microbiota-immune axis in autoimmune diseases, placing special emphasis on the role of microbial metabolites in regulating Th17/Treg equilibrium and possible alteration strategies aimed at this important control point.

## 2.Molecular Mechanisms of Microbial Metabolites in Regulating Th17/Treg Balance

Possessing a collective metabolism greater than what the human genome encodes, the gut microbiome is an ecosystem composed of raw microbial power, with life forms that exceed human life by trillions. Metabolomic regulatory roles, particularly concerning the inflammation suppressor Treg and Th17 immune warriors' backup of cell macrophages, call for the interplay with gut microbial metabolites to maintain a complex balance. As central controllers of immune tolerance, the balance between the two is crucial, as its failure leads to various autoimmune disorders.

The microbiota within the human gut is dominated by phyla of Firmicutes and Bacteroidetes, constituting almost 90% of the bacterial composition within the intestine. These microorganisms are quite remarkable in their metabolic activities, fermenting dietary components that recombine with the host enzymes. One extremely crucial metabolic function is the fermentation of certain dietary fibres to short-chain fatty acids—supplying sodium, propionate, and butyrate. Important producers of these SCFAs are Firmicutes members such as Faecalibacterium prausnitzii, Roseburia, and Eubacterium rectale species that use acetyl CoA and butyryl CoA:acetate CoA-transferase pathways. Bacteroidetes also play an important role in the production of acetate and propionate through the succinate pathway.

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As illustrated in Figure 1, SCFAs have been shown to immunomodulate via multiple, parallel, and lateral pathways at the molecular level. The pertinent metabolites interact with G-protein coupled receptors: GPR41 (FFAR3), GPR43 (FFAR2), and GPR109A (HCAR2), which bind to and are differentially expressed within the immune cell population. GPR43 and GPR41 have G-protein coupled receptors that are abundant within peripheral tissues like the colon. GPR109A, which is the receptor for butyrate and also for niacin, binds to dendritic cells, macrophages, and colonic epithelial cells. The triggering of these receptors initiates the signal transduction of reduced cAMP production, calcium mobilisation, and the activation of the ERK1/2 and MAPK pathways downstream, which are important for transcriptional regulation of immune cells.

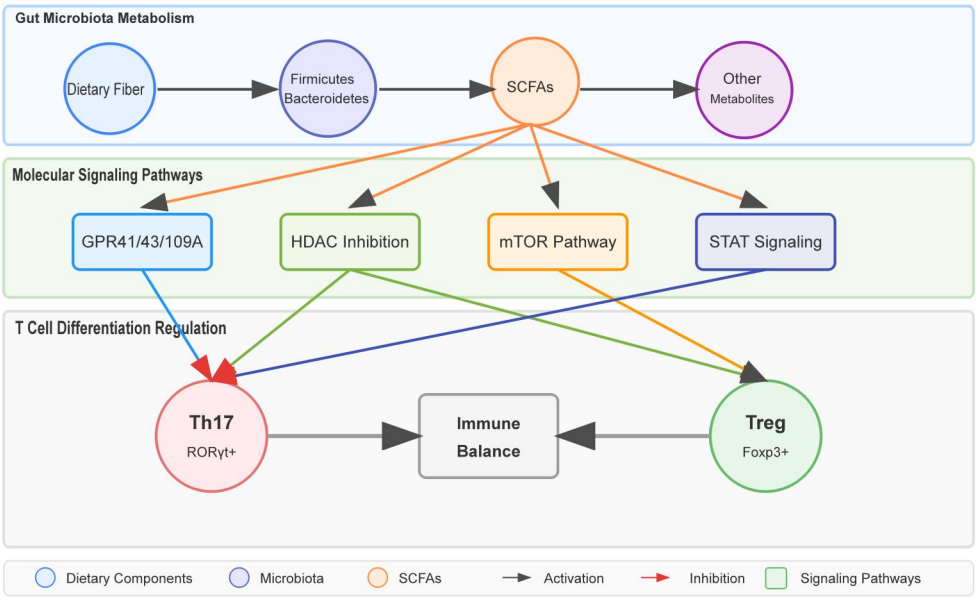


**Figure 1: Molecular Mechanisms of SCFAs in Regulating Th17/Treg Balance.**

As shown in the diagram, the gut microbiota, mainly Firmicutes and Bacteroidetes, metabolise dietary fibres to produce short-chain fatty acids (SCFAs) that, along with modulating T cell differentiation via various pathways. SCFAs are known to activate their respective GPR41/43/109A receptors, inhibit HDACs, and modulate mTOR and STAT signalling pathways. Collectively, these functions promote Treg differentiation and inhibit the development of Th17 cells.

Dendritic cells (DCs) are crucial mediators bridging between metabolites resulting from microbial activity and adaptive immunity. They are known to sculpt the maturation, migration, and cytokine secretion of DCs, but SCFAs alter DC function. Treatment with butyrate and propionate decreases secretion of pro-inflammatory IL-12 and IL-6 while increasing the anti-inflammatory IL-10, thus supporting a tolerogenic DC phenotype. Changes to this cytokine milieu support the conversion of T cells to immunoregulatory Tregs instead of pro-inflammatory Th17 cells. Moreover,

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butyrate is known to enhance the expression of enzymes responsible for retinoic acid synthesis in DCs, further augmenting Treg development via retinoic acid.

In SCFA immunomodulation, one important mechanism of action is regulation of gene expression on a cellular level. Propionate and butyrate function as HDAC enzyme inhibitors by blocking deacetylation of histone proteins. This modification in turn cis-regulates the Foxp3 locus, the master regulator of Treg gene expression, which increases transcription factor binding and expression. Simultaneously, SCFAs inhibit RORγt driven transcriptional processes required for Th17 cell differentiation. Together, these processes substantially mitigate Th17/Treg equilibrium towards the anti-inflammatory response. This homeostatic organism response is necessary to maintain the balance of intestinal inflammation and immune regulation.

Indole and tryptophan also act to stimulate AHR, resulting in enhanced IL-22 secretion, improving the function of the intestinal barrier, and regulating the balance between Th17 and Treg cells. Other SCFAs are also relevant. Secondary bile acids like lithocholic or deoxycholic acid exert their actions by binding to nuclear receptors such as FXR and TGR5, which in turn modulate the activity of dendritic cells by inhibiting pro-inflammatory signal transduction pathways.

The reverse regulatory network demonstrates the two-way relationship of microbiota and immune systems by showing how immune factors shape microbial communities. The epithelial and immune cells release antimicrobial peptides, secretory IgA, and some cytokines which promote beneficial commensal microbes and also restrict potential pathogens. Such advanced interactions compose a complex systems biology framework in which microbial metabolites and host immune factors communicate incessantly to sustain intestinal homeostasis and thwart pathological immune reactions common to autoimmune disorders.

## 3.Role of the Gut Microbiota-Immune Axis in Autoimmune Diseases

The emerging gut microbiota, as well as dysbiosis, is critical for understanding the pathophysiology of autoimmune disease because of the crucial interplay that exists between gut microbiota, immune system regulation, and autoimmune disease pathophysiology. Gut microbiota and its constituents have been deeply studied, resulting in various evidence of distinct microbial signatures across several autoimmune conditions.

However, what remains particularly interesting is how the gut microbiota correlate with, and potentially influence, the development and progress of dysbiosis which is characterised by altered microbial diversity and composition. Table 1 highlights recent comparative studies that rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and inflammatory bowel disease (IBD) each have characteristic - though distinct - microbial compositional changes. Still, it provides insight into the altered diversity of methanogenic archaea and strict anaerobes that are present across distinct autoimmune diseases. For example, MS patients with increased Methanobrevibacter abundances along with decreased

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Butyricimonas support compositionally-driven hypotheses of disease. Therefore, these described unique signatures imply that they could serve as potential microbial biomarkers for diagnosis and prognosis.

**Table 1: Distinctive Microbial Signatures Across Major Autoimmune Diseases**

| Autoimmune Disease | Increased Bacteria | Decreased Bacteria | Key Metabolite Changes | Associated Immune Alterations |
|---|---|---|---|---|
| Rheumatoid Arthritis | Prevotella copri, Collinsella | Faecalibacterium, Blautia | ↓ SCFAs, ↑ Pro-inflammatory metabolites | Expanded Th17 cells, ↓ Tregs, ↑ IL-17, TNF-α |
| Systemic Lupus Erythematosus | Ruminococcus gnavus, Bacteroides | Firmicutes, Lactobacillus | ↓ Butyrate, ↑ LPS exposure | ↑ IFN signature, Plasma cell expansion |
| Multiple Sclerosis | Methanobrevibacter, Akkermansia | Butyricimonas, Parabacteroides | ↓ Propionate, Altered tryptophan metabolism | Enhanced Th1/Th17 responses, ↓ IL-10 production |
| Inflammatory Bowel Disease | Escherichia coli, Fusobacterium | Faecalibacterium prausnitzii, Roseburia | Severe SCFA depletion, ↑ Sulfide compounds | Mucosal Th17 accumulation, Impaired Treg function |
| Type 1 Diabetes | Bacteroides, Clostridium | Bifidobacterium, Lactobacillus | Altered bile acid metabolism | Increased mucosal IFN-γ, β-cell autoimmunity |

The causal relationship between microbiota and autoimmune pathogenesis has been meticulously demonstrated in germ-free animal studies. In the case of experimental autoimmune encephalomyelitis (EAE), the mouse model of multiple sclerosis (MS), germ-free mice develop an attenuated form of the disease with an IL-17 producing Th17 response and fewer Th17 cells. These mice, however, developed exacerbated disease when colonised with specific microbiota obtained from MS patients as compared to those receiving microbiota from healthy controls. The underlying immunological mechanisms pertain to changes in T cell differentiation as described by the equation:

$$T_{balance} = \frac{[Th17]}{[Treg]} = f\left(\frac{[pro-inflammatory; factors]}{[regulatory; factors]}\right)$$

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where equilibrium between pro-inflammatory and anti-inflammatory signals determines T cell fate decisions pivotal to the development of autoimmunity.

The therapeutic effects of SCFA supplementation in models of autoimmune disease are remarkable. In models of collagen-induced arthritis, butyrate treatment markedly decreases clinical severity by enhancing Treg activity and inhibiting Th17 cell function. This relates to the mechanism of action via HDAC inhibition which may be quantified as:

$$HDAC_{inhibition} = \sum_{i=1}^{n} k_i [SCFA_i] \cdot [HDAC]$$

where $k_i$ represents the inhibition constant for each SCFA species.

Analysis of patient samples has shown significant changes in the microbial metabolite profiles relative to the disease activity. Active RA patients, as illustrated by figure one, cluster distinctly away from both remission and healthy control associated groups, primarily due to decreased SCFA and increased pro-inflammatory metabolites.

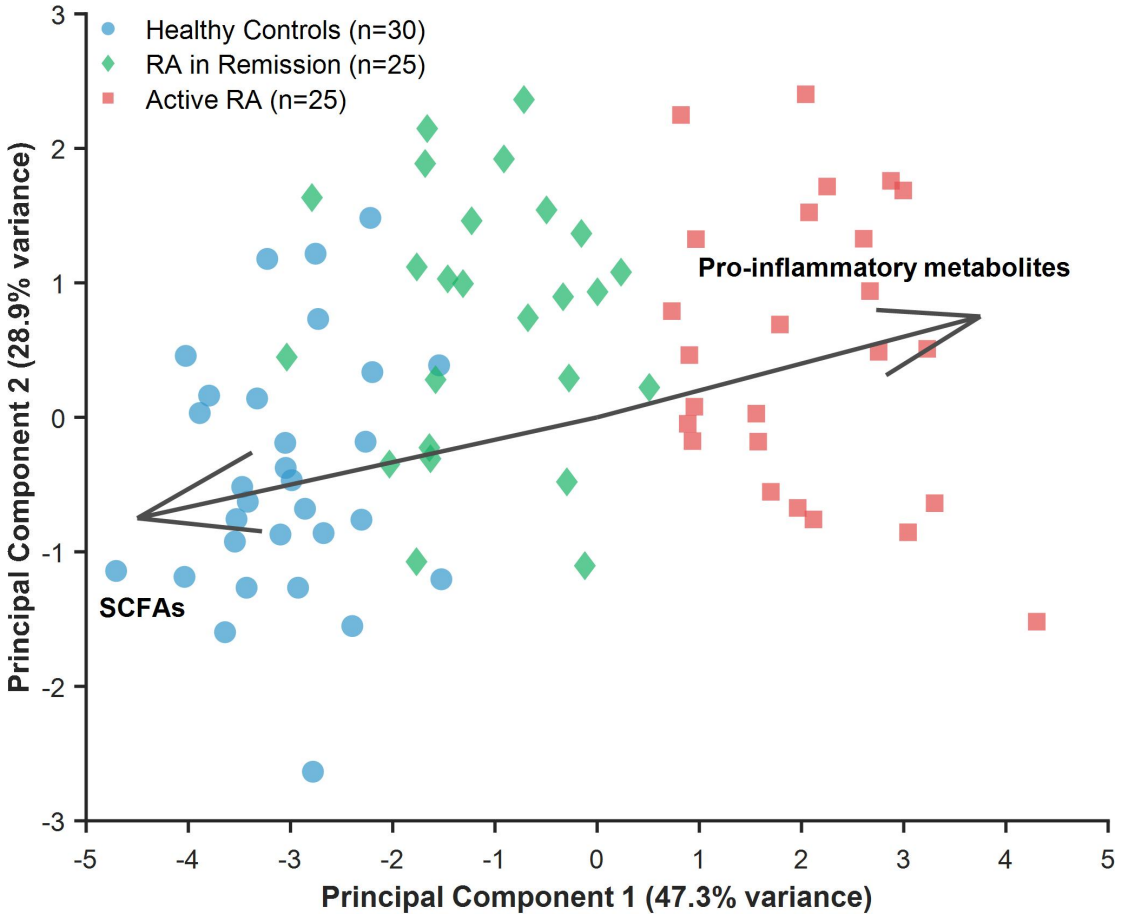


**Figure 1: Metabolomic Profile Clustering in Rheumatoid Arthritis Patients.** The metabolomic profiles were analysed using principal component analysis demonstrating that healthy controls (blue circles), RA patients in remission (green

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diamonds), and patients with active RA (red squares) are distinctly clustered. The vectors depicting the SCFAs' and pro-inflammatory metabolites' influence both point toward the healthy control group and toward the active RA patients, respectively. Ellipses show 95% confidence regions for each group.

Evidence of the role that gut microbiota play in autoimmunity has been substantiated through microbiota transplantation experiments. Microbiota from systemic lupus erythematosus (SLE) patients transplanted into germ-free mice not only developed lupus-like symptoms but also displayed an imbalanced Th17/Treg ratio. Likewise, faecal microbiota transplantation (FMT) from healthy donors to IBD patients has shown promising clinical responses in some studies, which is believed to be linked to microbial diversity restoration as well as increased SCFA production.

Our understanding of autoimmune diseases has been transformed with the application of high-throughput sequencing technologies, the multi-omics approach, and the interconnections of microbiota, metabolites, and the immune system. Specific altered metabolic pathways in certain disease states have been elucidated through integrating metagenomics, metatranscriptomics, and metabolomics. A case in point is the diminished abundance of butyrate-producing bacteria in MS patients, which both correlates with diminished regulatory T cell (Treg) function alongside heightened Th17 dominance, and has been confirmed by single-cell RNA sequencing of mucosal immune cells.

Research on clinical treatments aimed at the microbiota show mixed results, with targeted probiotics containing Lactobacillus and Bifidobacterium yielding modest improvements for patients with RA and IBD, linked to enhanced SCFA production as well as better Th17/Treg equilibrium. Inulin and fructooligosaccharides, as in prebiotic supplementation, enhance propionate and butyrate production, proving effective in probiotic settings. Mediterranean and high-fibre diets also benefit autoimmune patients by improving immune function alongside modulating microbiota.

Supplementation of SCFA and their analogues have shown potential as therapeutic interventions. The administration of sodium butyrate has been shown to be effective in the preclinical studies of MS, RA, and IBD. In early-phase clinical studies, propionate supplementation improved clinical outcomes of MS by enhancing Treg function. As illustrated in Table 1, the therapeutic response achieves baseline metabolite profile restoration and immune cell population normalization.

The microbiota-immune interface forms an appealing new avenue for exploration in the treatment of autoimmune pathologies. By manipulating certain groups of microorganisms and/or their specific metabolic products like SCFAs, it may be possible to develop more precise therapeutic strategies aimed at restoring immune equilibrium and curtailing the autoimmune damage.

## 4. Conclusion and Perspectives

The gut microbiota and the immune system exhibit reciprocal interplay which shifts our paradigms of the pathogenesis of autoimmune diseases and introduces new strategies for intervention aimed at redefining the legalistic approach to treatment.

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The ecology formed by the expenditure of the microbiota, microbial metabolites, and host immune system constitutes a system with changing parts which deeply influence the disease course and treatment possibilities.

This system is controlled by bacterial products like SCFAs that possess potent immunomodulatory capacity via target eluding mechanisms like HDAC inhibition, GPCR signalling, and gene expression control. From the standpoint of autoimmunity, their capability of reestablishing Th17/Treg balance makes them promising therapeutic agents. Regardless, a number of other challenges addressing effective clinical translation, optimal routes and timing of administration, and potential off-target effects of the proposed therapy remain unresolved.

The prospect of developing a microbiota-based classification system for autoimmune diseases could be achieved by identifying a distinct microbial signature shared across them. This is particularly important because microbial composition is now known to predict a patient's treatment responsiveness, allowing for greater precision in stratifying patients. However, these efforts are stymied until a consensus is reached on the standardisation of techniques for microbiome analysis and defining clinically significant dysbiosis.

To design personalised interventions at the microbiota level, these factors must be considered: host genetics, the environment, disease manifestations, and existing microbiota profiles. These interacting factors create a clinical framework of sheer complexity, requiring advanced algorithms and intelligent clinical decision support systems for actionable insight. In addition, integrated immunotherapy with targeted microbiome therapies and traditional immunotherapy tends to target multiple disease mechanisms at once, thereby potentially yielding more beneficial outcomes.

While moving towards clinical applications, microbiome therapeutics face major concerns of safety and ethics. The more one attempts to manipulate intricate microbial systems, the deeper one delves into unmonitored ecosystems. This suggests a clear need for rigorous oversight and regulation. There is also an ethical obligation to ensure fair access to these new emerging therapies across different demographics.

Progress in research is still stalled due to lack of longitudinal monitoring and functional characterisation of microbial communities. However, systems biology, single-cell sequencing, and metabolomic tools could accelerate progress. Defined causative relationships between microbiota and diseases should be elucidated along with targeted perturbation in dysbiotic microbiomes, intersectionally validated biomarkers, and framed interventions that derive pathway-based precision medicine.

The deepening understanding of the gut, brain, and immune system axis advances the field by proposing microbiota-based therapeutic interventions for dualistic neuropathic and immunologic diseases. For the purpose of translating intricate science into real-world beneficial outcomes for patients, the clinical integration of microbiome data with other clinical parameters will necessitate advanced bioinformatic frameworks and collaboration across multiple disciplines

## References

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