Proceedings of ICBioMed 2025 Symposium: Computational Modelling and Simulation for Biology and Medicine
DOI: 10.54254/2753-8818/2025.LD27922

The Impact of Gut Microbiota on Health and Disease from Metabolic Regulation to Immune Balance

Junye Lu

School of Biological Sciences, The University of Manchester, Manchester, United Kingdom
ariel.lu2004@foxmail.com

Abstract. The gut microbiota, often referred to as the "second genome" of the human body, plays a pivotal role in maintaining host physiological homeostasis. This review aims to summarize how the gut microbiota regulates host metabolism and immune function via its metabolic products and to explore its mechanistic roles in various diseases, including metabolic disorders and autoimmune diseases. Based on an analysis of recent literature, it describes the process by which key metabolites of the microbiota facilitate host fat catabolism and immune cell differentiation. It further explains how dysbiosis can impair host energy metabolism and reduce the efficiency of anti-inflammatory factor differentiation, thereby contributing to the development of obesity, diabetes, and inflammatory bowel disease. By summarizing the current research progress, this review highlights the potential of microbiota modulation in disease prevention and treatment. In addition, existing challenges such as individual variability and mechanistic complexity are discussed, with a perspective on future research directions for precision microbiota-based interventions.

Keywords: Gut microbiota, Energy metabolism, Immunologic balance, Intervention treatment

1. Introduction

The gut microbiota refers to all microorganisms colonizing the human gastrointestinal tract, predominantly bacteria, but also including fungi, archaea, viruses, and others. While the composition of the microbiota exhibits individual specificity, the subset of microorganisms responsible for core functions is relatively conserved. These core-function microbes have established a stable symbiotic relationship with the host over long-term evolution and participate in the regulation of various physiological processes. Its functions encompass nutrient metabolism, immune defense, and neural regulation, and are closely linked to the host's health status. Based on the literature, this review focuses on the multifaceted roles of the gut microbiota in metabolic regulation and immune balance, and further examines how disruption of these balances contributes to the pathogenesis of a range of metabolic and immune-related diseases.

The influence of the gut microbiota on metabolic regulation is manifested in multiple ways. By fermenting indigestible dietary fibers, gut microbial communities generate a series of bioactive metabolites, such as short-chain fatty acids (SCFAs), bile acids, and amino acid derivatives. These

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2025.LD27922

metabolites act as signaling molecules to modulate host energy homeostasis, glucose tolerance, and lipid metabolism [1]. Moreover, they can drive the development of gut-associated lymphoid tissue and refine innate immune response mechanisms [2]. After dysbiosis, the host's immune tolerance is disrupted and insulin sensitivity decreases, which promotes the occurrence of inflammatory bowel disease (IBD) and metabolic diseases. However, the mechanisms by which the gut microbiota integrates and coordinates host metabolic and immune networks remain incompletely understood. This review aims to systematically examine the specific mechanisms underlying the gut microbiota's role in metabolic regulation and immune modulation. By revealing the metabolic–immune crosstalk networks mediated by the gut microbiota, it is expected to provide a theoretical basis for the development of novel disease intervention strategies and to advance the progress of precision medicine.

2. Composition and function of gut microbiota

The gut microbiota, as a complex microbial community colonizing the human gastrointestinal tract, comprises approximately 1014 microorganisms, far outnumbering human cells. It is predominantly composed of four bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria [3]. Its specific composition is influenced by multiple factors, including diet, age, genetics, antibiotic exposure, and environmental conditions. For example, compared with lean individuals, those with genetic obesity exhibit about a 50% reduction in Bacteroidetes and a 50% increase in Firmicutes. This microbial composition shift enables the microbiota to extract and deliver more calories from food to the host [4].

The gut microbiota performs diverse essential functions that contribute to host health and homeostasis. Metabolically, it is an integral component of the host metabolic network, expressing carbohydrate-active enzymes to facilitate nutrient absorption and transformation. Indigestible dietary fibers can be degraded by β-glucosidase to produce SCFAs, mainly acetate, propionate, and butyrate. These fatty acids affect a variety of metabolic processes by binding to the surface receptors of different organs in the host. In barrier protection, commensal bacteria suppress pathogenic colonization by competing for nutrients and adhesion sites, while microbial metabolites induce epithelial cells to secrete antimicrobial peptides such as defensins. The gut microbiota is also a key driver of immune system development and maturation, interacting with the host via pattern recognition receptors to promote immune cell differentiation. Dysbiosis refers to abnormal alterations in microbiota composition, diversity, and function caused by disturbances in host internal or external environments, disrupting its symbiotic relationship with the hostIt is characterized by reduced microbial diversity, overgrowth of potentially harmful bacteria, or loss of beneficial microorganisms. Dysbiosis is considered a contributing factor in a variety of gastrointestinal and systemic diseases: energy metabolism imbalance and toxic metabolite accumulation may lead to obesity and diabetes, and uncontrolled inflammation or immune defense defects can result in IBD.

3. Metabolic regulatory mechanism and dysbiosis

Among the diverse metabolites produced by the gut microbiota, SCFAs, secondary bile acids, and serotonin play central roles in host metabolic regulation, with their molecular mechanisms and physiological functions have been extensively validated [5]. SCFAs are the principal fermentation products of dietary fiber, consisting mainly of acetate, propionate, and butyrate, with an approximate molar ratio of 3:1:1 in the human gut. Bacteroidetes are the primary producers of propionate, Firmicutes predominantly synthesize butyrate, and most anaerobic gut bacteria can generate acetate.

DOI: 10.54254/2753-8818/2025.LD27922

SCFAs regulate host metabolism through multiple mechanisms: butyrate supplies about 70% of the energy required by colonocytes and sustains epithelial vitality via enhanced glycolysis and oxidative phosphorylation; propionate enters the liver through the portal vein and activates gluconeogenesis to stabilize blood glucose; acetate circulates to adipose tissue, promoting lipolysis and energy expenditure.

Bile acids, key products of cholesterol metabolism, are secreted as primary bile acids into the intestine, where approximately 95% are reabsorbed into the enterohepatic circulation. The remaining fraction is converted into secondary bile acids by gut bacteria—primarily Bacteroidetes and Clostridium species—via dehydroxylation. Secondary bile acids activate the farnesoid X receptor (FXR) and G protein-coupled bile acid receptor (TGR5), thereby enhancing hepatic cholesterol metabolism, stimulating lipid breakdown, and reducing fat accumulation.

Gut hormones such as serotonin, glucagon-like peptide-1 (GLP-1), and peptide YY (PYY) are regulated by the gut microbiota or by SCFAs. Serotonin inhibits lipolysis and promotes fat storage. GLP-1 enhances insulin secretion from pancreatic β-cells, suppresses glucagon release, and reduces hepatic glucose production. PYY slows gastrointestinal motility, extending the time for nutrient absorption.

Dysbiosis disrupts the production and function of these key metabolites, thereby contributing to metabolic disorders such as obesity and type 2 diabetes. SCFA imbalance reduces GPR43 activation in muscle and adipose tissue, impairing glucose uptake, decreasing insulin sensitivity, and leading to defective glucose clearance. Reduced SCFAs also diminish GLP-1 and PYY secretion by enteroendocrine cells, resulting in hyperphagia and excessive energy intake [6]. Imbalance of secondary bile acids disrupts gut–liver axis communication, decreases FXR and TGR5 activation, and promotes lipid synthesis while limiting lipolysis. Collectively, these changes drive a vicious cycle of hyperphagia, energy surplus, insulin resistance, and chronic inflammation, ultimately promoting disease development.

4. Immune regulatory mechanism and dysbiosis

Innate immunity serves as the host's first line of defense against pathogen invasion, and the gut microbiota plays a crucial regulatory role within this system. Lactobacillus and Bifidobacterium can enhance the expression of mucin (MUC2) and tight junction proteins such as claudin and occludin, thereby maintaining intestinal barrier integrity. Among microbial metabolites, butyrate can specifically bind to GPR41 or GPR43 on intestinal epithelial cells, activating the AMPK signaling pathway to promote epithelial cell proliferation and differentiation, while further enhancing the expression of tight junction proteins. In addition, the PI3K/Akt and PKC pathways regulate transcription factors to reduce the release of pro-inflammatory cytokines, thus limiting inflammatory damage to the intestinal barrier.

Gut microbiota can also be recognized by pattern recognition receptors (PRRs) on intestinal epithelial and immune cells to activate innate immune responses. TLR2, in a heterodimer form with TLR1 or TLR6, recognizes bacterial lipopeptides and lipoteichoic acid. This activation specifically stimulates PKC-α and PKC-δ, leading to phosphorylation that stabilizes the tight junction protein ZO-1 and strengthens epithelial barrier sealing. Lipopolysaccharides (LPS) bind to TLR4, activating downstream NF-κB signaling and inducing the production of pro-inflammatory cytokines, thereby enhancing the host's pathogen clearance capacity [7].

Through antigen presentation and immune signaling, the microbiota shapes adaptive immunity mediated by T cells and B cells. Commensal bacteria promote the differentiation of intestinal plasma cells and the production of secretory IgA, which neutralizes potential pathogens in the lumen and

DOI: 10.54254/2753-8818/2025.LD27922

limits their adhesion to epithelium, accounting for over 70% of systemic immunoglobulin production [8]. In gut-associated lymphoid tissue such as Peyer's patches, dendritic cells capture microbial antigens and present them to naïve T cells, inducing their differentiation into distinct subsets. Certain commensals, such as segmented filamentous bacteria (SFB), promote Th17 cell differentiation and elevate IL-17A and IL-22 levels, supporting defense against extracellular bacteria.

Dysbiosis is linked to diseases such as IBD and rheumatoid arthritis (RA). In IBD, beneficial bacteria such as Bifidobacterium and Lactobacillus are markedly reduced, while pathogenic Escherichia coli increase. This compromises epithelial barrier function, allowing pathogens and harmful molecules to penetrate the mucosa, activating both innate and adaptive immune responses and triggering excessive inflammation [9]. In RA, Prevotella species have been implicated as contributing factors, as they can produce a specific 27 kDa protein that induces Th1 responses, initiating immune attacks on synovial tissue, ultimately leading to joint inflammation and damage [10].

5. Metabolism-immune cross-interaction

These regulatory mechanisms do not operate in isolation; microbial metabolites can precisely modulate immune cell function to maintain immune balance, and in turn, changes in immune status can in turn influence host metabolic processes. As metabolic products, SCFAs also exert broad effects on adaptive immune responses. Butyrate promotes regulatory T cell (Treg) differentiation by inhibiting histone deacetylases (HDACs), enhancing their ability to secrete IL-10 and TGF-β, thereby suppressing excessive immune responses. Propionate activates GPR43 or GPR41 to stimulate dendritic cells to produce the anti-inflammatory cytokine IL-10, reducing Th17 cell differentiation. The receptors FXR and TGR5 activated by secondary bile acids can not only inhibit the release of pro-inflammatory cytokines such as TNF-α and IL-6, but also promote the polarization of macrophages towards the anti-inflammatory phenotype. Indole derivatives, produced by microbial tryptophan metabolism, can induce regulatory B cells to secrete IL-10, suppressing excessive immune activation.

Immune responses can affect host metabolic balance by altering the intestinal environment and microbiota composition, with cytokines acting as key signaling molecules in metabolic regulation. Under normal immune homeostasis, IL-10 from Tregs suppresses adipose tissue inflammation and enhances glucose uptake and utilization by adipocytes. Reduced intestinal Treg abundance has been shown to impair SCFA utilization, leading to fat accumulation and hyperglycemia [11]. During acute infection or chronic inflammation, TNF-α inhibits insulin signaling in adipocytes, promoting lipolysis and insulin resistance, while IL-6 stimulates hepatic gluconeogenesis, resulting in elevated blood glucose levels.

Immunoglobulin A (IgA) can bind and coat bacterial surfaces through specific glycosylation patterns, a process known as the IgA coating pattern. Changes in this pattern selectively inhibit the colonization of certain bacteria, thereby altering microbial metabolic profiles. For example, IgA coating of Bacteroides thetaiotaomicron outer membrane polysaccharide utilization proteins upregulates polysaccharide utilization loci (PUL) expression, promoting its colonization in the mucus layer and enhancing butyrate metabolism [12]. Therefore, for diseases such as IBD, diabetes and obesity, the characteristics of metabolic dysfunction or excessive activation of immune cells often manifest simultaneously in patients.

DOI: 10.54254/2753-8818/2025.LD27922

6. Intervention strategies for regulating the gut microbiota

Gut microbiota dysbiosis is closely associated with the onset and progression of various diseases. Consequently, targeted modulation of microbial composition and function to maintain health or improve disease outcomes has become a major research focus. Current strategies include probiotic supplementation, fecal microbiota transplantation (FMT), and dietary modification. Diet is the most direct environmental factor influencing gut microbiota, and altering dietary composition offers a relatively safe approach. The core mechanism of dietary regulation lies in providing nutritional substrates for specific microbiota or indirectly regulating microbiota-host interactions through metabolic products. High-fiber diets promote the growth of SCFA-producing bacteria, which enhance intestinal barrier integrity, suppress inflammation via activation of receptors such as GPR43 or GPR41, and regulate energy metabolism. Clinical trials have reported that, compared with low-polyphenol diets, long-term polyphenol intake significantly increases beneficial taxa such as Bifidobacterium and Lactobacillus [13]. Formulating personalized plans based on host genotype and microbiota characteristics to implement precise dietary intervention can enhance efficacy. Probiotics are defined as live microorganisms that, when administered in adequate amounts, confer health benefits to the host [14]. Common probiotic strains include Bifidobacterium, Lactobacillus, Enterococcus faecalis and yeast, etc. The functions of different strains are specific. They restore microbial balance by competing with pathogens for nutrients and, like commensal microbiota, modulate host metabolism and immune homeostasis. First, the maintenance of intestinal barrier function is achieved by increasing the expression of tight junction proteins. Second, modulating immune responses by activating pattern recognition receptors to promote the differentiation of regulatory T cells, or by secreting anti-inflammatory mediators to suppress excessive inflammatory reactions. Third, Facilitating SCFA production through fermenting dietary fiber to promote fat catabolism and improve microbial metabolism. Clinical evidence supports their therapeutic potential: in randomized controlled trials on IBD, Lactobacillus reduced pro-inflammatory IL-6 levels and colonic myeloperoxidase (MPO) activity, thereby alleviating mucosal injury caused by leukocyte recruitment [15]. Bifidobacterium increased SCFA levels, lowered MPO activity, improved clinical symptoms, and reduced recurrence risk in refractory cases [16].

For recurrent or treatment-resistant IBD, FMT has shown efficacy by reconstructing microbial communities via transplantation of processed fecal material from healthy donors. In recurrent Clostridioides difficile infection (CDI), vancomycin achieved a 31% cure rate, whereas FMT reached 81% [17]. However, despite its remarkable efficacy, FMT carries risks such as pathogen transmission and post-transplant microbiota instability, underscoring the need for standardized protocols to optimize safety and therapeutic outcomes.

7. Conclusion

The gut microbiota has emerged as a highly plastic therapeutic target, offering new opportunities for disease prevention, diagnosis, and treatment. Through diverse metabolic activities, it actively regulates host energy homeostasis, thereby influencing the pathogenesis of obesity and type 2 diabetes. In parallel, the microbiota shapes immune development and function by maintaining intestinal barrier integrity, promoting immune cell differentiation, and balancing pro-inflammatory and anti-inflammatory signaling pathways. Consequently, gut microbiota dysbiosis has become a common hallmark linking metabolic dysfunction and immune imbalance to disease onset and progression.

DOI: 10.54254/2753-8818/2025.LD27922

However, significant challenges remain. Microbiota composition, shaped by genetic, dietary, environmental, and lifestyle factors, varies considerably between individuals, making it difficult to identify universally effective therapeutic strategies. Moreover, difficulties in tracking the long-term dynamics of gut microbial communities hinder predictive capability, while the reliance on animal models in preclinical research may not fully capture the complexity of human–microbiota interactions. Addressing these challenges will require the integration of multi-omics approaches—including metagenomics, metabolomics, transcriptomics, and proteomics—t along with computational modeling, to enable a more comprehensive analysis of microbiota–host interactions and identification of key microbial drivers of disease. It will also be essential to optimize clinical trial design by accounting for personalized microbial profiles and host–environment interactions, thereby enhancing translational potential. Continued advances in this field hold great promise for transforming microbiome research into clinically applicable, individualized therapies, ultimately improving human health and disease management.

References

[1] Yuan X, Wang R, Han B, Sun C, Chen R, Wei H, et al. Functional and metabolic alterations of gut microbiota in children with new-onset type 1 diabetes. Nature Communications. 2022 Oct 26; 13(1).

[2] Ramanan D, Pratama A, Zhu Y, Venezia O, Sassone-Corsi M, Chowdhary K, et al. Regulatory T cells in the face of the intestinal microbiota. Nature Reviews Immunology [Internet]. 2023 Jun 14; 1–14. Available from: https: //www.nature.com/articles/s41577-023-00890-w

[3] Thursby E, Juge N. Introduction to the Human Gut Microbiota. Biochemical Journal [Internet]. 2017 May 16; 474(11): 1823–36. Available from: https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC5433529/

[4] Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Human gut microbes associated with obesity. Nature. 2006 Dec; 444(7122): 1022–3.

[5] Martin AM, Sun EW, Rogers GB, Keating DJ. The Influence of the Gut Microbiome on Host Metabolism Through the Regulation of Gut Hormone Release. Frontiers in Physiology [Internet]. 2019 Apr 16; 10. Available from: https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC6477058/

[6] Liu BN, Liu XT, Liang ZH, Wang JH. World Journal of Gastroenterology Gut microbiota in obesity Manuscript source: Invited manuscript. World J Gastroenterol [Internet]. 2021 Jul 7; 27(25): 3837–50. Available from: https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC8291023/pdf/WJG-27-3837.pdf

[7] Ghosh S, Whitley CS, Haribabu B, Jala VR. Regulation of Intestinal Barrier Function by Microbial Metabolites. Cellular and Molecular Gastroenterology and Hepatology. 2021 Feb; 11(5).

[8] Li Y, Ye Z, Zhu J, Fang S, Meng L, Zhou C. Effects of Gut Microbiota on Host Adaptive Immunity Under Immune Homeostasis and Tumor Pathology State. Frontiers in Immunology. 2022 Mar 10; 13.

[9] Santana PT, Rosas SLB, Ribeiro BE, Marinho Y, de Souza HSP. Dysbiosis in Inflammatory Bowel Disease: Pathogenic Role and Potential Therapeutic Targets. International Journal of Molecular Sciences. 2022 Mar 23; 23(7): 3464.

[10] Drago L. Prevotella Copri and Microbiota in Rheumatoid Arthritis: Fully Convincing Evidence? Journal of Clinical Medicine. 2019 Nov 1; 8(11): 1837.

[11] Bhaskaran N, Quigley C, Paw C, Butala S, Schneider E, Pandiyan P. Role of Short Chain Fatty Acids in Controlling Tregs and Immunopathology During Mucosal Infection. Frontiers in Microbiology [Internet]. 2018 Aug 24 [cited 2019 Dec 9]; 9. Available from: https: //www.ncbi.nlm.nih.gov/pmc/articles/PMC6117408/

[12] Nakajima A, Vogelzang A, Maruya M, Miyajima M, Murata M, Son A, et al. IgA regulates the composition and metabolic function of gut microbiota by promoting symbiosis between bacteria. Journal of Experimental Medicine [Internet]. 2018 Jul 24; 215(8): 2019–34. Available from: https: //rupress.org/jem/article/215/8/2019/46045/IgA-regulates-the-composition-and-metabolic

[13] Yang Q, Liang Q, Balakrishnan B, Belobrajdic D, Feng QJ, Zhang W. Role of Dietary Nutrients in the Modulation of Gut Microbiota: A Narrative Review. Nutrients. 2020 Jan 31; 12(2): 381.

[14] Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria [Internet]. Fao.org. 2002. Available from: https: //openknowledge.fao.org/items/db384295-64d9-47e2-b65b-3c918efc5140

DOI: 10.54254/2753-8818/2025.LD27922

[15] Ma Y, Yang D, Huang J, Liu K, Liu H, Wu H, et al. Probiotics for inflammatory bowel disease: Is there sufficient evidence? Open Life Sciences [Internet]. 2024 Jan 1; 19(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10998680/

[16] Nagasaki A, Takahashi H, Iinuma M, Uchiyama T, Watanabe S, Koide T, et al. Ulcerative Colitis with Multidrug-Resistant Pseudomonas aeruginosa Infection Successfully Treated with Bifidobacterium. Digestion. 2010; 81(3): 204–5.

[17] van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. The New England journal of medicine. 2013; 368(5): 407–15.