(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 6, Issue 5 , Page No: 1-33
September-October 2023

IJMSCR

Microbiome and The Immune System: Interactions During Development, Diseases, and Microbiome-based therapies

Chawakrit Wilawan[1], Thayada Phimphilai[2], Throntun Rojviroon[3], Pusuda Konyanee[4], Chadapus Rueangsang[5], Napasrawee Tariyamongkonrat[6], Sisarin Teethan[6], Mona Charakorn[6], Siwakorn Sirimattayapant[7], Nalin Ongwuthitham[8], Praifah Nagaranurak[8], Santapong Srimontayamas[9], Mathasit Mungkalarungsi[10]

Magee Secondary School[1], Chiangmai University Demonstration School[2], Patumwan Demonstration School[3], Yothinburana School[4], Montfort College[5], Triam Udom Suksa School[6], PSU.Wittayanusorn school[7], Srinakharinwirot University Demonstration School Prasarnmit[8], Suankularb Wittayalai School[9], Horwang School[10]

***Corresponding Author:**
Chawakrit Wilawan
Magee Secondary School

Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

The immune system plays a vital role in protecting the body against harmful pathogens. Recent research has highlighted the significant influence of human microbiota on various aspects of human immunity. This review examines the current understanding of human microbiota and their respective roles in health, disease, human development, and the molecular mechanisms underlying these interactions in various organs. Additionally, this review draws upon the potential for microbiome-targeted therapeutic interventions based on this knowledge. The complex interactions between commensal microbiota and the immune system influence immune system development and homeostasis in both health and disease. They play a crucial role in training and developing major components of the innate and adaptive immune system, while the immune system maintains the symbiotic relationship with the host-microbe community. The composition of the microbiome changes throughout life stages due to environmental factors, diet, and hormonal fluctuations. In adults, the microbiome remains relatively stable until old age, when it becomes less diverse, making individuals more susceptible to disease. Imbalances in microbiota-immunity interactions are believed to contribute to the pathogenesis of various immune-mediated disorders. Disruptions can result in dysbiosis, impairing the crosstalk between the immune system and microbiota, and contributing to the development of diseases. Human host genes and microbial genes influence the microbiome, leading to variations that can impact overall well-being through metabolic activities and interactions with the immune system. The landscape for microbiome treatment holds tremendous potential for the development of groundbreaking biotherapeutics. Microbiome-based therapies are highly personalized and non-invasive, mitigating risks associated with traditional treatments.

Keywords: Immune system, Microbiota, Microbiome, microbiota-immunity interactions, Dysbiosis

Introduction

The immune system is a complex network of organs, tissues, and cells that work cooperatively to defend the body against harmful pathogens: such as bacteria, viruses, and fungi.[1] The immune system serves as the body's defense mechanism by identifying and destroying invading organisms; while also differentiating them from the body's own healthy cells and tissues. The immune system functions through a highly coordinated response, involving constituent components: including, but not limited to,

white blood cells, antibodies, lymph nodes, spleen, and thymus.[2] Its primary objective is to perpetuate the body's overall well-being, thus playing a crucial role in maintaining health and preventing infections and diseases.

In recent years, the human microbiota, the trillions of microorganisms residing within our bodies, has emerged as a key player in health and disease. Bacteria came into existence about 3.8 billion years ago and the eukaryotic lineage, including humans, came after respectively. These bacteria stayed free-living single cells, however, some became host-associated, creating the microbiome we know today.[3] The human microbiome, also known as the human microbiota, refers to the community of microorganisms which resides in various parts of the body, such as the gastrointestinal tract or the skin. They contribute to the digestion and absorption of nutrients, as well as protection against harmful pathogens.[4] The composition of the human microbiota is unique to each individual, forbye the microbiome adapts and modifies throughout the course of the host's life. The changes can be the result of both evolution and ecological factors that stimulate the community simultaneously, which can exert a substantial impact on the host's body.[5]

The microbiome plays a profound role in influencing the immune system. These microbes aid with the training of the immune system to recognize harmless substances and tolerate them while mounting an appropriate response against pathogens.[6] Furthermore, the microbiome assists in the production of antimicrobial compounds, vitamins, and short-chain fatty acids, which strengthen the immune defense.[7] Conversely, the immune system helps maintain a balanced and diverse microbiome composition; preventing the overgrowth of harmful bacteria and preserving beneficial microbial communities. Disruptions in this intricate balance, such as an inexpedient use of antibiotics, can negatively impact the immune function and enlarge the risk of immune-related disorders.[8] Hence, the interplay between the microbiome and immunity is crucial for maintaining a robust and vigorous immune response and overall health.

The human microbiome is well known to coevolve with the host, and they also shape up the host's phenotypes along the process. The adaptation of the microbiome makes it inevitable for the host to function without assistance from the microbiome, considering the fact that they are acutely multifunctional and play many pivotal roles in the system they inhabit. The roles on which we will be focusing, are the interaction between the microbiome and the immune system, the genetics trend in the microbiome and the host, including the impact on the development throughout the host's life, how some diseases arose due to the changes of the microbiome, and the response to stimuli such as prebiotics, antibiotics, and microbial transplants and more. The main systems which will be discussed in this review are the gastrointestinal system and the immune system because the interaction between these systems and the microbiome has a significant influence on the occurrence of numerous diseases, together with the development of the host.

This review delves into the mechanisms underlying the influence of the microbiota on the immune system, both during early-life imprinting and in long-term effects. Our focus is primarily on the role of the microbiota in shaping adaptive immunity and the wide-ranging impact these immune responses have on maintaining host homeostasis. Throughout this review, we provide a comprehensive overview of the current understanding and key concepts linking the microbiome to immune system development and function. We highlight significant studies that have dissected the intricate dialogues between the microbiome and immunity in both healthy and diseased states. Additionally, we address the challenges and potential opportunities of microbiome-targeted strategies for investigating disease pathogenesis and developing novel treatments.

It is important to note that the vast body of evidence regarding host immune-microbiome interactions cannot be fully captured in a single review. Therefore, our goal is to present essential concepts and examples of these interactions and their potential implications for human health and disease risk. Our understanding of how the microbiota influences various aspects of human health has opened up new avenues for personalized medicine and novel therapeutic approaches. Over the course of this review, we reference other recent publications that investigate specific aspects of these emerging interactions.

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Instrument

We conducted a comprehensive systematic review of scientific literature to explore the relationship between microbiota and immunity. Our search encompassed various electronic databases, including MEDLINE®, Springer, ACS Publications, Google Scholar, and ScienceDirect, without any restrictions on publication dates, while focusing on English language publications. We utilized specific keywords and Medical Subject Headings (MeSH) such as "microbiota," "microbiome," "relationship," "association," "Gut Microbiome," "immunity," "pathophysiology," "disease," and "Human Microbiome" to identify relevant studies. Furthermore, we examined the interplay between microbiome-immunity interactions and their roles in both health and disease. To ensure inclusiveness, we manually screened the reference lists of relevant articles to identify additional eligible studies that may have been missed during the initial search. Additionally, we extended our search to include abstracts from recent international congresses on the Human Microbiome. This review intends to provide a comprehensive insight into the morphology, pathophysiology, and pharmacology of the Microbiome.

Immune system

The immune system is a complex network of cells, tissues, and organs that work together to protect the body from harmful pathogens, such as bacteria, viruses, and parasites, as well as abnormal cells like cancer cells. Its main function is to identify and destroy foreign invaders while also recognizing and tolerating the body's healthy cells. It consists of two major components: the innate immune system and the adaptive immune system.

Innate Immune System:

The innate immune system is the body's first line of defense against pathogens. It provides immediate, nonspecific protection and is always ready to respond. The innate immune response is unable to recognize or memorize the same pathogens that the body has been exposed to; it has no immunologic memory. Key components of the innate immune system include: (1) Physical and Chemical Barriers: The skin, mucous membranes, and secretions (e.g., saliva, tears) act as physical barriers, preventing pathogens from entering the body. Chemical barriers, such as stomach acid and antimicrobial peptides, can kill or inhibit the growth of pathogens. (2) Phagocytes: Phagocytes, including neutrophils and macrophages, engulf and destroy pathogens through a process called phagocytosis. (3) Natural Killer (NK) Cells: NK cells are specialized lymphocytes that can recognize and kill virus-infected cells and tumor cells. (4) The complement system assists the immune response by opsonization of pathogens for phagocytic and adaptive immune component recognition, recruitment of other immune components to the site of infection, and formation of the membrane attack complexes leading to the clearance of bacteria and other pathogens. And (5) Inflammatory Response: When tissue is damaged or invaded by pathogens, the innate immune system triggers an inflammatory response. This response involves the release of pro-inflammatory molecules, such as cytokines and chemokines, to recruit immune cells to the site of infection or injury.[9]

Adaptive Immune System:

The adaptive immune system provides specific, long-lasting protection against pathogens. It takes time to mount an effective response but has the ability to recognize and remember specific pathogens, providing immunity upon subsequent exposures. The key components of the adaptive immune system include: (1) Lymphocytes: Two main types of lymphocytes are involved in the adaptive immune response: B cells and T cells. B cells produce antibodies, which can bind to specific pathogens and neutralize them. In contrast, T cells play a role in cell-mediated immunity, directly killing infected cells or activating other immune cells. (2) Antigen Presentation: Antigens are molecules on pathogens that can trigger an immune response. Antigen-presenting cells, such as dendritic cells, capture antigens, process them, and present them to T cells, initiating an adaptive immune response. (3) Memory Cells: Following initial exposure to a pathogen, memory cells are formed. These cells "remember" the specific pathogen, allowing for a faster and more efficient immune response upon re-exposure. (4) Humoral and Cellular Immunity: The adaptive immune system can mount both humoral immunity (mediated by antibodies) and cellular immunity (mediated by T cells). These two arms of the adaptive immune system work together to eliminate

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pathogens. (5) Immunological Memory: One of the remarkable features of the adaptive immune system is its ability to generate immunological memory. Memory B and T cells allow for a quicker and more robust response upon encountering the same pathogen in the future.[10]

Overall, the innate and adaptive immune systems work in concert to provide an effective defense against pathogens. The innate immune system acts as the first line of defense, while the adaptive immune system provides a tailored response to specific pathogens, establishing long-term immunity. This interplay between the innate and adaptive immune systems is crucial for maintaining immune homeostasis and protecting the body from infections and diseases. While the immune system orchestrates the maintenance of key features of host-microbe symbiosis, the microbiome plays critical roles in the training and development of major components of the host's innate and adaptive immune system. In general, imbalances in microbiota-immunity interactions under defined environmental contexts are believed to contribute to the pathogenesis of a multitude of immune-mediated disorders.[6]

Microbiome

In the human body, there is a community of microbes, all the microbes in the human body we call the microbiome. The microbiome is the genetic material collection of all microbes, such as fungi, viruses, bacteria, protozoa, and their genes, that live inside our bodies and on the human body. These microbes, or small animals living in our bodies, can protect our bodies against pathogens, help our immune system, and enable us to digest food in order to produce energy and vitamins, for example, vitamins B12, B, and K which necessitate the blood coagulation.[11] The microbiome is important for humans to attain nutrition; they are the bridge between the environment and our bodies, thus affecting human health in many ways. Each person has an individualized microbiome depending on things we eat, lifestyle, and social. Therefore, there is a slight difference in diversity from person to person; people who were related or living together tend to have similar microbiomes, too. The mammalian system is covered with a complex innate and adaptive immune system that extends throughout all tissue components. The main function of this immune system provides the host protection from all various potentially harmful exterior agents and perturb.

Body Systems and Microbiome Habitation

Microorganisms are not found in sterile sites. Since they are more protected from the outside, microorganisms are often situated deeper in the body such as the brain, heart, liver, ovary, bone marrow, joint fluid, blood, etc.[12] Nevertheless, our body has trillions of microorganisms living in each organism in the body systems, which are connected with the environment from air, food, or touching. Microbes are good for humans, as they provide needed help to humans in addition to providing benefits to the environmental source. Furthermore, these groups of microorganisms can change in response to host environmental factors, for instance, medication, exercise, diet, and other exposures.[13] The microbiome resiin many body systems. As described below:

Microbiomes in the Oral cavity

The oral microbiota is an important part of humans and includes several thousand varieties of species.[14] The oral cavity is a diverse ecosystem inhabited by a wide range of microorganisms, primarily bacteria. These bacteria include Streptococcus, which can be either harmful, causing dental caries, or beneficial, promoting oral health. Prevotella species contribute to periodontal diseases by promoting inflammation, while Porphyromonas bacteria degrade gum tissue, leading to periodontal damage. Fusobacterium species are associated with periodontal diseases and contribute to plaque formation and inflammation. Actinomyces bacteria are commonly found in dental plaque and can cause dental caries and oral infections. Aside from bacteria, fungi also play a role in oral health, with *Candida albicans* being the most prominent fungal species found in the oral cavity. It can cause oral thrush and infections, especially in individuals with weakened immune systems. Viruses, such as herpes simplex virus (HSV), Epstein-Barr virus (EBV), and human papillomavirus (HPV), can also be present in the oral cavity, although their role is not as well understood. Some of these viruses are associated with oral lesions like cold sores and oral warts.

Microbiomes in the Respiratory System

In the past, the respiratory system was thought to be a sterile environment. However; It is now discovered

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that it contains a variety of microorganisms.[15] Microbes enter the body by breathing air that includes microbes. The extermination of microbes depends on the mechanisms of mucociliary clearance, coughing, and the immune systems of the host. While the growth conditions of a normal lung microbiome are influenced by pH levels, temperature, oxygen levels, nutrient availability, and the activation of inflammatory cells in the host, it changes dramatically during illness to modulate for the injured airways.[16] The host immune system's ability to respond to the inflammation in the lungs depends on its symbiotic connection with the microbiome.[17]

Microbiomes in the Urinary tract system

The urinary system plays a crucial role in filtering toxins and waste products from the human body. While it shares some similarities with other body systems in terms of microbiome categories, the urinary microbiome is unique in terms of its population, which is less diverse and less abundant compared to the gut, vagina, and skin. Variations in anatomical structures and hormones between males and females result in distinct differences in the urinary microbiome. Additionally, age contributes to variations in the microbiome population, possibly due to changes in diet, personal hygiene, and voiding patterns. The urinary microbiome consists of microorganisms residing within the urinary tract, including the bladder and urethra. Although not as diverse as other body sites, recent studies have identified a range of bacterial species in the urinary microbiome. Commensal bacteria like *Lactobacillus, Streptococcus, and Corynebacterium* play a crucial role in maintaining a healthy urinary microbiome. They compete with pathogenic bacteria, preventing their overgrowth and maintaining a balanced microbial community. However, under certain circumstances, pathogenic bacteria can disrupt this balance, leading to urinary tract infections (UTIs). Common uropathogens include *Escherichia coli, Klebsiella pneumoniae,* and *Enterococcus faecalis*. Fungi, particularly *Candida* species, can also be present in the urinary microbiome, with *Candida albicans* being the most commonly identified species associated with urinary tract fungal infections. Imbalances in the urinary microbiome, whether caused by changes in bacterial or fungal composition, can contribute to urinary tract disorders and infections. Factors such as antibiotic use, hormonal changes, and immune dysfunction can disrupt the microbial balance, leading to dysbiosis and an increased risk of infection.[18]

Microbiomes in the Skin system

The skin, which is the largest organ of the body, is a resident of microorganisms known as the skin microbiome. Various kinds of skin microbiomes inhabit differently due to layers of the skin and environmental biodiversity.[19] The skin microbiome motivates the immune system to produce molecules that are vital for maintaining homeostasis such as the skin's pH and hydration. It also effectively prevents pathogens from growing by competing for resources and space on the skin's surface. Furthermore, many common skin diseases such as acne, chronic wounds, and eczema are associated with changes in microbiomes called dysbiosis, which is caused by the changing of skin bacteria to pathogens.[20]

Microbiomes in the Digestive System

There are a vast variety of microbes, especially in the gastrointestinal system, in which the organs include the mouth, stomach, duodenum, jejunum & ileum, and colon. The gut microbiota is crucial to the health of our digestive system, making a positive impact on our health, for instance, the Firmicutes phyla, create resistant endospores that endure sustainability in the environment and germinate within the intestine to enable transmission[21] It is also essential for our nutrition and metabolism, by influencing satiety and hunger through being indirectly connected to other tissues and organs.[19] Some Firmicutes species, on the contrary, such as Staphylococcus aureus and Clostridium perfringens, can cause sickness quickly if they overgrow. Ninety percent of the gut microbiota are made up of the phyla Firmicutes and Bacteroidetes,[22] there are possibilities that some microbes in the gut might over-colonize and later on cause infections, some strains for instance, *E. coli* can induce infections that result in diarrhea and vomiting, this is through unclean food or food that has gone rotten.[23]

Microbiomes in the reproductive system

The reproductive microbiome can be defined as the microbiome that lives in or on any organ, fluid, or tissue which is associated with the reproductive system, such as the vagina in females and semen in males. They play vital roles in reproductive health,

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fertility, and overall well-being.[24] Vaginal microbiota in the female reproductive system is dominated by *Lactobacillus* which maintains vaginal health. However, other bacterial species can also be crucial, including *Gardnerella vaginalis*, which is associated with bacterial vaginosis, and *Atopobium vaginae* which may contribute to the overgrowth of harmful bacteria. Some species of *Prevotella* and *Streptococcus* can also be part of the vaginal microbiota, with potential implications for infections during pregnancy.[25] Similarly, the male reproductive system has its own unique microbiota, primarily studied in semen. *Lactobacillus* are found in the male reproductive system and may contribute to reproductive tract health. *Corynebacterium* species are commonly present as well, but their impact is still being investigated. *Staphylococcus* species, including *Staphylococcus epidermidis*, can also be found. While some strains are harmless, others may be associated with infections such as epididymitis or prostatitis. Additionally, *Propionibacterium* species have been detected in the male reproductive microbiome, though their specific role is not yet fully understood[26]

Examples of microbiome species in each body system and organs

The number of microbes in the human microbiome is nearly equivalent to the body's cell count. The total microbial biomass in an average adult is approximately 0.2 kg.[27] However, there is no precise estimate of the overall number of microbial species in the human microbiome. Researchers speculated the variety of the species of the microbes to be over 1000 species.[28] The gastrointestinal tract have been established and categorized. The combination of bacterial species in the human microbiome changes over time and these changes can be crucial when a person is ill or takes antibiotics.[27]

These microbes inhabit different parts of the body, whether it is the eye, skin, mouth, and so on. To roughly introduce, the human gut is the most discussed habitat for colonizing microorganisms, especially bacteria. Below are examples of microbiomes in different body systems or organs.

Out of all the areas in the body, the gastrointestinal system contains the most diversity of microbes, with the number of 1000 species of bacteria[29] and one quadrillion quantities of microbial cells.[30] Examples of these microbes include: Lactobacillus spp, Streptococcus spp, Staphylococcus spp, Enterobacteriaceae, Bifidobacterium spp, Bacteroides spp, Eubacterium spp, Clostridium spp, Peptostreptococcus spp, Fusobacterium spp, Bacteroides spp, Eubacterium spp, Peptostreptococcus spp, Fusobacterium spp, Firmicutes, Fusobacteria, Proteobacteria, and so on. (Table 1)

The human skin which has an estimated area of 25 m2 and is the most exposed to the external environment part of the body,[31] contains around 1000 species of microbes[32], some of these include, Staphylococcus spp., Corynebacterium spp, Propionibacterium spp, Firmicutes, Bacteroidetes, and Actinobacteria and so on. (Table 1)

The Urogenital system is expected to be mostly sterile in the body of a healthy person. It is also found to be quite difficult for microbes to persist in the environment, since urine, being a bodily fluid, is hostile to the survival of bacteria. The consistency of flushing in the system also makes it challenging for any microorganisms to endure in the bladder.[33] Examples of the microbes present in the Urogenital system would be, Lactobacillus spp, Prevotella spp, Dialister spp, Clostridiales, and Prevotellaceae families, etc. (Table 1).

Table 1 Examples of microbiome species in each body system and organs (Cohut *et al*., 2020).

	Microorganisms
Body systems	
Gut (gastrointestinal system)	*Firmicutes* and *Bacteroides spp*

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Female urogenital areas	*Lactobacillus spp, Prevotella spp, Dialister spp*
Male urogenital areas	*Clostridiales* and *Prevotellaceae families*
Organs	
Stomach	*Lactobacillus spp, Streptococcus spp, Staphylococcus spp, Enterobacteriaceae*
Duodenum	*Lactobacillus spp, Streptococcus spp, Staphylococcus spp, Enterobacteriaceae*
Jejunum & Ileum	*Bifidobacterium spp, Bacteroides spp, Lactobacillus spp, Streptococcus spp, Enterobacteriaceae*
Colon	*Bifidobacterium spp, Bacteroides spp, Eubacterium spp, Clostridium spp, Peptostreptococcus spp, Fusobacterium spp, Lactobacillus spp, Streptococcus spp, Enterobacteriaceae*
Mouth	*Firmicutes, Fusobacteria, Proteobacteria,*
Skin	*Staphylococcus spp., Corynebacterium spp., Propionibacterium spp, Firmicutes, Bacteroidetes,* and *Actinobacteria* (Hassan *et al.* 2022)
Eye	*Pseudomonas spp., Propionibacterium spp, Bradyrhizobium spp*
Lungs	*Prevotella spp, Veillonella, Firmicutes*

Interaction between microbiota organ immunity

The microbiota plays a crucial role in the induction, training, and function of the immune system. The host and the microbiota share a symbiotic type of relationship. The collaboration of the immune system and microbiota allows the maintenance of regulatory pathways and the induction of protective responses against pathogens.[4] The gut microbiota, for example, digests complex carbohydrates and protein, synthesizes vitamins, and produces metabolic products.[34] The microbiota maintains homeostasis in healthy individuals.[35]

The Role of Microbiota in immune homeostasis

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Research studies have revealed that the microbiota contributes to immune homeostasis through several mechanisms. Firstly, the microbiota aids in the development and maturation of the immune system during early life. Interactions with the microbiota help shape the development and maturation of the immune system. The presence of beneficial bacteria helps train the immune system to distinguish between harmless and harmful stimuli, preventing unnecessary immune responses. Secondly, the microbiota plays a vital role in inducing immune tolerance, ensuring that the immune system does not overreact to harmless substances. Through interactions with the microbiota, the immune system learns to tolerate commensal bacteria and harmless antigens, thereby maintaining immune balance.[4]

Furthermore, the microbiota helps shape the balance between pro-inflammatory and anti-inflammatory immune responses. Certain beneficial bacteria produce short-chain fatty acids (SCFAs) through the fermentation of dietary fiber. SCFAs have been shown to exert anti-inflammatory effects and promote the differentiation and function of regulatory T cells. By modulating the immune response, the microbiota helps prevent chronic inflammation.[36] The microbiota also aids in maintaining the integrity of the epithelial barrier, which acts as the first line of defense against pathogens. A healthy microbiota promotes a robust barrier function, preventing the invasion of harmful microorganisms and reducing the risk of immune activation. In the immunomodulatory Effects, the microbiota influences the development and function of Treg, a specialized subset of immune cells responsible for suppressing excessive immune responses. Treg helps prevent autoimmune reactions and maintain immune tolerance. The microbiota communicates with immune cells, such as dendritic cells and macrophages, through pattern recognition receptors. This communication helps fine-tune immune responses, promoting appropriate reactions to pathogens while avoiding unnecessary inflammation.[37] A diverse and balanced microbiota is crucial for immune homeostasis. Loss of microbial diversity, known as dysbiosis, has been associated with various immune-related disorders. By promoting healthy and diverse microbiota, we can enhance immune function and reduce the risk of immune dysregulation. Finally, beneficial bacteria within the microbiota can compete with pathogenic microorganisms for resources and attachment sites. This competitive exclusion helps prevent the overgrowth of pathogens and maintains a balanced microbial ecosystem.[38]

The Role of Microbiota in Dysbiosis

Dysbiosis is characterized by a decrease in microbial diversity, an excess of harmful bacteria, or a loss of beneficial microbiota. Many factors can contribute to dysbiosis, including genetics, diseases, lifestyle, nutrition, xenobiotics, and hygiene.[39] Microbiota dysbiosis can cause diseases such as cancer, cardiovascular diseases, and respiratory diseases. It may also result in dysregulation of bodily functions. The gut microbiota is recognized as the most crucial factor in maintaining our health.[40]

Gut dysbiosis involves an expansion of facultative anaerobic *Enterobacteriaceae*. When SCFAs (short-chain fatty acids) accumulate and the environment turns acidic, the competitive advantage that facultative anaerobes like *Enterobacteriaceae* gain from O2 and NO3 respiration are reversed. PPAR-γ signaling pathway suppression, on the other hand, results in metabolic reprogramming, gut dysbiosis, and SCFA exhaustion. The Warburg effect, a result of this reprogramming that steers colonocytes away from oxidative metabolism and toward anaerobic glycolysis, significantly raises the amount of oxygen, nitrate, and lactate in the gut lumen. This negative feedback cycle promotes pathogen growth while demonstrating a causal link between microbiota-derived metabolism and the gut epithelium.[34]

Crosstalk between microbiota and extra-intestinal organ immunity

Microbes have the ability to influence immune reactions not only at the site of colonization but also in distant anatomical locations. This can occur through various mechanisms. (1) bacterial products like lipopolysaccharides (LPSs) can translocate from mucosal sites to systemic circulation. (2) The "domino effect" mechanism refers to a process where signals originating from the microbiota are transmitted to nearby cells. These cells then circulate throughout the body, relaying this information to other locations. This transmission can occur through various molecules such as cytokines, metabolites, or other signaling molecules. (3) The dissemination of microbiota-derived metabolites (metabolite second

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messenger model), involves the transmission of metabolites produced by the microbiota throughout the body. These metabolites can be found in different tissues and have the potential to be detected by the immune system at those sites.[41]

Distal immune stimulation has been observed in various tissues such as the bone marrow, liver, peritoneum, and spleen. The dissemination of bacterial antigens to the spleen and mesenteric lymph nodes can trigger the production of Immunoglobulin G; IgG, which provides systemic protection against bacterial infection.

Moreover, recent studies suggest that the response to HIV and potentially other viruses can be influenced by prior exposure to microbiota-derived antigens with cross-reactivity. Researchers have found that HIV vaccine-induced CD4+ T and B cell responses may originate from a group of intestinal immune cells that cross-react with commensal bacteria. In the study, a majority (82%) of anti-HIV antibodies in the ileum, specifically targeting the gp41 protein, showed cross-reactivity with commensal bacteria. Furthermore, 43% of these antibodies exhibited reactivity to non-HIV-1 antigens. This finding highlights the potential impact of the microbiota on shaping immune responses to viral infections like HIV.[41]

Liver

The gut-liver axis describes the anatomical and functional connection between the gastrointestinal tract and the liver. The liver is constantly exposed to bacterial products from the gut microbiome through the portal venous circulation and bile duct system. In certain contexts, intestinal commensals and their products can translocate to the liver and impact hepatic immune responses.

Microbial-associated molecular patterns (MAMPs) derived from gut bacteria can directly influence the number, function, and maturation of hepatic Kupffer cells (KCs), which are critical components of the liver's innate immune system. Intestinal pathogens can activate dendritic cells (DCs) and natural killer T (NKT) cells in the liver, exacerbating immune-mediated liver injury. Certain probiotics containing glycolipid antigens have been reported to stimulate hepatic NKT cells in a strain- and dose-dependent manner.

Bacterial lipopolysaccharide (LPS) can directly stimulate hepatic stellate cells, the main cells responsible for liver fibrosis, by inducing Toll-like receptor 4 (TLR4) signaling. This leads to the upregulation of chemokines and adhesion molecules. The activation of various Toll-like receptors, including TLR4, TLR9, and TLR5, by gut-derived microbial products has been shown to impact liver inflammation in the context of non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH).

The gut microbiota has also been implicated in liver inflammation associated with primary sclerosing cholangitis (PSC), a chronic inflammatory and cholestatic liver disease. The pathobiont Klebsiella pneumoniae, isolated from PSC patients, can damage the intestinal epithelial barrier, leading to bacterial translocation and the promotion of Th17 cell responses in the liver. Alterations in the bile microbiota, characterized by reduced biodiversity, increased abundance of Enterococcus faecalis, and elevated levels of taurolithocholic acid, have been observed in PSC patients. However, it is still unclear whether these alterations play a causal role in PSC or are merely a consequence of biliary disease.[6]

Central nervous system

The gut microbiome plays a significant role in modulating brain cell function and neuro-immunity, contributing to the development of a healthy brain and balanced immune responses. Microglia, the primary innate immune cells in the central nervous system (CNS), are influenced by the microbiota, with short-chain fatty acids (SCFAs) potentially playing a role in microglial homeostasis. The maternal microbiome also impacts microglial development during prenatal stages, and perturbations in microglia associated with the absence of microbiota can manifest in a sex-dimorphic manner. Microbial dysbiosis and microglial dysfunction have been observed in various neurological disorders.

SCFAs derived from the diet have been reported to promote regulatory T cells, counteracting autoimmunity in the CNS. The intestinal microbiota can also modulate meningeal IL-17+ γδ T cells, which impact the pathogenesis of ischemic brain injury. However, the understanding of the interplay between the microbiome and neuro-immunity in health and disease is still in its early stages. Depletion

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of gut commensal bacteria through antibiotic treatment has been shown to dampen the progression of experimental autoimmune encephalomyelitis in mice, possibly mediated by the induction of IL-10-producing regulatory T cells. Offspring of pregnant mice harboring specific gut bacteria associated with T helper 17 response have an increased risk of developing neurodevelopmental disorders.

There is growing interest in characterizing low-biomass microbiomes in organs previously thought to be sterile, such as the skin, lungs, reproductive organs, and bile ducts. However, caution is needed in interpreting these findings due to challenges related to contamination and sequencing artifacts. Contaminating microbial DNA can originate from various environmental sources, and strategies to control contamination must be considered when working with low microbial biomass tissues.[6]

Lung

A crosstalk between the gut microbiome and the lung is known as the "gut-lung axis." Changes in the gut microbiome and its byproducts can affect lung immunity, particularly in the context of pulmonary diseases. Gut bacteria play a role in regulating antiviral immunity in the respiratory tract during influenza infection by activating inflammasomes. Studies on germ-free mice have shown that the absence of gut microbes leads to impaired clearance of pathogens in the lungs.

Metabolites derived from the gut microbiome, such as SCFAs, promote the production of immune cells in the bone marrow. These cells then migrate to the lungs, shaping the lung's immune response and providing protection against airway inflammation. Another product derived from a specific gut bacterium, Clostridium orbiscindens, called desaminotyrosine, has distal effects on the lung and helps protect against influenza by modulating type I interferon signaling.

Recent evidence suggests the presence of a distinct lung microbiota that may impact pulmonary immunity. In mice, the rapid formation of an airway microbiome during the early postnatal weeks is critical for immune tolerance to inhaled allergens through mechanisms related to Programmed death-ligand 1(PD-L1). Similarly, in humans, the lower respiratory tract microbiome forms within the first two months after birth, coinciding with lung immune maturation. Alterations in the lung microbiota have been implicated in exacerbating chronic pulmonary diseases such as chronic obstructive pulmonary disease, asthma, and cystic fibrosis.

Different lung microbes are associated with distinct cellular immune responses. For instance, the enrichment of Pseudomonas and Lactobacillus in mouse models of chronic lung inflammation or specific profiles derived from diseased human bronchoalveolar systems are related to an enhanced Th17-type immune response. On the other hand, pathobionts, such as certain members of the Proteobacteria group, can induce severe airway inflammation and lung immunopathology independently of TLR2. Certain lung commensals have also been linked to the development of pulmonary adenocarcinoma by activating γδ T cells that produce IL17, highlighting the potential role of the lung microbiome in lung cancer.[6]

Microbiota-Immune system interaction during human development

The neonatal

Throughout pregnancy, fetal immune development is supported by microbial metabolites originating from the maternal microbiota and dietary compounds. Innate immune cell populations, including monocytes, Innate Lymphoid Cells (ILCs), and neutrophils belong to the most affected immune cells at this stage. According to research, the event of birth illustrates the change from the sterile environment in utero to the rapid colonization of all body surfaces. During and immediately after birth, the newborn is exposed to complex microbial communities in the external environment. For a vaginally born baby, this is initiated by vertical transmission of microbes when passing the birth canal and primarily includes microbes inhabiting the maternal gut lumen.[42] In terms of the close similarity between the maternal oral microbiota and the placental and infant oral microbiota. Several studies suggested that maternal–fetal microbial transmission may occur. Intriguingly, maternal periodontal infection is associated with a disturbed oral microbiome and has been associated with preterm birth and Small for Gestational Age (SGA) in some studies, suggesting that the oral cavity may act as a storehouse of microbes, which may ultimately interact with the developing fetus.[43]

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Neonatal innate immune memory has emerged as a critical mechanism providing protection against infectious agents. Nevertheless, in neonates, inexperience to antigenic exposure together with rapidly changing environmental and microbial exposures in the post-natal period would mainly have a vital impact on the immune responses and are often associated with severe immune pathological conditions. Despite significant scientific progress, the precise cellular and molecular mechanisms underlying defective neonatal innate immunity remain incompletely defined.[44]

Toddler

In human toddlers, the relationship between the microbiota and the immune system is crucial in shaping immune development and overall health. This relationship begins early in life and continues to evolve throughout the toddler years. Various factors, including mode of delivery, breastfeeding, diet, and exposure to the environment influence the establishment of a healthy and diverse microbiota during this period.

The microbiota interacts with the immune system in multiple ways, educating and training it to promote its maturation and activation. The presence of specific microbial species and their byproducts can stimulate the production of immune cells and the development of immune tolerance, which is crucial for preventing allergies and autoimmune diseases. Furthermore, the microbiota helps maintain the integrity of the gut barrier and influences the balance between pro-inflammatory and anti-inflammatory responses, preventing excessive immune activation and maintaining immune homeostasis.

Disruptions in the microbiota-immune system interaction during toddlerhood can result in significant health consequences. Factors such as antibiotic use, dietary changes, and exposure to environmental toxins can alter the composition of the microbiota, leading to immune-related disorders such as allergies, asthma, and autoimmune diseases. Overall, a healthy and diverse microbiota is essential for immune maturation and proper immune system functioning.

Adult

During human adult life, the interaction between the microbiota and the immune system continues to play a major role in maintaining immune homeostasis and overall health. This dynamic relationship between the microbiota and the immune system remains active throughout adulthood. The microbiota interacts with the immune system in multiple ways. Firstly, it helps train and modulate the immune response, ensuring an appropriate balance between tolerance and defense against pathogens. The presence of beneficial bacteria stimulates the development and activation of immune cells, including T cells, B cells, and antigen-presenting cells. This interaction is essential for maintaining immune surveillance and mounting effective immune responses when needed.

Moreover, the microbiome contributes to the maintenance of the intestinal barrier function. It promotes the integrity of the gut lining, preventing the translocation of harmful pathogens or toxins into the bloodstream. The microbiota also stimulates the production of mucus and antimicrobial peptides, which act as physical and chemical barriers against invading pathogens. This interaction between the microbiome and the gut barrier is crucial in preventing chronic inflammation and autoimmune disorders. The composition of the microbiota can influence the production and function of immune molecules. Beneficial bacteria produce short-chain fatty acids (SCFAs), which serve as an energy source for colonocytes and have anti-inflammatory effects. SCFAs also promote the differentiation of regulatory T cells, which play a vital role in maintaining immune tolerance and preventing excessive immune activation.

Furthermore, the microbiota helps shape the systemic immune response beyond the gut. It communicates with immune cells through signaling molecules and metabolites, influencing immune cell migration, activation, and overall immune function. This systemic interaction between the microbiome and the immune system impacts not only gastrointestinal health but also the immune response in other tissues and organs. Factors such as poor diet, stress, medication, and aging can disrupt this interaction and lead to dysbiosis, which is associated with immune-mediated disorders.

Late-life

The microbiome undergoes significant changes during old age, which is referred to as dysbiosis. Dysbiosis is characterized by a decline in beneficial

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bacteria and an increase in potentially harmful microorganisms, which can have a profound impact on immune function. Alterations in the microbiota composition during the elder years can lead to immune dysfunction and increased susceptibility to infections, chronic inflammation, and age-related diseases, including inflammation. Aging has been shown to negatively impact the diversity of the microbiota, with conflicting results on age-related changes in the two major phylogenetic groups. One study found high levels of *Escherichia coli* and *Bacteroidetes* in the gut microbiota of the elderly, as well as a significant difference in the *Firmicutes* to *Bacteroidetes* ratio between adults and elderly individuals.[45] Another study reported a significant reduction in the overall numbers of microbes in elderly subjects compared to young adults, with lower numbers of *Firmicutes* and an increase in *Bacteroidetes.*[46]

A study that included young, elderly, and centenarian citizens found that aging is associated with a decrease in microbiome diversity.[47] The composition of the microbiota was similar between the young and elderly groups, with dominant portions of *Firmicutes* and *Bacteroidetes*. However, the centenarian group showed a significant decrease in the Clostridium cluster XIV subgroup and an increase in Bacilli and opportunistic pathogens. This rearrangement of the microbiome was associated with an increased level of circulating inflammatory cytokines, which were inversely associated with bacteria belonging to Clostridium cluster XIV and Clostridium cluster IV, the main butyrate-producers in the gut. The study suggests that this rearrangement of the microbiota is not favorable for aging subjects and may contribute to age-related inflammation.[48]

Human Genetics Trend in Microbiome and Immune System

One of the many environmental variables that hold an effect on the gut microbiome is host genetics. Host genetics are generally referred to as the result of ancient to modern human genomes that have adapted through the process of coevolution with other pathogens.[49]

How The Host Genes and Environment Modify Microbiome's Genetics.

According to the evolutionary trend of host genetics, studies have shown that human genomes can approximately explain in estimated amount of 2%-8% of the causes which led to microbiome variation.[50] However, the variation in the microbiome can both generate beneficial traits and defective traits. For instance, the ability to resist antibiotics and medicines, absorb nutrients, and interface with the host immune system. The processes which complement such traits are relatively involuted, the reason of which is due to the complicated relationship of environmental and evolutionary variables in microbiomes, including the consistent changing trend in the host's genomes.[51] These traits can determine the susceptibility to peculiar microbes, including the route of septicity in certain individuals. In addition, a study conducted in 1980 outlined the increased chance of fatality from infectious diseases in infancy which correlates with their biological parents who are also susceptible to the same group of infectious diseases. This indicates that host genes play a major role in the susceptibility to infections in humans.[49]

Evolutionary Trend in Human Microbiome's Hosts.

The process of the modification of the microbiome's genetics from the variation of the host genes is acquired through the process of evolution. Evolution in general, is referred to genetic modifications which occurred by genetic forces, including multiple sources such as mutation, genetic drift, natural selection, and recombination. According to a study on the origins of the microbiome in hosts, it is discovered that 90% of the microbes come from the environment, whereas the other 10% come from their parents. Thus it can signify that the host acquired 10% of the microbes from the parental contribution, or throughout their entire lifespan, their parent contributed an amount of 10% of the microbial conformation.[52]

Environmental Effects on Microbiome Genetics Variation.

Another major factor that makes the genetic variations in the microbiome occur is the ecosystem which frequently interacts with evolutionary trends. The gut microbiome can be the best example for showing how the ecological system associates with the evolutionary trend in the microbiome's genetics.

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The diverse population of the strains isn't fixated entirely, they rather stay around with transitional frequencies for a certain period of time.[53,54] Moreover, the trend frequencies can fluctuate at the same time with the acquisition of new genetic adaptations. This is due to the numerous potential competitors in the gut ecosystem, which may impart fewer chances for a strain to adapt to the system before being replaced with secondary succession.[55]

Plasticity in microbiome

Throughout the development of the microbiome in hosts, the term "plasticity" means a process that shapes a life trait via environmental exposures, it is a term used to describe changes due to response to the exterior provocation. The plasticity of the microbiome has a fixed pattern, making it possible to note the response as graphs. The microbiome generates static responses until the stimulation exceeds the threshold, which will lead to possible diseases. The plasticity of the microbiome happens at separate time scales scoping from sleep cycles and diet periods to adaptations to environmental results from each individual stage of life at the outset of the fetus in the womb to advanced years. Throughout the course of life, humans experience the most diversity in microbiota at an early age, additionally, it is one of the crucial factors which affect the susceptibility in each individual. This is because, in the early stages of life, the baby will receive microbiomes directly from the mother through many processes from the birthing process to breastfeeding. It is very significant to look into the importance of the window of opportunity, which refers to this specific time scale. In comparison, infants who consume breast milk have a greater diversity in microbiota which will construct a strong immune system as a result. In contrast, infants who consume formula milk are prone to be more susceptible to diseases later in life.

Although acquiring microbiota from the mother shapes up some aspects of the host's immune system in general, the child's gut microbial community will change drastically when they are first introduced to solid food. The gut microbiome will adapt genetically and physically due to a diverse nutritional mixture. Around this time of development, dietary exposures may influence the inception of the microbiota, the disruption can cause childhood asthma.

Taking everything into consideration, the plasticity in microbiota is gained at around the age of 2, when the microbiomes are established and the gut microbiota has been heavily imprinted. It is relatively a fundamental key point to the formation of a healthy gut microbiome in infants. Nevertheless, the lifestyle in adulthood will also determine the susceptibility to diseases later on in life.[56]

Microbiome's response to stimulus taken by hosts

It is clear that the evolutionary trend differs from the ecological system comparatively, even so, the environmental change which correlates with microbiome genetic variations also plays an important role in the drastic variation of microbes within hosts. Many aspects of the environment around each host can affect microbiomes in various ways, and it can be done accidentally or intentionally by the hosts for instance, by taking antibiotics, prebiotics, and having microbial transplants. Each of the prior examples can accumulate a contrasting effect on the ecological system.

To further illustrate, when a host takes antibiotics, it will generate multiple effects on the microbiome. In view of the fact that all antibiotics kill both pathogens and bacteria which are the normal flora, this can consequently cause side effects such as decreased diversity, and exposure to the antibiotics can create dysbiosis in the human microbiome. This can stimulate the susceptibility to certain diseases which are caused by the disruption of the diversity in the community. Another side effect that can be seen from taking antibiotics is a selection of resistant bacteria, some bacteria can be resistant to the antibiotics, which makes them gain the upper hand in the community. As other microbes subside, the resistant strains survive and multiply. Many bacteria are capable of transferring their genetic material through conjugation and transduction or transformation, thus making the surviving strains able to pass on the resistant genes to other bacteria. Additionally, the strains will cause severe infections. Other side effects involved antibiotic-associated diarrhea. For example, *Clostridium difficile* is a pathogen that is found in healthy hosts, but the use of antibiotics can nurture this pathogen, which can result in severe diarrhea and gastrointestinal infections.[57]

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Other factors like taking prebiotics can have a contrasting effect on the microbiome's community because prebiotics is beneficial for microbial growth. In contrast to probiotics, which eliminate bacteria in the community, prebiotics helps bacteria to prosper. Whereas microbial transplants are shown to be useful in therapeutic methods, as most babies who are delivered through c-sections have a lack of colonization with lactobacilli and bifidobacteria from the mother. These bacteria are acquired through the mother's vaginal microbiota during the birth process in normal children. The lack of certain microbes can lead to possible health problems in adulthood, in addition, to solve the problem, microbial transplants are required.[58]

How Microbiome Genetics Adapt and The Modification of Their Genes

Although human host genes have a vital role in microbiome variations, it is also discovered by multiple studies that microbiome genes also have an impact on the mutation themselves. Additionally, the human microbiome's genetics are mostly heterogeneous, expressing that most of these cells are likely to carry various mutations within themselves. These mutations stimulate the microbiome's variations within the host. The range of modifications varies in each specific species. And each species' variations can differ from single-nucleotide variants (SNVs) which usually conclude short deletions and insertions to other more complex structural variants which involve a more complicated mutation such as duplications, and inversions.[51]

Despite the extensive studies conducted on the topic of microbiome's structures and functions, its species' genetic variations are less explored in the biomedical field. Furthermore, the information on how the microbiome's genes mutate is relatively still underdeveloped because most of the records come from studying each species in isolation from one another.[59]

Dysregulation of microbiome-immunity interaction in disease

The microbiome and the immune system have a complex and symbiotic relationship that plays a significant role in human health and disease. The microbiome, particularly in the gut, influences various aspects of our well-being through its metabolic activities and interactions with the immune system. Disruption of the microbiome can lead to dysbiosis and impair the immune-microbiome crosstalk, resulting in systemic effects and the development of diseases such as inflammatory bowel disease, metabolic syndrome, and neurodegenerative disorders. While our understanding of the microbiome and immune system interactions has advanced in recent years, there are still many challenges to overcome. Further research in this field will deepen our understanding of the intricate relationship between the microbiome and the immune system. This continued exploration will pave the way for innovative interventions and improved health outcomes, ultimately enhancing our ability to prevent and treat various diseases.[60]

Cancer

The gut microbiota significantly influences the host's well-being by impacting cancer development, tumor growth, and immunotherapy response. The pathogenesis of microbiomes in cancer is a complex and multifaceted process. One of the key mechanisms by which microbiomes contribute to cancer is through chronic inflammation. Certain microorganisms have the ability to trigger and sustain inflammation within the host, creating an environment that promotes the growth and survival of cancer cells. Chronic inflammation can lead to DNA damage, mutations, and the dysregulation of cellular processes, all of which contribute to tumor initiation and progression. Research studies have revealed intriguing connections between the microbiome and cancer. For example, a well-studied model suggests that dysbiosis, an imbalance in the composition of the gut microbiome, can increase the risk of colorectal cancer. Continuous intra-abdominal infections and the use of antimicrobial drugs contribute to dysbiosis, which disrupts the normal microbial ecosystem in the gut. This dysbiosis can promote inflammation, alter immune responses, and affect the metabolism of dietary components, all of which can influence tumor development and growth.[61,62]

Another important aspect of microbiome-induced cancer pathogenesis is the modulation of the host immune response. Microbes can interact with the immune system, either directly or indirectly, influencing immune cell function and the overall immune surveillance against cancer cells. For

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instance, some bacteria have been found to inhibit the activity of natural killer (NK) cells, which are crucial in detecting and eliminating cancer cells. This immune evasion strategy employed by certain microorganisms can enable tumor cells to evade immune surveillance and establish a favorable microenvironment for their growth. A previous study showed that the presence of specific bacteria, such as Fusobacterium nucleatum, in the tumor microenvironment has been found to directly inhibit the killing of tumors by natural killer (NK) cells. This inhibition occurs through the binding of the bacterium's Fap2 protein to the human TIGIT receptor. Furthermore, higher levels of *F. nucleatum* in colorectal cancer tissue have been associated with a lower density of CD3+ T cells, a population linked to a more positive clinical outcome.[63]

Besides, microbiomes can also affect the efficacy of cancer treatments, including immunotherapy. Recent studies have shown that the composition of the gut microbiome can influence the response to immune checkpoint inhibitors, a type of immunotherapy that helps unleash the immune system's ability to fight cancer. Specific bacterial species within the gut microbiome have been identified to enhance or inhibit the effectiveness of immunotherapy, highlighting the impact of microbiomes on treatment outcomes.[64]

Antimicrobial Resistance

Antimicrobial resistance (AMR) is a growing global health threat that refers to the ability of microorganisms such as bacteria, viruses, and fungi to resist the effects of antimicrobial drugs that were previously effective in treating infections. It is primarily caused by the overuse and misuse of antimicrobial agents in human and veterinary medicine and agriculture. Factors such as improper prescribing and use of antibiotics, inadequate infection prevention, and control measures, and the use of inferior or counterfeit drugs contribute to the development and spread of resistant strains of microorganisms.

The role of the microbiome in the antimicrobial resistance phenomenon is increasingly recognized by the acquisition of resistance genes by bacteria within the microbiome. Bacteria have the ability to acquire resistance genes through horizontal gene transfer. This transfer can occur within the microbiome, allowing the spread of resistance genes among the microbial community. As a result, the presence of resistant bacteria within the microbiome can contribute to the overall pool of antimicrobial resistance genes. Furthermore, the use of antimicrobial agents, such as antibiotics, can disrupt the balance of the microbiome and promote the development of antimicrobial resistance. Antibiotics are designed to kill or inhibit the growth of bacteria, but they can also affect the beneficial bacteria within the microbiome. When these beneficial bacteria are depleted, it creates an opportunity for resistant bacteria to thrive and multiply, leading to the expansion of antimicrobial resistance. Another pathway is through the production of enzymes that can inactivate or modify antimicrobial agents. Some bacteria within the microbiome naturally produce enzymes, such as beta-lactamases, that can degrade antibiotics and render them ineffective. These enzymes can be transferred to other bacteria, including pathogens, further promoting antimicrobial resistance. Additionally, the microbiome can influence the effectiveness of antimicrobial treatments. Certain bacteria within the microbiome can produce substances that inhibit the activity of antimicrobial agents, making them less effective in eradicating infections. This phenomenon is particularly relevant in the gut microbiome, where the presence of certain bacteria can reduce the efficacy of orally administered antibiotics.[65,66]

Autoimmune disease

Autoimmune diseases (AD) occur when the immune system mistakenly targets and attacks the body's own tissues, resulting in chronic inflammation, tissue damage, and dysfunction in various organs and body systems.[67]

The microbiome plays a significant role in the development of autoimmunity by influencing immune tolerance. During early development, the microbiome helps educate and shape the immune system, promoting the establishment of immune tolerance. However, disruptions in the composition and diversity of the microbiome, known as dysbiosis, can impair immune tolerance and contribute to the development of autoimmune diseases. Dysbiosis can also lead to an overactive immune response, triggering chronic inflammation and autoimmune reactions. Additionally, dysbiosis can compromise

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the integrity of the intestinal barrier, resulting in increased permeability, commonly referred to as "leaky gut." This allows microbial products, including bacterial antigens, to translocate into the systemic circulation, eliciting immune responses and further contributing to the development of autoimmune diseases.[68]

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic inflammatory condition that affects the intestinal tract, causing symptoms such as abdominal pain, intestinal bleeding, weight loss, and diarrhea. The two main forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC). The incidence of IBD has significantly increased in developed countries over the past few decades, which is believed to be linked to modernization and the adoption of Western lifestyles. Environmental factors play a pivotal role in IBD development and the global rise in its occurrence. Although the exact cause of IBD remains unknown, it is believed to develop in individuals with a genetic predisposition who are exposed to triggers such as microbes, diet, and the environment.

In IBD, both mucolytic bacteria and pathogenic bacteria contribute to the breakdown of the protective mucosal barrier, allowing pathogens to penetrate the intestinal tissues. Dysbiosis, an imbalance in the gut microbiota composition, is often associated with IBD. The gut microbiota composition has shown significant associations with the development and progression of IBD. Individuals with IBD typically exhibit a decrease in beneficial bacteria, such as *Firmicutes*, and an increase in potentially harmful bacteria, including *Proteobacteria*, *Bacteroidetes*, *Enterobacteriaceae*, and *Bilophila*. These imbalances disrupt the delicate equilibrium of the gut ecosystem. Furthermore, many bacterial species that promote inflammation are found to be coated with immunoglobulin A (IgA) in both IBD patients and mouse models of colitis. Reduced microbial diversity, a common feature in IBD patients, is associated with increased disease severity. The loss of bacterial species diversity affects the functional capacity of the microbiota, compromising its ability to maintain gut barrier integrity and immune homeostasis. In IBD, dysbiosis can trigger abnormal immune responses, leading to chronic inflammation. Innate immune cells, such as dendritic cells and macrophages, respond to signals from the microbiota, while adaptive immune cells, including T cells and B cells, mount inflammatory responses against gut microbes, exacerbating tissue damage. Dysbiosis can also compromise the integrity of the mucosal barrier, allowing bacteria and their byproducts to breach the barrier and trigger an inflammatory response.

Evidence suggests that gut microbes play a direct role in the development of IBD. Transplanting gut microbes from mice with IBD into germ-free mice leads to the development of IBD in the recipient mice. Similarly, mother mice with IBD can transmit an "IBD microbiota" to their offspring, resulting in reduced microbial diversity and a decrease in class-switched memory B cells and Treg cells in the colon of the pups.

Allergies; Asthma

Allergies and asthma are characterized by an excessive immune response to harmless substances, such as pollen, dust mites, or certain foods. They are chronic inflammatory diseases of the airways that involve the action of immunoglobulin E (IgE). These conditions are part of a group of IgE-mediated or "atopic" diseases, including atopic dermatitis (eczema), allergic rhinitis, and food allergies. Typically, these conditions emerge in early childhood and can persist throughout life, causing ongoing challenges. In recent decades, asthma has become the most common childhood disease, affecting one in ten children in developed countries. The causes of asthma are complex, resulting from a combination of genetic and environmental factors, leading to significant variations in the disease. While having a family history of asthma increases the risk, it alone is insufficient to determine an individual's susceptibility. Substantial evidence supports the role of microbial triggers in asthma exacerbations among children.[69] Studies indicate that early-life exposure to a diverse range of microorganisms, particularly during infancy, is associated with a reduced risk of developing allergies and asthma. This suggests that the composition and diversity of the microbiome during early life can influence the maturation of the immune system and the development of tolerance to allergens.[70,71]

The pathogenesis of microbiomes in allergy and asthma involves multiple mechanisms. One crucial mechanism is the modulation of immune system

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responses. The microbiome interacts with the immune system, shaping its development and functioning. Microbes can influence the balance between pro-inflammatory and anti-inflammatory responses, impacting the immune system's ability to appropriately respond to allergens and pathogens. Additionally, individuals with allergies and asthma exhibit alterations in the composition of airway microbes compared to healthy individuals, with a predominance of "commensal-dominated" microbial composition in the upper airways, which reduces the risk of illness or exacerbations. Such an imbalance in the microbiome composition has been linked to immune dysregulation, promoting an exaggerated allergic response. Furthermore, the microbiome can affect the integrity and function of the epithelial barrier, which serves as a physical barrier between the external environment and underlying tissues. Disruption of this barrier can lead to increased exposure to allergens and sensitization, contributing to the development of allergies and asthma. Microbes present in the respiratory and gastrointestinal tracts can influence the integrity of the epithelial barrier, potentially leading to increased permeability and enhanced penetration of allergens.[72]

Rheumatoid arthritis

Our understanding of the pathogenesis of rheumatoid arthritis (RA), a systemic autoimmune disease characterized mainly by joint inflammation, is increasing. Prevotella, a microbial genus, is potentially significant in the development of RA, which affects approximately 1% of the global population, and its pathogenesis may be influenced by genetic and environmental factors. Currently, we have limited knowledge about the specific mechanisms underlying RA pathogenesis. However, it has been suggested that the imbalance of gut microbiota leading to RA may be related to the regulation of immune function by metabolites produced by gut microbes.[73] The mucosal immune T and B cells exhibit site-specific phenotypes and functions that are influenced by the microbiota. In the synovial tissue of RA patients, bacterial peptidoglycan components have been identified, which may contribute to inflammation within the joint's microenvironment. Extensive data published in recent years indicate that an altered composition of the gut microbiota in RA patients is a significant factor triggering abnormal systemic immunity.[74] Importantly, different strains of gut bacteria can have distinct regulatory effects on immune system function. Some strains can stimulate an immune response, benefiting immunocompromised patients, while others can suppress the immune response, impacting immune regulation in RA patients.[75] In the early stage of rheumatoid arthritis (RA), there is an increase in levels of Prevotella copri and Lactobacillus, while Bacteroidetes, Bifidobacteria, and Eubacterium rectale levels are decreased. During the active phase of RA, there is an increased abundance of Lactobacillus salivarius, Collinsella, and Akkermansia, while Haemophilus spp. levels are decreased. The gut microbiota can cause damage to the epithelium and disrupt the paracellular pathway, allowing contact with immune cells beneath the epithelial layer and resulting in inflammation. Bacterial antigens further stimulate the activation of autoreactive B and T cells in lymphoid tissues, leading to an imbalance between regulatory T cells (Tregs) and T helper 17 (Th17) cells, ultimately promoting an expansion of the inflammatory response. Activated B cells produce autoantibodies such as anti-citrullinated protein antibodies and rheumatoid factor. Imbalances in the gut microbiota can trigger the migration of autoreactive cells to the joints, causing damage to cartilage and bone.

The process unfolds as follows: Bacterial antigens trigger inflammation in the synovial membrane, attracting leukocytes into the tissue. Autoreactive cells then activate macrophages, leading to the production of inflammatory cytokines. Finally, these cytokines induce fibroblasts to produce MMPs (matrix metalloproteinases) and RANKL (receptor activator of nuclear factor κB ligand), which contribute to the destruction of bone and cartilage tissue, ultimately driving the development of RA. Therefore, the dysbiosis of gut microbiota, inflammatory factors, and immune responses are interconnected and collectively influence the progression of RA.[76]

Type II diabetes and metabolic syndrome

Diabetes—Type 1 diabetes (T1D) is an autoimmune disorder in which pancreatic beta cells are attacked by effector T cells. This renders the pancreas incapable of producing insulin for use in metabolic regulation. Patients with T1D inject insulin in order to combat rising blood glucose levels, which result in

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high blood sugar levels or hyperglycemia if unchecked. There is currently no cure for T1D, and insulin injection is the only effective treatment. Because of the variability in microbiota composition, it is difficult to find a specific link between exact microbiota changes and any disease; however, the gut microbiome of infants has been observed in order to establish a connection between it and the onset of T1D. A study conducted in Finland and Estonia suggests that infants predisposed to T1D-susceptible human leukocyte antigen (HLA) alleles and later diagnosed with early-onset diabetes show lower gut microbiota diversity along with higher levels of human beta-defensin 2.[77] This finding demonstrates that infants predisposed to T1D may have pro-inflammatory and less diverse microbiota when compared to other infants. Since the microbiota goes through a dynamic change through birth and infancy, this period could be a highly relevant area of research on connections between the microbiota and T1D. There could also be specific compositional differences in the microbiota of people diagnosed with T1D. Diabetic children have shown an increase in Bacteroidetes and a subsequent decrease in Lambring et al. Page 9 Crit Rev Immunol. Author manuscript; available in PMC 2020 July 15. Author Manuscript Author Manuscript Author Manuscript Author Manuscript Actinobacteria and Firmicutes when compared against healthy children.[78] The link between bacterial composition and T1D should continue to be investigated in order to find better diagnoses and treatment options.

Obesity

Obesity, a global concern, is a complex disorder influenced by multiple factors. Increasing evidence highlights the role of the microbiome in nutrient acquisition, fat storage, and energy regulation, all of which contribute to obesity development.[79] Microbiota dysbiosis is one key mechanism through which the microbiome influences obesity. In obesity, there is a reduced microbial diversity and an overabundance of specific bacterial taxa like Firmicutes, while the abundance of Bacteroidetes is decreased. This dysbiosis disrupts gut homeostasis, contributing to metabolic dysfunction. Certain microbial species possess enzymes that break down complex carbohydrates and fibers, which human enzymes cannot digest. This microbial fermentation process generates short-chain fatty acids (SCFAs) that are absorbed and can impact host energy metabolism. Dysbiosis in obesity enhances energy harvest from the diet, promoting adiposity and weight gain. Moreover, obesity-associated dysbiosis often leads to impaired gut barrier function, commonly known as "leaky gut." This condition allows the translocation of microbial components, such as lipopolysaccharides (LPS), from the gut into the systemic circulation. Elevated circulating LPS levels trigger chronic low-grade inflammation, known as metabolic endotoxemia, which is implicated in insulin resistance and obesity-related comorbidities. Microbial metabolites and signaling molecules also influence appetite regulation, energy expenditure, and fat storage in the host. Specific bacteria produce signaling molecules that affect host satiety and hunger hormones, ultimately influencing food intake and energy balance. Additionally, dysbiosis in obesity is associated with alterations in immune cell populations and increased production of pro-inflammatory cytokines. These immune system changes further contribute to metabolic dysfunction and the chronic low-grade inflammation observed in obesity.[80]

Mental health

At the intersection between neuroscience, microbiology, and psychiatry, the enteric microbiome has the potential to become a novel paradigm for studying the psychobiological underpinnings of mental illness. Several studies provide support for the view that the enteric microbiome influences behavior through the microbiota–gut–brain axis. Moreover, recent findings are suggestive of the possibility that dysregulation of the enteric microbiota (i.e., dysbiosis) and associated bacterial translocation across the intestinal epithelium may be involved in the pathophysiology of stress-related psychiatric disorders, particularly depression. In the early 1990s, it became evident that excessive production of immunomodulatory signaling molecules, particularly proinflammatory cytokines, might contribute to the onset and persistence of depressive illness.[81] Initially, researchers reported elevated levels of interleukin-6 (IL-6), interferon-gamma (IFN-γ), and acute-phase proteins in the blood, and it is now widely accepted that these and other cytokines, including tumor necrosis factor (TNF) in particular, are elevated in individuals with depression.[82] This inflammatory profile is also considered a significant factor in

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treatment resistance among depressed patients. Consequently, scientists have been exploring the effects of anti-inflammatory compounds as potential antidepressant treatments. Studies have demonstrated that specifically blocking TNF improves depressive symptoms in patients with high levels of inflammatory biomarkers at baseline.[83] Additionally, treating the hepatitis C virus with proinflammatory agents like interferon-alpha (IFN-α) has resulted in depressive symptoms in one out of four patients.[84] Considering the anti-inflammatory properties of various antidepressant medications[85], neuroimmune mechanisms are now recognized as central to the development of depressive symptoms. Moreover, the current article reviews preliminary evidence linking the enteric microbiota and its metabolites to psychiatric illness, along with separate lines of empirical inquiry on the potential involvement of psychosocial stressors, proinflammatory cytokines, and neuroinflammation, the hypothalamic–pituitary–adrenal axis, and vagal nerve activation, respectively, in this relationship.

Osteogenesis and Osteoporosis

Osteogenesis is the process of new bone formation, which plays a crucial role in bone growth, remodeling, and fracture repair. Additionally, gut microbes produce metabolites such as butyrate and lactate, which have been shown to promote bone formation and influence the activity of osteoblasts, the cells responsible for bone formation. Therefore, the supplementation of probiotics can enhance mineral absorption and regulate inflammation, while prebiotics can promote the growth of beneficial bacteria that contribute to overall bone health.[86,87]

Osteoporosis is a chronic condition characterized by reduced bone density and an increased risk of fractures. Traditionally, factors like age, hormonal changes, and nutritional deficiencies have been associated with its development. However, emerging evidence suggests that the microbiota, the community of microorganisms in our gut, may also contribute to the development of osteoporosis. The gut microbiota has a complex interaction with the host, and it can influence bone health. Specific bacteria in the gut produce metabolites called short-chain fatty acids (SCFAs) that have an impact on bone metabolism. These SCFAs can regulate the activity of osteoblasts and osteoclasts, the cells responsible for bone formation and resorption, respectively, thus affecting bone turnover. However, an imbalance in the gut microbiota, known as dysbiosis, can lead to low-grade inflammation, which in turn increases osteoclast activity and results in bone loss. Immune cells, including T cells and cytokines, play a crucial role in this process.[88]

Microbiota diagnostic and therapeutic applications

Recent research has revealed the intricate interplay between the microbiome and the immune system, highlighting their mutual influence on overall well-being. In response, therapeutic approaches targeting the modification of microbiomes in hopes of influencing the immune system have emerged as promising strategies to promote health.

Microbiota and Diagnostic Biomarkers:

The human microbiota has emerged as a promising source of diagnostic biomarkers for various health conditions. Oral health, for example, has been linked to numerous systemic conditions, including cardiovascular disease, diabetes, and even Alzheimer's disease.[89] These microbiota-based diagnostic tests or “microbiome diagnostics” aim to detect the presence of specific microbial biomarkers or patterns that can aid in the early diagnosis, prognosis, and personalized treatment of various diseases.[90] Microbiome-derived biomarkers work by analyzing the genetic material (DNA or RNA) of the microbial community present in a sample, typically through metagenomic or metatranscriptomic sequencing.[91] For instance, gut microbiomes have been found to be associated with the development of colorectal cancer (CRC); in regards, microbiome-derived biomarkers can serve as an early diagnosis.[92] These microbiome-based diagnoses can be achieved in various ways, such as traditional culture-based, quantitative polymerase chain reaction (qPCR), 16R ribosomal RNA (16S) sequencing, and shotgun metagenomic sequencing (MGS).

The process of traditional culture-based microbiology involves isolating the culturing microorganisms in the laboratory; identifying them through morphological, physiological, and biochemical properties. Despite the long-established use of traditional culture-based, they are often not suitable for comprehensive characterization of the

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microbiome. One major drawback includes the difficulties relating to culturing certain types of microorganisms: such as anaerobes and low-abundance microbes.[93] Consequently, culture-based microbiome diagnostics are primarily limited to targeted identification of specific taxa or antibiotic resistance patterns.[94]

qPCR offers a powerful and sensitive method for quantifying specific DNA sequences, allowing for the measurement of microbial abundance and the detection of specific microbial taxa or functional genes within a complex microbial community. The technique involves the use of specific primers that target the DNA sequences of interest, facilitating the amplification and detection of the targeted DNA sequences.[95] qPCR in microbiome research offers superiority in its sensitivity, simultaneous detection and quantification of multiple microbial targets, and speed, notwithstanding pPCR requires prior knowledge of the target sequences to construct its specific primers.[96]

16S sequencing is a widely used method for studying microbial communities. The 16S rRNA is a highly conserved region of the bacterial and archaeal genomes that encodes a component of the ribosome.[97] In 16S sequencing, the 16S rRNA gene is amplified from a sample and then sequenced to be identified with reference to databases. They provide a comprehensive snapshot of microbial diversity within a sample. In studies of IBD, researchers have identified specific microbial taxa, such as *Faecalibacterium prausnitzii*, which could serve as potential biomarkers for predictive purposes.[98]

Unlike 16S sequencing, MGS enables the analysis of all DNA present in a sample, including the host DNA.[99] The DNA from a microbial community is extracted and sequenced, then aligned to reference genomes or assembled to reconstruct the microorganisms' genetic information.[100] This approach allows for a complex analysis of microbial functional potential, gene expression, and the identification of novel microorganisms.

Microbiota-Based Therapies:

Conventional therapies have a great risk of antibiotic resistance, and resistance to chemotherapy, and often fail to possess disease specification. Microbes are natural to the human body, thus manifestation of biotherapeutics can be accomplished while avoiding consequential side effects. Thus far, microbiome therapeutics can be categorized in three distinct ways: subtractive therapy, modulatory therapy, and additive therapy.[101]

Subtractive therapies

Antibiotic therapy: is a widely used treatment approach for bacterial infections, however with the increased antibiotic resistance, Bacteriocins have emerged as a safer alternative in the realm of antimicrobial therapies. Bacteriocins are ribosomally synthesized peptides produced by certain bacteria: such as *Bacillus thuringiensis* bacterial group.[102] Bacteriocins have attracted attention for their potential therapeutic applications, as they can selectively target specific bacteria without harming the beneficial ones. They work by inhibiting the growth of similar bacteria; binding to specific receptors of the surface, disrupting their cellular structure, or interfering with DNA replication.[103] This specifically makes them an appealing alternative to broad-spectrum antibiotics, which can disrupt the delicate balance of the microbiome. Researchers are exploring the potential of bacteriocins as a targeted antimicrobial therapy, as well as their use in combination with probiotics to promote a healthy microbiome.

Bacteriophages: are viruses that infect and replicate within bacteria. They have gained significant attention in recent years due to their potential applications in microbiome research and therapy. These phages can influence the composition and diversity of the gut microbiome by selectively infecting and controlling the growth of specific bacterial species. This approach offers a more precise and tailored alternative, as they preserve the beneficial bacteria in the microbiome.[104] However, it is essential to recognize the challenges that arise with the use of phages, as potential resistance development must be appropriately addressed with their respective efficacy assessment.[105] Nonetheless, the exploration of phages and their interaction with the microbiome holds promise for developing targeted therapies that can selectively modulate the microbiome for improved health outcomes.

Modulatory therapies

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The gut microbiota can be restored or modulated through different means, including changes in diet, exercise, and the use of antibiotics, all of which can influence the composition of the gut microbiome. Since the microbiome is influenced by the food we consume, dietary interventions are particularly important for altering the gut microbiome. Making modifications to our diet has a significant impact on the composition and function of the gut microbiome.

Specific dietary components, such as prebiotic fibers and fermented foods, can selectively promote the growth of beneficial bacteria: such as *Bifidobacteria and Lactobacilli*, leading to a more balanced and diverse microbiome.[106] Prebiotics serve as a fuel source for beneficial microbes, stimulating their growth and activity. In contrast, alcohol consumption, smoking, and drugs also influence the diversity of the microbiome

Prebiotics, such as inulin, oligofructose, and certain types of dietary fibers, are not digested in the upper gastrointestinal tract but reach the colon intact. Once in the colon, they serve as a fuel source for specific groups of beneficial bacteria. These bacteria ferment prebiotics, producing SCFAs as byproducts: for example acetate, propionate, and butyrate.[107] Fermented foods, such as yogurt, kefir, sauerkraut, and kimchi, contain live microorganisms that can colonize the gut and interact with the existing microbial community.[108] These beneficial microbes can help break down complex nutrients, produce additional SCFAs, and compete with potentially harmful bacteria for resources and space.[109]

Alcohol consumption is known to have detrimental effects on the gut microbiome. Excessive alcohol intake can alter microbial diversity and abundance, favoring the growth of harmful bacteria while reducing beneficial species. They are found to increase the abundance of Bacteroidetes and Proteobacteria[110], whilst reducing Lactobacili content.[111] This imbalance can contribute to increased intestinal permeability inflammation, and a higher risk of conditions such as alcoholic liver disease (ALD), gastrointestinal disorders, and systemic inflammation.[112]

Studies have shown that smokers tend to have a distinct microbial profile compared to non-smokers.[113] Smoking can decrease the abundance of *Bifidobacteria and Lactobacilli* in the mouth microbiome, while promoting the growth of potentially harmful species, such as *Porphyromonas*, which is linked to periodontal disease. These changes in the gut microbiome may contribute to an increased risk of respiratory infections, inflammatory bowel disease, and cardiovascular diseases, apart from the increased potential for lung cancer among smokers.[114]

Drug use, particularly the long-term and excessive use of certain drugs, can impact the gut microbiome as well. For example, antibiotics, while essential for treating infections, can have broad-spectrum effects, disrupting both harmful and beneficial bacteria. Prolonged or inappropriate antibiotic use can lead to dysbiosis and potential complications[39], such as antibiotic-associated diarrhea and increased susceptibility to opportunistic infections.[115] Other drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs), have also been associated with changes in the gut microbiota composition.[116,117]

Physical exercise is linked to a more favorable microbiome profile. A diverse microbiome is associated with improved metabolic, immune function, and overall well-being. Exercise-induced changes in the gut microbiome have been linked to the production of beneficial metabolites, such as SCFAs, which have anti-inflammatory properties and support gut barrier function.[118] Studies have also observed that exercise can promote the abundance of certain beneficial bacteria, such as Akkermansia muciniphila, which is associated with improved metabolic health and reduced inflammation.[119] Exercise has also been shown to reduce the levels of potentially harmful bacteria, such as those belonging to the Firmicutes phylum, which is associated with obesity and metabolic disorders.[120]

Psychobiotics: refer to live bacteria or other microorganisms that, when ingested, influence the gut-brain axis and consequently modulates mental health.[121] Certain strains of bacteria, such *Lactobacillus* and *Bifidobacterium*, have been identified as potential psychobiotics due to their ability to produce neurotransmitters (such as interleukin-10), regulate stress response, and modulate immune and inflammatory pathways. By influencing these pathways, psychobiotics may have the potential to alleviate symptoms of anxiety,

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depression, and other mental health conditions.[122] Psychobiotics, particularly FMT, have demonstrated positive outcomes in addressing diverse mental disorders including Parkinson's disease[123], Tourette syndrome[124], and autism.[125] While more studies are required, the emerging evidence suggests that certain strains of bacteria may have the potential to modulate the gut-brain axis and provide benefits for mental health and well-being. As research in this field progresses, psychobiotics may offer novel therapeutic options to support mental health and contribute to a comprehensive approach to mental health care.

Additive therapies

Faecal microbiota transplant (FMT): also known as a stool transplant, is a medical procedure in which fecal matter containing a healthy balance of gut bacteria is transferred from a donor to a recipient. The goal of FMT is to restore the appropriate natural balance of microorganisms in the recipient's gut. It is utilized to treat various gastrointestinal disorders, particularly those caused by an imbalance or disruption of the gut microbiome; such as *Clostridium difficile infection.*[126] During the procedure, the donor stool is carefully screened and processed to remove any potential pathogens prior to being introduced into the recipient's digestive system. Delivery methods include colonoscopy, enema, or oral capsules.[127] Ongoing research is exploring the potential of FMT in managing other disorders, for example, inflammatory bowel disease and irritable bowel syndrome; emphasizing the crucial role of gut microbiota in overall health.

Prebiotics: Apart from the modulatory means, probiotics are also used to supplement the existing microbial composition in the gut. They are administered as live microorganisms, such as bacteria or yeast; through certain foods like yogurt, kefir, and fermented vegetables. Alternatively, probiotic therapy can be employed through genetically engineered microbes as a standalone treatment. When ingested, these microorganisms can colonize the gut and interact with the resident microbiota, directly increasing the abundance and diversity of beneficial bacteria in the gut, thereby positively influencing the microbial composition and activity. Probiotics have been found to effectively alleviate digestive disorders, such as diarrhea[128] and irritable bowel syndrome.[129] Furthermore, probiotics have shown potential in managing conditions outside of the digestive system, including allergies, eczema,[130], and to a certain extent, mental health disorders.[131] It is important to note that the effectiveness of probiotic therapy can vary depending on the specific strains used, individual factors, and underlying health conditions.

Although therapeutic approaches targeting microbiome and immune system interactions offer exciting prospects for improving human health and managing various diseases, the field of microbiome therapeutics also faces several challenges that need to be addressed prior to its complete translation into clinical practice. One of the primary challenges is the complexity and diversity of the microbiome itself. Understanding the precise mechanisms and their specific roles by which the microbiome influences the immune system and overall health is still a subject of ongoing research. Elucidating these mechanisms is crucial in the development of targeted microbial therapeutic strategies. Through continued research and clinical applications, the complete potential of the microbiota in transforming healthcare, enhancing patient outcomes, and shaping the future of medicine can be fully realized.

The industry for microbiome therapy is rapidly expanding and holds significant potential for addressing various health conditions. With the increased recognition of microbiome influences on overall health, there has been a surge in research and development efforts to leverage microbiome-based therapy. The market is expected to grow from USD $350 million (2022) to USD $4,620 by 2035.[132] Currently, the market for microbiome therapeutics is primarily driven by the development of probiotics and prebiotics products, including fecal microbiota transplantation (FMT) in clinical settings.[133] Beyond probiotics, prebiotics, and FMT, there is a growing interest in the development of novel microbiome-based therapeutics, such as genetically modified bacteria, microbial consortia, and microbial metabolites. These innovative approaches aim to harness the therapeutic potential of specific microbial strains to target various diseases, such as inflammatory bowel disease, metabolic disorders, and even certain cancers. Conclusively, the microbiome therapeutics market holds tremendous potential to revolutionize healthcare and improve patient outcomes in the coming years.

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Conclusion

In conclusion, the overview of the microbiome in the human body is extremely complex and diverse. This system has many types of microbes (healthy microbes, commensal microbes, bad microbes). The microbiome generates many distinct aspects of the overall health of each individual, though some aspects can be noticed without any effort, some are more complicated than it may seem. Many causes of each aspect are acquired through microbiome genetic variations. These aspects create various traits in humans such as the susceptibility to certain infectious diseases, and the ability to resist antibiotics which can be the result of numerous factors from both host genes and the cellular structure of each species in its community. These factors range from initiating different kinds of mutations to the correlation of the evolutionary trend and the ecological interaction within the host, and the microbial system throughout the course of life, and the trend of genetic variation in microbiomes. Still, it is principally dependent on each host's environment and genes altogether. Whether the effect of the mutation is advantageous or not, the host's genes examination should be performed by professionals. Nevertheless, the trend could be considered to preferably develop an advantageous outcome and good result, owing to the fact that the majority of the population tends to adapt and inherit the beneficial traits in preference. The population in the microbial system is relatively diverse and complicated, therefore the assumption of what causes these traits to arise is still oblivious, as the sources of the evolutionary trend in microbiota are explored individually in different isolation, however, the response of the immune system proposes to protect the human body. Microbiome diagnosis is the tool for human disease using microbial signatures of different types. A dysbiosis microbiome can compromise the gut barrier and make tissues and organs to be flooded with molecules from the diet. This can lead to the development of the technology of medicine to support the human microbiome system.

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