Molecular Microbiology Research 2024, Vol.14, No.1, 10-19
http://microbescipublisher.com/index.php/mmr

Review and Progress Open Access

# Microbiome and Chronic Diseases: Association, Causal Relationship, and Therapeutic Potential

Jiayao Zhou
Institute of Life Science, Jiyang College of Zhejiang A&F University, Zhuji, 311800, China
Corresponding author email: 2013478397@qq.com

Molecular Microbiology Research, 2024, Vol.14, No.1 doi: 10.5376/mmr.2024.14.0002
Received: 22 Nov., 2023
Accepted: 03 Jan., 2024
Published: 18 Jan., 2024



**Preferred citation for this article:**
Zhou J.Y., 2024, Microbiome and chronic diseases: association, causal relationship, and therapeutic potential, Molecular Microbiology Research, 14(1): 10-19 (doi: 10.5376/mmr.2024.14.0002)

**Abstract** The research on the microbiome and chronic diseases is of great significance in understanding the pathogenesis and progression of chronic diseases, developing novel treatment methods, and realizing personalized healthcare. This review introduces the basic concepts and importance of the microbiome, as well as the definition, classification, and global impact of chronic diseases. It delves into the association between the microbiome and various chronic diseases, including cardiovascular diseases, diabetes, obesity, and autoimmune diseases. The review also analyzes the relationship between the composition, function, and metabolites of the microbiome and the development of chronic diseases. It explores the impact of microbiome differences among different populations on chronic diseases, the potential mechanisms by which the microbiome affects the development of chronic diseases, and the interactions between the microbiome and various host systems. It summarizes the applications and potential of the microbiome in the treatment of chronic diseases and provides insights into future research directions and potential breakthroughs. This review aims to reveal the deep connection between the microbiome and chronic diseases, provide new ideas and methods for the prevention and treatment of chronic diseases, and promote the development of personalized healthcare.

**Keywords** Microbiome; Chronic diseases; Association; Causality; Treatment potential

In the diverse realm of human health, the study of the microbiome is gradually revealing its immense potential and value. The microbiome, encompassing all microorganisms both inside and outside the human body, including bacteria, fungi, viruses, and protozoa, collectively forms a complex and delicate ecosystem alongside human cells. Chronic diseases such as cardiovascular diseases, diabetes, obesity, autoimmune diseases, etc., have become significant global health issues (Ogunrinola et al., 2020). In recent years, with the rapid development of bioinformatics, molecular biology, and other technologies, scientists have begun to explore the pathogenesis of chronic diseases from the perspective of the microbiome, aiming to find new preventive and therapeutic strategies.

The association between the microbiome and chronic diseases is not only a hotspot in modern scientific research but also a profound transformation in the field of medicine. Increasing evidence suggests that the microbiome plays a crucial role in the pathogenesis of chronic diseases. For instance, the dysbiosis of the gut microbiome is closely related to inflammatory bowel disease, diabetes, and other diseases; changes in the oral microbiome are tightly linked to periodontal disease, cardiovascular diseases, etc. These findings not only deepen our understanding of chronic diseases but also provide new insights for disease prevention and treatment (Pascal et al., 2018).

Studying the relationship between the microbiome and chronic diseases not only helps understand the mechanisms of disease occurrence and development but also provides important evidence for developing new therapeutic methods and achieving personalized medicine. By modulating the composition and function of the microbiome, targeted interventions can be made to improve treatment outcomes and even prevent disease occurrence (Kho and Lal, 2018). This study aims to thoroughly explore the association and causality between the microbiome and chronic diseases, as well as to uncover the potential of the microbiome in the treatment of chronic diseases. It is hoped that through a systematic review of existing research results and the integration of multidisciplinary

knowledge and technologies, new strategies and methods can be provided for the prevention and treatment of chronic diseases. Furthermore, this endeavor seeks to advance the application and development of microbiomics in the medical field, contributing to the realization of personalized medicine.

## 1 Association Between Microbiota and Chronic Diseases

### 1.1 Association between microbiota and various chronic diseases

Research on the association between microbiota and various chronic diseases reveals their intricate yet crucial connections. These connections are manifested not only in the direct impact of microbiota on the occurrence and development of chronic diseases but also in the interactions between microbiota and various systems within the host.

Taking cardiovascular disease as an example, studies have found a close correlation between alterations in the gut microbiota and the risk of cardiovascular disease. Certain gut bacteria can produce metabolites such as trimethylamine N-oxide (TMAO), which promote vascular inflammation and atherosclerosis, while the intake of probiotics may reduce the risk of cardiovascular disease by modulating the balance of gut microbiota (Cingi et al., 2019).

In the field of diabetes, research on microbiota has also made remarkable progress. Increasing evidence suggests that dysbiosis of the gut microbiota may lead to insulin resistance and abnormal blood sugar regulation, thereby promoting the development of diabetes. Additionally, some studies have found that alterations in oral microbiota may also be associated with the risk of diabetes.

Obesity, as a global health issue, is also closely associated with microbiota. Studies have shown significant differences in the diversity and composition of gut microbiota between obese and healthy individuals, which may be related to metabolic abnormalities and inflammatory responses associated with obesity (Pothmann et al., 2019).

Autoimmune diseases are a complex category of diseases often associated with abnormal attacks by the immune system on self-tissues. Research on microbiota provides a new perspective for understanding the pathogenesis of autoimmune diseases. For example, dysbiosis of the gut microbiota may lead to abnormal immune responses to intestinal cells, thereby triggering autoimmune diseases such as inflammatory bowel disease and multiple sclerosis (Chiu et al., 2019).

### 1.2 Microbiome composition, function, and their metabolic products related to chronic diseases

The microbiome, as a vast ecosystem, is characterized by the types and quantities of its microbial species and their relative abundances, which together determine its functionality. These microbes produce various substances through metabolism, including beneficial and potentially harmful compounds. These substances interact with host cells, thereby affecting host health. Studies on microbial communities and their interactions with hosts show that these microbes perform biochemical activities that influence carcinogenesis, tumor progression, and immune therapy responses (Figure 1).

During the development of chronic diseases, the composition of the microbiome often changes, with increases in harmful microbes or decreases in beneficial ones potentially triggering or exacerbating disease progression. For example, in the intestines of diabetic patients, a reduction in certain acid-producing bacteria and an increase in bacteria associated with inflammation and insulin resistance are often observed. These changes can lead to metabolic abnormalities in the host, further aggravating the symptoms of diabetes (Figure 1).

The function of the microbiome is also directly related to the development of chronic diseases. The microbiome contributes to the maintenance of internal environmental stability in the host by participating in nutrient metabolism, synthesizing vitamins, and regulating immune responses. Impairment of microbiome functions can lead to metabolic imbalances and immune disorders in the host, thus increasing the risk of chronic diseases (Wise et al., 2018).

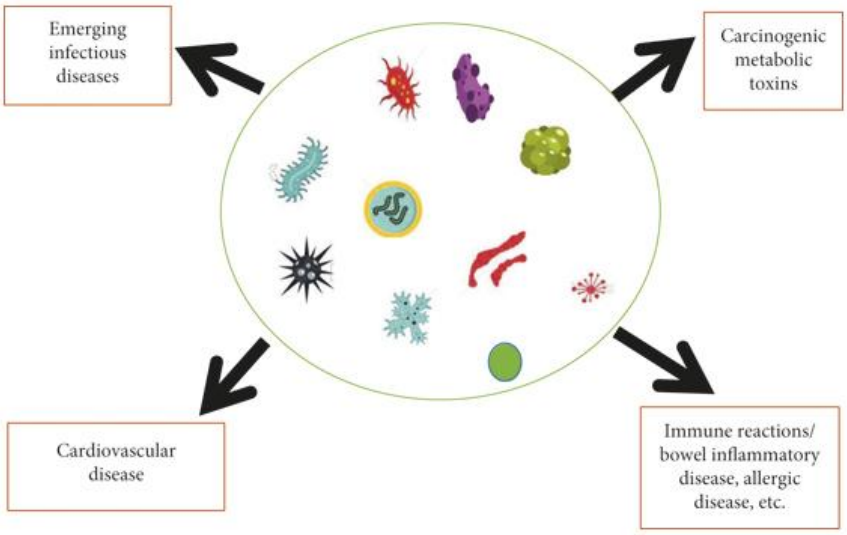


Figure 1 Dysbiotic flora and its impact on human health (Ogunrinola et al., 2020)
Note: Carcinogenic metabolic toxins produced from dysbiotic flora may trigger the progression of cancer and immune reaction in the gastrointestinal tract. In addition, hepatic oxidation of trimethylamine to trimethylamine N-oxide contributes to cardiovascular and emerging diseases

The metabolic products of the microbiome, such as short-chain fatty acids and secondary metabolites, have a direct impact on host health. Some studies suggest that these metabolic products may be involved in the onset and development of chronic diseases by regulating gene expression and affecting signaling pathways.

### 1.3 Differences in the microbiome across different populations and their impact on chronic diseases

The variations in the microbiome across different populations not only affect an individual's susceptibility to diseases but may also influence the treatment outcomes and prognosis of diseases. Age is a significant influencing factor; the microbiome of newborns is relatively simple, and as they age, microbial diversity increases, closely associated with the development and maturation of the immune system. In old age, the microbiome may undergo further changes, increasing the risk of age-related chronic diseases (Vatanen et al., 2018).

Gender is also a notable factor. Studies indicate differences in the microbiomes of males and females, particularly in the reproductive system and the gut. These differences may explain why certain chronic diseases exhibit variations in incidence and progression between genders.

The impact of geographical distribution on the microbiome reflects the diversity of environment and lifestyle. Populations in different regions, due to factors such as diet, climate, and lifestyle habits, may exhibit significant differences in the composition and functionality of their microbiomes. These differences may result in varying susceptibilities to chronic diseases among different geographical populations (Vijay and Valdes, 2022).

## 2 Discussion on the Causal Relationship between Microbiota and Chronic Diseases

### 2.1 Potential mechanisms of microbiota impact on the occurrence and development of chronic diseases

The potential mechanisms of microbiota impact on the occurrence and development of chronic diseases constitute a complex system with multiple layers and pathways. It involves intricate interactions between microbiota and the host, including direct microbial infection, generation and absorption of metabolic products, immune regulation, and more. Zheng et al. (2020) found that certain bacteria or fungi in the microbiota may directly promote the occurrence of chronic diseases by releasing toxins or triggering inflammation. For instance, some intestinal bacteria can produce harmful substances, disrupt the intestinal barrier, induce chronic inflammation, and consequently increase the risk of cardiovascular diseases or diabetes.

Moreover, metabolic products of microbiota also play crucial roles in the development of chronic diseases. Metabolites produced by certain microbiota, such as short-chain fatty acids, vitamins, etc., are essential for host health. Their deficiency or excess may affect the metabolic balance of the host, thereby increasing the risk of chronic diseases (Palmu et al., 2020).

Microbiota also indirectly influence the occurrence of chronic diseases by affecting the host immune system. Microbiota can train and regulate the host immune system, affecting its response to foreign pathogens and self-cells. When microbiota balance is disrupted, it may lead to an overreactive or inadequate immune response, thereby triggering or exacerbating chronic diseases.

**2.2 Interaction between the microbiota and host system and its impact on chronic diseases**

The interaction between the microbiota and the host immune and metabolic systems constitutes a complex network for human health. The microbiota exerts profound effects on the host immune system through its diversity, the release of metabolites, and direct communication with host cells. Valdes et al. (2018) found that the gut microbiota can stimulate specific immune responses in the host to combat pathogens while also helping to maintain immune system balance and prevent overreaction. However, imbalance in the microbiota may disrupt immune system function, thereby increasing the risk of chronic diseases such as inflammatory bowel disease or autoimmune diseases.

Simultaneously, the relationship between the microbiota and the metabolic system is also significant. The microbiota influences host metabolism by participating in the metabolism of nutrients, synthesizing essential vitamins, and producing short-chain fatty acids, among other functions. For example, certain gut bacteria can affect the host's metabolism of carbohydrates, thereby influencing blood sugar levels and the risk of diabetes. This interaction between the microbiota and the metabolic system makes the microbiota a key factor in regulating host metabolic balance.

The occurrence and development of chronic diseases are often associated with imbalances in the interaction between the microbiota and the host immune and metabolic systems. When this interaction goes awry, it may lead to abnormal immune responses, metabolic disorders, and ultimately the onset or exacerbation of chronic diseases.

**2.3 The impact of chronic diseases on the microbiota and potential feedback mechanisms**

The impact of chronic diseases on the microbiota is multifaceted and profound. Under the state of chronic illness, the host's internal environment equilibrium is disrupted, directly leading to dysbiosis of the microbiota. For instance, in diabetes, the elevated blood sugar levels alter the osmotic pressure in the gut, affecting the survival and metabolism of microorganisms, resulting in a decrease in beneficial bacteria and an increase in harmful ones. Similarly, cardiovascular diseases and autoimmune diseases also lead to changes in the microbiota, with the inflammatory environment and metabolic abnormalities associated with these diseases negatively impacting the microbiota (Wells et al., 2020).

Chronic diseases may also indirectly affect the microbiota by influencing the host immune system. Aberrant immune system responses may cause changes in the composition and function of the microbiota. For example, in inflammatory bowel disease, an overactive immune system leads to decreased diversity in the gut microbiota and an increase in harmful bacteria. Research by Ogunrinola et al. (2020) found that end products released by gut microbiota can affect the coverage of intestinal cells, promoting carcinogenesis or inhibiting tumor occurrence. Apart from colorectal cancer, the gut microbiota also plays a role in extraintestinal cancers (such as hepatocellular carcinoma) through systemic dissemination to other parts of the body (Figure 2).

It is worth noting that the relationship between the microbiota and chronic diseases is not unidirectional. The microbiota may also influence the development of chronic diseases through its metabolic products and interactions with host cells, forming feedback mechanisms. For example, metabolites produced by certain

microbiota may further exacerbate inflammation or metabolic disorders, thereby promoting the development of chronic diseases. This feedback mechanism renders the relationship between the microbiota and chronic diseases even more complex and elusive.

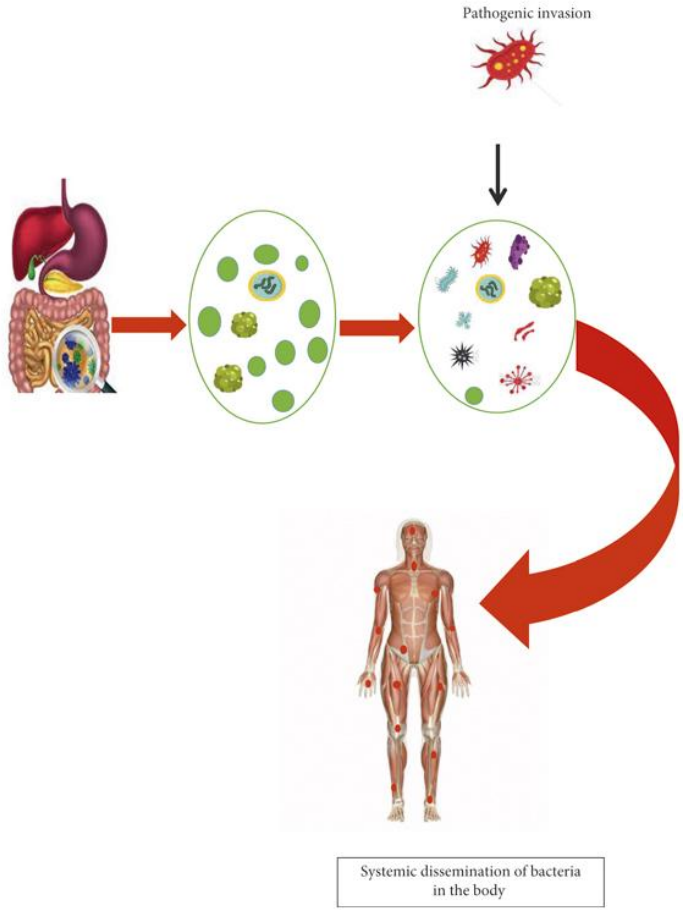


Figure 2 An alteration in the gut microbiota leads to systemic translocation of organisms from damaged gut epithelium to other extraintestinal sites (Ogunrinola et al., 2020)

## 3 Potential of the Microbiome in the Treatment of Chronic Diseases

### 3.1 Application and effects of microbiome regulation strategies in the treatment of chronic diseases

The application and potential effects of microbiome regulation strategies in the treatment of chronic diseases are gradually gaining attention. Among them, probiotics, as a common means of microbiome regulation, aim to regulate the balance of the intestinal microbiota, enhance immunity, and improve the progression of chronic diseases by supplementing beneficial live or dead bacteria to the body. Ogunrinola et al. (2020) showed that probiotics have demonstrated certain effects in improving intestinal inflammation, alleviating diarrhea, and potentially benefiting the treatment of chronic diseases such as inflammatory bowel disease and irritable bowel syndrome (Figure 3).

Prebiotics, serving as the "food" for probiotics, indirectly regulate the microbiome by promoting the growth and activity of beneficial bacteria. Their application has shown certain effectiveness in improving constipation, promoting intestinal health, and holds positive implications for the prevention and treatment of certain chronic diseases related to microbiota imbalance (Figure 3).

Fecal microbiota transplantation (FMT) is a more aggressive treatment method that aims to reconstruct the intestinal microbiota balance of patients by transplanting the gut flora of healthy individuals into the patient's body.

This method has achieved significant results in the treatment of refractory intestinal diseases such as Clostridium difficile infection, offering new possibilities for the treatment of certain chronic diseases (Punt et al., 2017).

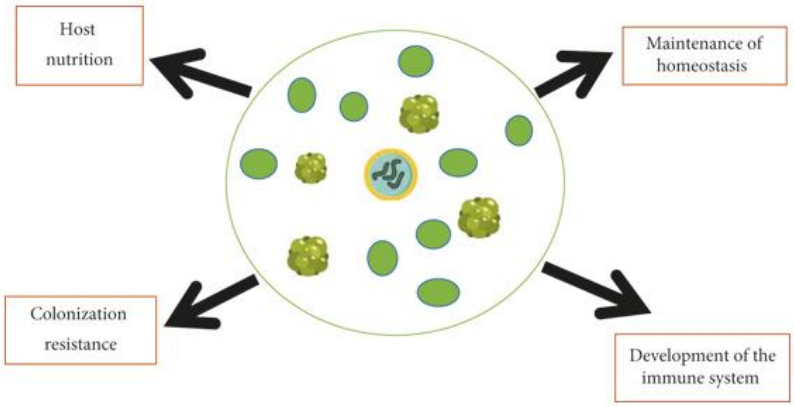


Figure 3 Symbiotic interaction between eubiotic flora and the human body results in the maintenance of homeostasis, regulation, and development of the immune system, hosts nutrition, and colonization resistance (Ogunrinola et al., 2020)

However, despite the effectiveness of these microbiome regulation strategies in the treatment of chronic diseases, their efficacy and safety remain controversial. There are significant differences in response between different diseases and individuals, and further research and validation are needed on the long-term effects and safety of their application. Therefore, in practical application, it is necessary to develop reasonable treatment plans based on the specific circumstances of the patient and closely monitor the efficacy and adverse reactions.

### 3.2 The potential of microbiome-based personalized medicine in the treatment of chronic diseases

Microbiome-based personalized medicine holds immense potential in the treatment of chronic diseases. Each individual's microbiome is unique, closely linked to their health status, lifestyle habits, and environmental factors in composition and function. By deeply analyzing and understanding an individual's microbiome characteristics, tailored precision treatment strategies can be developed (Tajik et al., 2020).

In the treatment of chronic diseases, microbiome-based personalized medicine entails customizing treatment plans according to the patient's microbiome features. For example, adjusting the patient's diet, supplementing specific probiotics or prebiotics, or even employing fecal microbiota transplantation can improve or restore the balance of the patient's microbiome, thus achieving the goal of treating the disease (Alpizar-Rodriguez et al., 2019).

Compared to traditional "one-size-fits-all" treatments, microbiome-based personalized medicine is more precise and effective. It not only enhances treatment outcomes and reduces unnecessary drug side effects but also lowers the risk of disease recurrence. With the advancement of microbiome research and technological progress, microbiome-based personalized medicine will become a critical direction in the future treatment of chronic diseases.

### 3.3 Drug development related to the microbiome and practical cases in the treatment of chronic diseases

Currently, drug development related to the microbiome is still in its early stages, but there are practical cases of microbiome-related drug development in the treatment of chronic diseases. Specifically, certain drugs may exert their effects by inhibiting the growth of harmful bacteria or promoting the proliferation of beneficial bacteria. They may also influence the host's physiological processes by modulating metabolites produced by the microbiome, such as short-chain fatty acids (Jack et al., 2018). Additionally, research is exploring the use of specific microbes or their metabolites from the microbiome to develop new drugs or treatment methods.

3.3.1 Berberine and probiotic combination therapy as an effective strategy for improving postprandial hyperlipidemia in type 2 diabetes patients

Research shows that non-fasting lipid abnormalities are associated with cardiovascular disease risk and are equally important as fasting lipid abnormalities. In a randomized, placebo-controlled, multicenter clinical trial, the effect of combined therapy with probiotics and berberine on lipid abnormalities in newly diagnosed T2D patients was evaluated. This treatment regimen was found to effectively reduce postprandial lipid levels in T2D patients. Compared to berberine alone, the addition of probiotics did not show additional effects in improving postprandial triglycerides. However, the effect of combination therapy remained significant after excluding patients taking lipid-lowering medications. This indicates that berberine effectively lowers fasting lipid levels but has limited impact on postprandial cholesterol levels, which may require synergistic action with probiotics (Maifeld et al., 2021).

Further research revealed the specific mechanisms by which combination therapy affects lipid metabolism through liquid chromatography/mass spectrometry analysis. The results showed that combination therapy influenced 20 out of 31 postprandial lipid metabolites, including long-chain to medium-chain fatty acids, acylcarnitines, and various glycerophospholipids. Changes in these key lipid metabolites were closely associated with improvements in low-density lipoprotein cholesterol and total cholesterol levels, as well as improvements in triglycerides and glycemic indices. This suggests that the reduction of various postprandial free fatty acids and phospholipids after combination therapy may contribute to the overall reduction in lipid levels. This study demonstrates the effectiveness of oral probiotic and berberine combination therapy in improving lipid abnormalities in newly diagnosed T2D patients, providing a new microbiome-related drug strategy for lipid management in T2D patients (https://international.biocloud.net/zh/article/detail/34923903).

3.3.2 Intestinal antimicrobial peptides shape protective gut microbiota in neonates to counteract pancreatic autoimmunity

Alterations in the gut microbiota are associated with the development of autoimmune type 1 diabetes (T1D), as demonstrated in both human and non-obese diabetic (NOD) mouse models. However, how dysbiosis in the gut ecosystem arises and promotes autoimmune responses remains a lingering question. Research investigates whether early events influencing the intestinal homeostasis of neonatal NOD mice can explain the development of pancreatic autoimmunity in humans. Liang et al. (2021) analyzed the transcriptome and colonic microbiota between neonatal NOD mice and non-autoimmune strains. A seminal defect was identified in the intestinal homeostasis of neonatal NOD mice, elucidating the mechanistic link between this defect and adult diabetic responses. Liang et al. (2021) determined defective expression of cathelicidin-related antimicrobial peptide (CRAMP) in the colon of neonatal NOD mice, resulting in dysbiosis. Dysbiosis stimulates colonic epithelial cells to produce type I interferon, which pathologically imprints the neonate's local immune system. This pathological immune imprint later promotes adult pancreatic autoimmunity and diabetes development. Restoration of colonic homeostasis, cessation of diabetic responses, and prevention of autoimmune diabetes were achieved by local CRAMP treatment or probiotic supplementation to enhance colonic CRAMP expression in neonatal NOD mice (Liang et al., 2021).

The study identified whether defects in colonic expression of CRAMP antimicrobial peptide lead to dysbiosis, thereby causing pancreatic autoimmunity. Therefore, manipulation of intestinal antimicrobial peptides may be considered a relevant therapeutic approach for preventing autoimmune diabetes in high-risk children (Figure 4).

3.3.3 Dietary supplements based on metabolites in type 1 diabetes patients are associated with microbiota and immune regulation

Short-chain fatty acids (SCFAs) produced by the gut microbiota have beneficial anti-inflammatory and gut homeostasis effects and can prevent type 1 diabetes (T1D) in mice. Reduced SCFA production indicates loss of beneficial bacteria, which is often associated with chronic autoimmune and inflammatory diseases, including T1D

and type 2 diabetes. Here, Kirstine et al. (2022) discussed whether metabolism-based dietary supplements affect T1D patients. Kirstine et al. (2022) conducted a feasibility trial using acetylated and butyrated high-amylose maize starch (HAMSAB) to assess safety while monitoring changes in gut microbiota to adjust the immune system status.

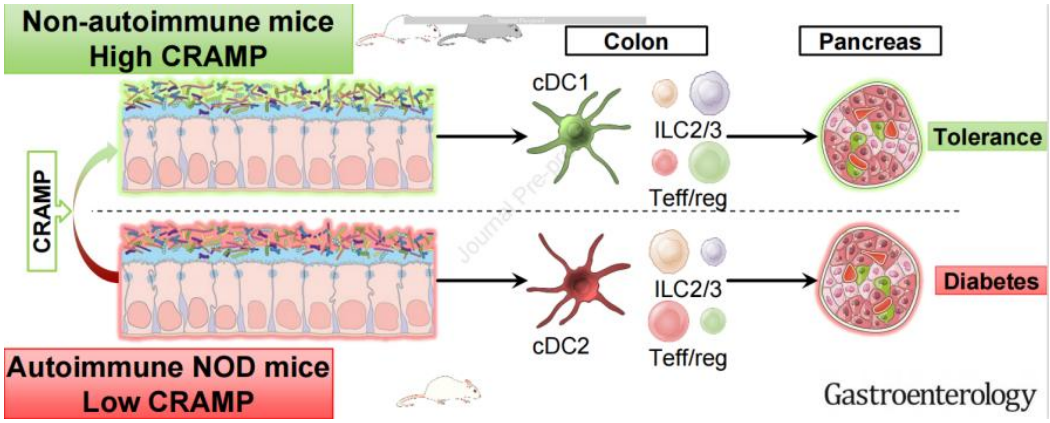


Figure 4 Using microbial diversity sequencing to investigate the immune response of mouse intestinal microbiota (Liang et al., 2021)

Results showed that adults with long-term T1D who took HAMSAB supplements for 6 weeks followed by a 12-week follow-up had increased concentrations of SCFA acetate, propionate, and butyrate in feces and plasma consistent with changes in gut microbiota composition and function. Although there were no changes in blood sugar control and insulin requirements, the individuals with the highest SCFA concentrations had the best blood sugar control. Increased production of Bifidobacterium, Lactobacillus, and vitamin B7 was associated with lower HbA1c and baseline insulin requirements. After intervention, circulating B cells and T cells formed a more regulatory phenotype.

Changes in gut microbiota composition, function, and immune status after supplementing with HAMSAB were associated with increased SCFAs in feces and plasma. The persistence of these effects suggests that targeting dietary SCFAs may be a mechanism for altering immune characteristics, promoting immune tolerance, and improving blood sugar control in T1D treatment (Kirstine et al., 2022).

## 4 Summary and Outlook

With the deepening of scientific research, the correlation between the microbiome and chronic diseases has gradually drawn attention. The microbiome, especially the gut microbiome, as the largest ecosystem within the human body, exhibits complex and subtle interactions with the host. These interactions not only influence the physiological and metabolic processes of the human body but are also closely related to the occurrence and development of numerous chronic diseases. Various chronic diseases, such as inflammatory bowel disease, diabetes, cardiovascular diseases, autoimmune diseases, have been found to be associated with dysbiosis of the microbiome or overgrowth of specific microbes (Liang et al., 2021). The onset of these diseases often coincides with changes in the composition and function of the microbiome. For instance, in diabetic patients, the decrease in beneficial bacteria and increase in harmful bacteria in the gut are closely related to changes in blood glucose levels and inflammatory status. This correlation suggests that the microbiome plays an important role in the occurrence and development of chronic diseases.

As research progresses, more evidence indicates a causal relationship between the microbiome and chronic diseases. The microbiome affects host health through the production of metabolites, regulation of immune responses, and other means. Meanwhile, the status of chronic diseases also influences the composition and function of the microbiome, forming a vicious cycle. This causal relationship provides new insights for the prevention and treatment of chronic diseases. Based on the association between the microbiome and chronic

diseases, the microbiome demonstrates great potential in the treatment of chronic diseases. By adjusting the composition and function of the microbiome, such as using probiotics, prebiotics, fecal microbiota transplantation, etc., the symptoms of chronic diseases can be effectively improved, even achieving a cure. This brings new hope for patients who have long been troubled by chronic diseases.

Looking ahead, research on the microbiome and chronic diseases will increasingly focus on personalization. Each person's microbiome is unique, thus personalized medicine based on the microbiome will become an important direction in the future. In addition, interactions between the microbiome and other organisms, such as microbiomes in other parts of the body, environmental microbiomes, etc., will also become hotspots of research. With the continuous advancement of technology and deepening of research, it is expected to gain a deeper understanding of the causal relationship between the microbiome and chronic diseases and develop more precise and effective treatment methods. These breakthroughs will provide new perspectives and approaches, increasingly highlighting the important role of the microbiome in the prevention and treatment of chronic diseases.

**References**

Alpizar-Rodriguez D., Lesker T.R., Gronow A., Gilbert B., Raemy E., and Lamacchia C., 2019, Prevotella copri in individuals at risk for rheumatoid arthritis, Ann Rheum Dis., 78: 590-593.
https://doi.org/10.1136/annrheumdis-2018-214514

Chiu C.Y., Chan Y.L., Tsai M.H., Wang C.J., Chiang M.H., and Chiu C.C., 2019, Gut microbial dysbiosis is associated with allergen-specific IgE responses in young children with airway allergies, World Allergy Organization Journal, 12: 3.
https://doi.org/10.1016/j.waojou.2019.100021

Cingi C., Muluk N.B., and Scadding G.K., 2019, Will every child have allergic rhinitis soon? International Journal of Pediatric Otorhinolaryngology, 118: 53-58.
https://doi.org/10.1016/j.ijporl.2018.12.019

Jack A.G., Martin J.B., Caporaso J.G., Janet K.J., Susan V.L., and Rob K., 2018, Current understanding of the human microbiome, Nature Medicine, 24: 392-400.
https://doi.org/10.1038/nm.4517

Kho Z.Y., and Lal S.K., 2018, The human gut microbiome-a potential controller of wellness and disease, Frontiers in Microbiology, 9: 1835.
https://doi.org/10.3389/fmicb.2018.01835

Kirstine J.B., Sonia S., Tillett B.J., McGuire H.M., Bordbar S., Yap Y.A., Nguyen L.T., Wilkins M.R., Corley S., Brodie S., Duong S., Wright C.J., Twigg S., de St Groth B.F., Harrison L.C., Mackay C.R., Gurzov E.N., Hamilton-Williams E.E., and Marino E., 2022, Metabolite-based dietary supplementation in human type 1 diabetes is associated with microbiota and immune modulation, Microbiome, 14(7): 162.

Liang W.J., Enée E., Cédric A.V., Falcone M., Sun J., and Diana J., 2021, MIntestinal cathelicidin antimicrobial peptide shapes a protective neonatal gut microbiota against pancretic autoimmunity, Gut Microbes, 22(6)

Maifeld A., Bartolomaeus H., Löber U., Avery E.G., Steckhan N., and Markó L., 2021, Fasting alters the gut microbiome reducing blood pressure and body weight in metabolic syndrome patients, Nat Commun., 12: 1970.
https://doi.org/10.1038/s41467-021-22097-0

Ogunrinola G.A., Oyewale J.O., Oshamika O.O., and Olasehinde G.I., 2020, The human microbiome and its impacts on health, International Journal of Microbiology, 20(6).
https://doi.org/10.1155/2020/8045646

Palmu J., Salosensaari A., Havulinna A.S., Cheng S., Inouye M., and Jain M., 2020, Association between the gut microbiota and blood pressure in a population cohort of 6953 Individuals, J Am Heart Assoc., 9: e016641.
https://doi.org/10.1161/JAHA.120.016641

Pascal M., Perez-Gordo M., and Caballero T., 2018, Microbiome and allergic diseases, Frontiers in Immunology, 9: 1584.
https://doi.org/10.3389/fimmu.2018.01584

Pothmann A., Illing T., Wiegand C., Hartmann A.A., and Elsner P., 2019, The microbiome and atopic dermatitis: A review, Am J Clin Dermatol., 20: 749-761.
https://doi.org/10.1007/s40257-019-00467-1

Punt C.J.A., Koopman M. and Vermeulen L., 2017, From tumour heterogeneity to advances in precision treatment of colorectal cancer, Nat. Rev. Clin. Oncol., 14: 235-246.
https://doi.org/10.1038/nrclinonc.2016.171

Tajik N., Frech M., Schulz O., Schälter F., Lucas S., and Azizov V., 2020, Targeting zonulin and intestinal epithelial barrier function to prevent onset of arthritis, Nat Commun., 11: 1995.
https://doi.org/10.1038/s41467-020-15831-7

Valdes A.M., Walter J., Segal E., and Spector T.D., 2018, Role of the gut microbiota in nutrition and health, BMJ., 361: k2179.
https://doi.org/10.1136/bmj.k2179

Vatanen T., Franzosa E.A., Schwager R., Tripathi S., Arthur T.D., and Vehik K., 2018, The human gut microbiome in early-onset type 1 diabetes from the TEDDY study, Nature, 562: 589-594.
https://doi.org/10.1038/s41586-018-0620-2

Vijay A., and Valdes A.M., 2022, Role of the gut microbiome in chronic diseases: a narrative review, European Journal of Clinical Nutrition, 76: 489-501.
https://doi.org/10.1038/s41430-021-00991-6

Wells P.M., Adebayo A.S., Bowyer R.C.E., Freidin M.B., Finckh A., and Strowig T., 2020, Associations between gut microbiota and genetic risk for rheumatoid arthritis in the absence of disease: A cross-sectional study, Lancet Rheumatol., 2: 418-427.
https://doi.org/10.1016/S2665-9913(20)30064-3

Wise S.K.,Lin S.Y., and Toskala E., 2018, Internat consensus statementon allergy and rhinology:allergic rhinitis, International Forum of Allergy & Rhinology, 8(2): 85-107.
https://doi.org/10.1002/alr.22070

Zheng D., Liwinski T., and Elinav E., 2020, Interaction between microbiota and immunity in health and disease, Cell Res., 30: 492-506.
https://doi.org/10.1038/s41422-020-0332-7