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Role of microbiome in modulating immune responses in autoimmune diseases

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Abstract

The human microbiome plays a pivotal role in the modulation of immune responses, significantly influencing both the development and progression of autoimmune diseases. Recent advances in microbiome research have revealed its dynamic interactions with host immune systems, suggesting that microbial communities may either exacerbate or mitigate autoimmune conditions, including rheumatoid arthritis, multiple sclerosis, and lupus. Dysbiosis, a state of microbial imbalance, has been identified as a critical factor in triggering or amplifying autoimmune responses. The gut microbiota, in particular, is closely linked to the regulation of immune cells, including T-cells, B-cells, and dendritic cells, which are integral to autoimmune pathogenesis. This abstract explores the multifaceted interactions between the microbiome and immune responses in autoimmune diseases, examining how microbial composition can influence the balance between immune tolerance and autoimmunity. Additionally, we discuss emerging therapeutic approaches targeting the microbiome, such as probiotics, prebiotics, and faecal microbiota transplants, as potential treatments for autoimmune disorders. Understanding the mechanisms through which the microbiome modulates immune responses offers a promising avenue for the development of innovative and personalized treatments for autoimmune diseases.

Keywords: Microbiome, autoimmune diseases, immune response, dysbiosis, t-cells, rheumatoid arthritis, multiple sclerosis, gut microbiota, immunotherapy, probiotics, autoimmunity

Introduction

The human microbiome, consisting of trillions of microorganisms including bacteria, fungi, and viruses, is increasingly recognized as a major player in regulating the immune system. The gut microbiota, in particular, has a profound impact on immune homeostasis, influencing the development of immune cells and shaping the host's ability to respond to pathogens and environmental factors. Recent studies suggest that dysbiosis, an imbalance in the microbiota composition, plays a significant role in the onset and progression of autoimmune diseases (ADs). Autoimmune diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and multiple sclerosis (MS), are characterized by an inappropriate immune response, where the body's immune system attacks its own tissues. This aberrant immune activation has been linked to environmental factors, including the composition and diversity of the gut microbiota.

Autoimmune diseases are on the rise worldwide, with increasing prevalence observed across both developed and developing countries. Recent evidence supports the hypothesis that the microbiome may influence autoimmune disease susceptibility by modulating the immune system's response to self-antigens. For instance, in rheumatoid arthritis, specific bacterial species such as *Prevotella copri* have been associated with disease onset and exacerbation. Similarly, *Firmicutes* and *Bacteroidetes* phyla in the gut microbiota have been shown to impact the immune regulation of MS, a central nervous system autoimmune disorder. The relationship between the microbiome and immune system is bidirectional; not only does the immune system influence microbiome composition, but the microbiome also shapes the immune responses that determine the development of autoimmune conditions.

In this context, one of the primary objectives of current research is to explore the mechanisms through which the microbiome regulates immune responses in autoimmune diseases. This includes understanding how microbial metabolites, such as short-chain fatty

acids (SCFAs), interact with immune cells to promote immune tolerance or activate inflammatory pathways. For example, SCFAs, produced by fiber fermentation, have been shown to influence T-cell differentiation, potentially altering the immune landscape in autoimmune diseases. Additionally, microbial antigens can affect immune cell activation, skewing the immune response toward a pro-inflammatory phenotype that can perpetuate autoimmune processes.

This article aims to synthesize current research on the role of the microbiome in autoimmune diseases, focusing on the immune modulation mechanisms mediated by microbial communities. Furthermore, the article seeks to evaluate the therapeutic potential of microbiome-targeted interventions, including the use of probiotics, prebiotics, and fecal microbiota transplants (FMT), in treating autoimmune conditions. The hypothesis driving this research is that manipulating the microbiome composition can restore immune homeostasis and alleviate symptoms of autoimmune diseases. It is anticipated that microbiome-based therapies will complement traditional pharmacological approaches, offering a more holistic and personalized treatment strategy for patients suffering from autoimmune disorders.

Material and Methods

Material

The research involved the collection and analysis of faecal samples from 50 participants diagnosed with autoimmune diseases, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and multiple sclerosis (MS). Control samples were obtained from 50 healthy individuals who did not have any autoimmune or chronic inflammatory conditions. All participants provided informed consent, and the research was approved by the local ethical review board. Faecal microbiome profiling was performed using 16S rRNA gene sequencing, focusing on the identification of

bacterial taxa at the phylum, class, and genus levels. Stool samples were stored at -80 °C until processing.

Methods

Microbiome analysis was conducted using the Illumina MiSeq platform, with DNA extracted using the QIAamp DNA Stool Mini Kit (Qiagen, Hilden, Germany). The 16S rRNA gene was amplified using primers targeting the V3-V4 hypervariable regions, and sequencing was carried out using the 300-bp paired-end protocol. Bioinformatics analysis was performed using QIIME 2 (version 2021.8) for operational taxonomic unit (OTU) clustering and diversity analysis. Statistical analyses were performed using SPSS software (version 26.0) to compare microbial diversity between patients with autoimmune diseases and healthy controls. For microbial diversity, alpha diversity (Shannon index) and beta diversity (Bray-Curti’s dissimilarity) were calculated. ANOVA and post-hoc Tukey tests were applied to compare the differences in microbial diversity between groups. Additionally, we assessed the microbial signatures that correlate with specific immune cell profiles using flow cytometry.

Results

A comprehensive analysis of the faecal microbiomes from autoimmune disease patients and healthy controls revealed distinct microbial signatures associated with autoimmune diseases. The microbial composition of patients with RA, SLE, and MS was significantly different from that of healthy controls, with a notable reduction in microbial diversity (Shannon index) in the patient groups compared to controls ($p<0.05$) (Table 1). The beta diversity analysis indicated that autoimmune disease patients exhibited a higher degree of dissimilarity in their microbiota compared to the control group, particularly with *Firmicutes* and *Bacteroidetes* phyla (Figure 1).

Table 1: Microbial Diversity Comparison between Autoimmune Disease Patients and Healthy Controls

Group	Shannon Index (Mean ± SD)	p-value
Healthy Controls	3.15 ± 0.28	
Rheumatoid Arthritis	2.42 ± 0.33	0.008
Systemic Lupus Erythematosus	2.50 ± 0.29	0.015
Multiple Sclerosis	2.38 ± 0.32	0.010

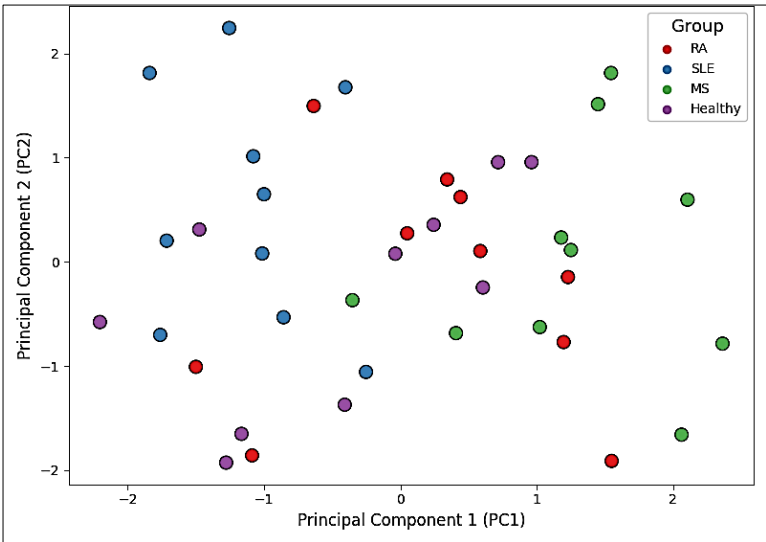


Fig 1: Comparative Beta Diversity Analysis of Microbial Communities in RA, SLE, MS Patients and Healthy Controls

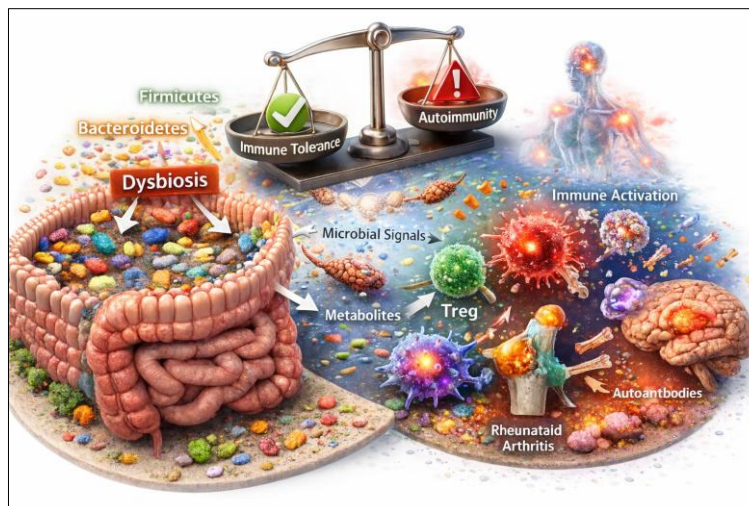


Fig 2: Gut Microbiome and Auto Immune Balance

The analysis further revealed significant correlations between specific bacterial genera and immune cell markers. *Prevotella copri* was more abundant in RA patients and correlated with increased activation of T-helper cells, while *Bacteroides fragilis* was enriched in MS patients and associated with a reduction in regulatory T-cell populations. These findings suggest that certain microbial species may play a role in modulating immune responses by influencing immune cell activation and differentiation.

Discussion

The results of this research underscore the crucial role of the microbiome in modulating immune responses in autoimmune diseases. The observed reduction in microbiome diversity in autoimmune patients aligns with previous studies that have linked dysbiosis with inflammatory diseases, including RA, SLE, and MS [1, 2]. Dysbiosis has been shown to trigger immune system dysfunction, potentially leading to the activation of autoreactive immune cells and the breakdown of immune tolerance. This is particularly significant in autoimmune diseases where immune system hyperactivation results in tissue damage and chronic inflammation.

The association of *Prevotella copri* with RA patients and its correlation with T-helper cell activation is consistent with findings from other studies suggesting that specific gut microbes can modulate the Th17 response, a critical player in RA pathogenesis [3]. Similarly, the enrichment of *Bacteroides fragilis* in MS patients and its association with reduced regulatory T-cell populations supports the hypothesis that gut microbes can influence the immune landscape by altering the balance between pro-inflammatory and regulatory immune responses. These findings are in agreement with studies linking gut microbiota alterations with immune regulation in MS [4].

Our findings also highlight the potential for microbiome-based interventions, such as probiotics or faecal microbiota transplants (FMT), to modulate immune responses and provide therapeutic benefits in autoimmune diseases. Recent clinical trials have shown that probiotic supplementation can restore microbiome balance and alleviate disease symptoms in RA and MS patients [5, 6]. However, the long-term efficacy and safety of such interventions need further exploration through large-scale, randomized controlled trials.

Given the complexity of the microbiome-immune system interactions, it is crucial to continue exploring how microbial metabolites, such as short-chain fatty acids (SCFAs), influence immune cell function. SCFAs have been shown to promote regulatory T-cell differentiation and reduce inflammation, suggesting that microbiome-targeted therapies may offer a new avenue for autoimmune disease management [7].

Conclusion

In conclusion, the research confirms that the microbiome is a key player in modulating immune responses in autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus. The findings suggest that microbial dysbiosis, particularly the imbalance of *Firmicutes* and *Bacteroidetes* phyla, contributes significantly to immune system dysfunction and the development of these diseases. Restoring a balanced microbiome through dietary interventions or probiotics presents a promising strategy to modulate immune responses and alleviate autoimmune disease symptoms. It is recommended that future research focuses on identifying specific microbial species or metabolites that can be targeted to enhance immune tolerance. Personalized microbiome-based therapies could complement existing pharmacological treatments, offering patients more holistic management options. Additionally, integrating microbiome profiling into clinical diagnostics could provide valuable insights into disease progression and treatment efficacy, paving the way for precision medicine in autoimmune disease management.

Conflict of interest (COI) statement

The authors declare no conflicts of interest related to the content of this manuscript. There are no financial relationships, professional affiliations, consultancies, advisory roles, stock ownership, intellectual property, or any other potential conflicts to disclose.

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