**Migration Letters**

Volume: 19, No: S2 (2022), pp. 1351-1356

ISSN: 1741-8984 (Print) ISSN: 1741-8992 (Online)

www.migrationletters.com

# The Role Of Microbiome Diversity In Autoimmune Diseases

Ahmed Abdulaziz Almousa, Abdullah Ali Alarrafi , Meshal Khunfor Alrashidi , Fahad Awadh Almotairy , Bayan Melfi Alharbi , Khadejah Abdullah Ahmed , Nabeel Ahmed Madkhali , Meshal Abdullah Alhilfi , Munif Hassan Ayyashi , Amira Nasser Aljaber , Hani Eid Alharbi , Ebtissam Mohammed Abdullah Sahli , Shadia Othman Mohammed Maghfuri , Mosleh Motesh Alghamdi , Ahmed Bakri Hassan Somili , Taher Hussain Sumayli

## Abstract

*The microbiome consists of bacteria that live in a mutually beneficial relationship with mammals. Microorganisms has the capacity to have an impact on several physiological systems, including the immune system, metabolism, and behavior. Recent research has emphasized the significance of the microbiome in the development of autoimmune disorders. It has been shown that there is a change in the composition of the gut bacteria in individuals with systemic lupus erythematosus, specifically a decrease in the ratio of Firmicutes to Bacteroidetes. On the other hand, alterations in the gut bacteria and the presence of periodontal disease have been suggested as significant contributors to the development of rheumatoid arthritis. Simultaneously, other autoimmune illnesses such as systemic sclerosis, Sjögren's syndrome, and anti-phospholipid syndrome also exhibit alterations in the microbiome of the gastrointestinal tract and mouth microbiota. In this article, we will discuss the function of the microbiome in maintaining immune system homeostasis, as well as the changes in microorganisms that take place in systemic autoimmune illnesses. Lastly, we will examine the use of probiotics and fecal transplantation as innovative therapeutic objectives.*

***Keywords:*** *anti-phospholipid, autoimmune disorders, fecal transplantation, microbiome, probiotics, systemic sclerosis, Sjögren's syndrome.*

## 1. Introduction

The human body has a high concentration of commensal and symbiotic microorganisms, with bacteria being the most abundant kind of microorganism. These microorganisms inhabit several environments, including the gastrointestinal tract, skin, vaginal area, and oral cavity. The composition and prevalence of microorganisms vary not just across various organs but also across different people. A microbiome is formed by the genes of these bacteria and their environments. The broad microbial variety may be attributed to factors such as nutrition, environment, host genetics, and mechanism of delivery [1]. The microbiome and microbial products play a crucial role in controlling the development and functioning of the host's immune system. In addition, commensal microbes have an impact on other physiological features of mammals, such as metabolism and behavior [2]. In recent times, several scientists have directed their attention on the significance of commensal bacteria in the development of various illnesses, including autoimmune disorders. The

objective of this review is to delineate the primary modifications of the microbiome that manifest in autoimmune disorders [1].

## 2. Changes of the microbiota during pregnancy and childhood

Throughout pregnancy, the microbiome experiences significant changes, particularly in the vaginal and intestinal regions. A recent study conducted by Koren et al. [2] revealed distinct variations in the microbiome of women during different stages of pregnancy. Specifically, the researchers observed that in the third trimester, there was a higher presence of Proteobacteria and Actinobacteria, while the levels of Faecalibacterium, a bacterium known for its butyrate-producing and anti-inflammatory properties, were significantly reduced. Dysbiosis, which refers to changes in the microbiome, may lead to weight gain, insulin resistance, and metabolic inflammation when microorganisms from the stomach of mice in the third trimester are transplanted to germ-free animals [2,3].

It is often assumed that the gastrointestinal system of a fetus is free from microorganisms, and the colonization of the gut by these bacteria occurs during the process of delivery via the birth canal [4,5]. In early life, the composition of the gut microbiome may be shaped by several environmental variables, including geographic location, breastfeeding, introduction of solid foods, and method of delivery. Infants born via the vaginal canal receive bacterial communities that closely resemble the microbiota present in their mother's vagina, which often consists of Lactobacillus, Prevotella, and Sneathia species. In contrast, newborns born after Caesarean-section have bacterial populations that closely resemble those found on the surface of the skin, such as Staphylococcus, Corynebacterium, and Propionibacterium [4,6].

The precise mechanism by which the gastrointestinal mucosa of newborns adapts to the colonization of microbes remains incompletely known. In reality, colostrum and breast milk contain a high concentration of immunoglobulin (Ig)A, which plays a crucial role in neutralizing harmful pathogens and preventing their movement across the intestinal lining. This helps maintain a balanced relationship between beneficial gut bacteria and the mucosal lining of the intestines. Maternal milk includes several metabolites, including gangliosides, lactoferrin (Lf), and human milk oligosaccharides (HMOs), which provide defense against anti-infective drugs [1,7]. In addition, HMOs have prebiotic effects that promote the growth of certain bacteria, such as Bifidobacterium longum, which helps maintain the integrity of the intestinal barrier. In addition, the dendritic cells already present in breast milk may have a role in shaping the immune response to the antigens from the normal bacteria, thereby impacting the development of the newborn immune system [8–11].

The underdeveloped state of the newborn's immune system and the presence of elements that promote tolerance might account for the acceptance of the microbiome by the gut of the neonate. Hence, the interaction between commensals and the host is of utmost importance in the formation and maintenance of the immune system [1,12,13]. Pattern recognition receptors (PRRs) such as Toll-like receptor (TLR) families, nucleotide-binding oligomerization domains (NOD) as receptors (NLR), type C lectin receptors (CLR), cytosolic DNA receptors (CDR), and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) enable this process [14]. TLRs are primarily located on the surface of immune and epithelial cells and have the ability to identify conserved molecular patterns, such as microbial-associated molecular patterns (MAMPS) produced by the resident microbiota or pathogen-associated molecular patterns (PAMPS) created by invading microbes [15,16].

The commensal microorganisms are also involved in the formation of lymphoid structures in the digestive tract, such as Payer's patch and isolated lymphoid follicles. Additionally, they contribute to the maturation of epithelial cells and the growth of blood vessels in the gastrointestinal mucosa [1,17,18]. In addition, the symbiotic bacteria Bacteroides fragilis may impact the activation of invariant natural killer T (iNK T) cells

and train the immune system throughout adulthood via the formation of sphingolipids [19,20]. The role of the microbiome in inducing regulatory responses and immunological tolerance is now well-established via many mechanisms.

The regulatory T cell (Treg) forkhead box protein 3 (FoxP3+) plays a role in both the thymus and extrathymus. It produces regulatory cytokines such as transforming growth factor (TGF)-β, interleukin (IL)-10, and IL-35. It also modulates the function of antigen-presenting cells (APCs) through lymphocyte-activation gene 3 (LAG-3), cytotoxic T lymphocyte antigen (CTLA)-4, and granzyme/perforin. Additionally, it alters cellular metabolism through CD25, CD39/CD73, and indoleamine 2,3-dioxygenase (IDO) induction in dendritic cells (DC). These functions of Treg cells have been observed in various inflammatory contexts [21,22]. Commensal bacteria in the digestive tract may influence the activity of Treg cells by producing IL-10 and TGF-β.

Bacteroides fragilis generates a substance called polysaccharide A (PSA) that may stimulate the synthesis of IL-10 by T cells in the intestines. This helps to reduce the immune response known as T helper type 17 (Th17) during inflammation in the intestines [23]. Simultaneously, other bacterial metabolites, including short-chain fatty acids (SCFAs), particularly butyrate, enhance the activity of Treg cells and macrophages by suppressing the expression of the histone deacetylases gene (HDAC) [23,24]. Nevertheless, changes in the microbiome (dysbiosis) may occur due to exposure to many environmental variables, such as nutrition, chemicals, medicines, and viruses. Among them, gastrointestinal infections possess the highest capacity to induce microbial dysbiosis and may initiate inflammation both locally and systemically. The modification of the microbiome's composition and barrier function may lead to the emergence of autoimmune and chronic inflammatory disorders, metabolic dysfunction, and cancer [1,5].

## 3. The relationship between the microbiome and autoimmune disorders

Autoimmune disorders (AIDs) occur when an individual's immune system mistakenly attacks their own tissues. It is believed that AIDs have a global occurrence rate of about 3-5%. The entire understanding of the pathophysiology is lacking, however, it has been suggested that environmental variables such as lifestyle, nutrition, medicines, and infections, together with certain genetic backgrounds, may play a role [25,26]. Microbial composition alterations in the human microbiome may significantly contribute to the development of autoimmunity by disrupting immunological tolerance [1,5]. If the mechanisms of tolerance fail for various reasons, microorganisms might trigger the immune response against the host (Fig. 2) [27–29,30,31].

In a recent study, Rinaldi et al. [32] discovered that autoantibodies targeting the cell wall mannan of the yeast Saccharomyce cerevisiae (phosphopeptidomannan), which is a common microorganism that lives in harmony with the human body, were found in various autoimmune diseases with varying susceptibilities (such as rheumatoid arthritis, systemic lupus erythematosus, and anti-phospholipid syndrome). Anti-S. cerevisiae antibodies (ASCAs) are a serological marker that particularly indicates the presence of Crohn's disease (CD). They may be detected before the beginning of CD in 32% of patients. Furthermore, S. cerevisiae is used as an adjuvant in vaccines, which has prompted scientists to consider the potential danger of aberrant immune activation that might be linked to the development of an autoimmune/inflammatory syndrome induced by adjuvants (ASIA) [32,33].

Inflammatory bowel illnesses (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), provide as an illustration of how changes in the gut microbiota may lead to the development of disease. Multiple studies have shown that both Crohn's disease (CD) and ulcerative colitis (UC) are linked to a decrease in the diversity of the normal bacteria in the body and constant changes towards an unhealthy condition of the microbiota. Both Crohn's disease (CD) and ulcerative colitis (UC) exhibit a similar pattern to what is seen in

acute mucosal infections. This pattern involves the proliferation of certain phyla of bacteria, namely the proteobacteria phylum, with a particular focus on the Enterobacteriaceae family and Fusobacteriaceae [34-36]. Furthermore, persons with Crohn's disease are more likely to have higher prevalence of adherent-invasive E. coli, Yersinia, and Clostridium difficile compared to healthy individuals. In some animal models, these bacteria have been shown to play a significant role in the development of inflammatory bowel disease (IBD) [37–39].

Neuroscience research provides evidence indicating that the microbiome plays a crucial role in the development and maturity of the central nervous system, as well as in behavioral and cognitive functioning. The communication between the central nervous system and the gut is two-way, and it is known as the 'gut microbiota-brain axis'. The gastrointestinal system may communicate with the central nervous system via many routes, including commensal metabolism involving substances such short-chain fatty acids (SCAFs), 5-hydroxytryptamine (5-HT), and gamma-aminobutyric acid (GABA) [40,41]. Multiple sclerosis (MS) is an autoimmune disorder where immune cells (namely CD4 and CD8 T cells, B cells, and activated monocytes) invade the central nervous system, causing damage to the protective covering of nerve cells (demyelination) and resulting in various health issues [42].

Patients with multiple sclerosis (MS) show a reduction in the proportion of various Bacteroides species (namely B. stercoris, B. coprocola, B. coprophilus), Faecalibacterium, and SCAFs-producing bacteria. Additionally, there is an increase in Methanobrevibacter, Enterobacteriaceae, and Akkermansia in MS patients [43]. In contrast, the administration of disease-modifying medicines leads to a rise in Prevotella levels as compared to untreated individuals [44]. Moreover, the presence of C. perfringens type B in the intestines is linked to the recurrence of multiple sclerosis. The toxins generated by C. perfringens have the ability to cause microvascular problems, which may result in damage to neurons and oligodendrocytes [43–45]. Dysbiosis is believed by several studies to have a role in the development of type 1 diabetes mellitus (T1DM). A fascinating Chinese research found that the fecal samples of children with T1DM had a decreased number of bacteria compared to healthy controls. Specifically, the bacterium Intestinimonas, which is a recently discovered Gram-positive and anaerobic bacteria that produces butyrate, was shown to be particularly reduced. These individuals had a higher presence of Blautia compared to others, as shown by a study [46].

Microorganisms can trigger the immune response against the host when the mechanisms of tolerance fail in various ways. One such way is epitope spreading, which involves the development of autoimmune responses to internal epitopes after the release of self-antigens during an inflammatory response. This release is caused by a modification in protein structure, specifically the substitution of an arginine amino acid residue with citrulline. This can lead to an immune response targeting not only the original protein or its citrullinated form, but also other citrullinated proteins [27]. Molecular mimicry is a process in which infections can trigger autoimmunity by sharing sequence or structural similarities with self-antigens.

## 4. Conclusion

Immune responses may target peptides that have similar charge distribution and overall structure [28]. (iii) Bystander activation happens when microbial infection triggers Toll-like receptors (TLRs) and other pattern recognition receptors on antigen-presenting cells (APCs), causing the release of proinflammatory substances that can damage tissues [29]; and (iv) persistent infection with a virus, like EBV or HCV, can cause continuous activation and growth of T cells, leading to the production of monoclonal and polyclonal antibodies as well as immune complexes, which can result in loss of tolerance [30,31].

## References


1. Belkaid Y, Hand T. Role of the microbiota in immunity and inflammation. Cell 2014;157:121–41.
2. Koren O, Goodrich JK, Cullender TC et al. Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell 2012;150:470–80.
3. Chen X, Liu S, Tan Q, Yehuda S, Zeng Y. Microbiome, autoimmunity, allergy, and helminth infection: the importance of the pregnancy period. Am J Reprod Immunol 2017;78:e12654.
4. Arrieta M-C, Stiemsma LT, Amenyogbe Ny, Brown EM, Finlay B. The intestinal microbiome in early life: health and disease. Front Immunol 2014;5:427.
5. Samriz O, Mizrahi H, Werbner M, Shoenfeld Y, Avni O, Koren O. Microbiota at the crossroads of autoimmunity. Autoimmun Revi 2016;15:859–69.
6. Dominguez-Bello MG, Costello EK, Contreras M et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci USA 2010;107:11971–5.
7. Pacheco AR, Barile D, Underwood MA, Mills DA. The impact of the milk glycobiome on the neonate gut microbiota. Annu Rev Anim Biosci 2015;3:419–45.
8. Marcobal A, Sonnenburg JL. Human milk oligosaccharide consumption by intestinal microbiota. Clin Microbiol Infect 2012;18:12–5.
9. Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology 2012;22:1147–62.
10. Srutkova D, Schwarzer M, Hudcovic T et al. Bifidobacterium longum CCM 7952 promotes epithelial barrier function and prevents acute DSS-induced colitis in strictly strain-specific manner. PLOS ONE 2015;10:e0134050.
11. Perez PF, Dore J, Leclerc M et al. Bacterial imprinting of the neonatal immune system: lessons from matern cells? Pediatrics 2007;119:e724–32.
12. PrabhuDas M, Adkins B, Gans H et al. Challenges in infant immunity: implications for responses to infection and vaccines. Nat Immunol 2011;12:189–94.
13. Siegrist CA. Neonatal and early life vaccinology. Vaccine 2001;19:3331–46.
14. Valentini M, Piermattei A, Di Sante G, Migliara G, Delogu G, Ria F. Immunomodulation by gut microbiota: role of toll-like receptor expressed by T cells. J Immunol Res 2014;2014:1.
15. Guven-Maiorov E, Tsai C-J, Nussinov R. Structural host–microbiota interaction networks. PLOS Comput Biol 2017;13:e1005579.
16. Kollmann TR, Levy O, Montgomery RR, Goriely S. Innate immune function by Toll-like receptors: distinct responses in newborns and the elderly. Immunity 2012;37:771–83.
17. Hooper LV, Wong MH, Thelin A, Hansson L, Falk PG, Gordon JI. Molecular analysis of commensal host–microbial relationships in the intestine. Science 2001;291:881–4.
18. Stappenbeck TS, Hooper LV, Gordon JI. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. Proc Natl Acad Sci USA 2002;99:15451–5.
19. An D, Oh SF, Olszak T et al. Sphingolipids from a symbiotic microbe regulate homeostasis of host intestinal natural killer T cells. Cell 2014;156:123–33.
20. Olszak T, An D, Zeissig S et al. Microbial exposure during early life has persistent effects on natural killer T cell function. Science 2012;336:489–93.
21. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. Nat Rev Immunol 2008;8:523–32.
22. Shevach EM. Mechanisms of foxp3+ T regulatory cell-mediated suppression. Immunity 2009;30:636–45.
23. Chang PV, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc Natl Acad Sci USA 2014;111:2247–52.
24. Furusawa Y, Obata Y, Fukuda S et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. Nature 2013;504:446–50.
25. Miller FW, Pollard KM, Parks CG et al. Criteria for environmentally associated autoimmune diseases. J Autoimmun 2012;39:253–8.

26. Ramos-Casals M, Brito-Zerón P, Kostov B et al. Google-driven search for big data in autoimmune geoepidemiology: analysis of 394,827 patients with systemic autoimmune diseases. Autoimmun Rev 2015;14:670–9.
27. Vanderlugt CJ, Miller SD. Epitope spreading. Curr Opin Immunol 1996;8:831–6.
28. Guilherme L, Kalil J, Cunningham M. Molecular mimicry in the autoimmune pathogenesis of rheumatic heart disease. Autoimmunity 2006;39:31–9.
29. Getts DR, Chastain EM, Terry RL, Miller SD. Virus infection, antiviral immunity, and autoimmunity. Immunol Rev 2013;255:197–209.
30. Vojdani A. A potential link between environmental triggers and autoimmunity. Autoimmun Dis 2014;2014:1.
31. Agmon-Levin N, Ram M, Barzilai O et al. Prevalence of hepatitis C serum antibody in autoimmune diseases. J Autoimmun 2009;32:261–6.
32. Rinaldi M, Perricone R, Blank M, Perricone C, Shoenfeld Y. Anti-Saccharomyces cerevisiae autoantibodies in autoimmune diseases: from bread baking to autoimmunity. Clin Rev Allerg Immunol 2013;45:152–61.
33. Shoenfeld Y, Agmon-Levin N. 'ASIA' – autoimmune/inflammatory syndrome induced by adjuvants. J Autoimmun 2011;36:4–8.
34. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular–phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci USA 2007;104:13780–5.
35. Gevers D, Kugathasan S, Denson LA et al. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe 2014;15:382–92.
36. Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ. Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis 2015;26:26191.
37. Lamps LW, Madhusudhan KT, Havens JM et al. Pathogenic Yersinia DNA is detected in bowel and mesenteric lymph nodes from patients with Crohn's disease. Am J Surg Pathol 2003;27:220–7.
38. Navaneethan U, Venkatesh PGK, Bo S. Clostridium difficile infection and inflammatory bowel disease: understanding the evolving relationship. World J Gastroenterol 2010;16:4892–904.
39. Chassaing B, Rolhion N, de Vallée A et al. Crohn disease-associated adherent-invasive E. coli bacteria target mouse and human Peyer's patches via long polar fimbriae. Clin Invest 2011;121:966–75.
40. Wang HX, Wang YP. Gut microbiota–brain axis. Chin Med J (Engl) 2016;129:2373–80.
41. Mayer EA, Tillisch K, Gupta A. Gut/brain axis and the microbiota. J Clin Invest 2015;125:926–38.
42. Adamczyk Sowa M, Aldona M, Madej P, Michlicka W, Dobrakowski Hindawi P. Does the gut microbiota influence immunity and inflammation in multiple sclerosis pathophysiology? J Immunol Res 2017;2017:1.