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The gut microbiome: The complex ecosystem within us

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Abstract

The gut microbiome is a dynamic and intricate community of microorganisms residing within the human gastrointestinal tract. This review article explores the multifaceted world of the gut microbiome, covering its composition, functions, and profound impact on human health. This paper delved into factors shaping the microbiome, ranging from genetics to diet and environmental influences. Furthermore, this review examines its contributions to metabolic, immune, and neurological processes and its association with various health conditions. The article concludes by discussing emerging therapeutic strategies and future research directions in this exciting field.

Keywords: Gut microbiome; Probiotics; Gastrointestinal tract; Health

1. Introduction

The human gastrointestinal tract represents a distinctive ecosystem housing a wide-ranging and varied community of microorganisms. The gut microbiome refers to the complex community of microorganisms, including bacteria, viruses, fungi, and archaea, residing within the gastrointestinal tract of humans and other animals. It represents a dynamic ecosystem that plays a crucial role in various aspects of host health and physiology. The gut microbiome holds profound significance for human health and well-being. It contributes to essential functions, such as nutrient metabolism, immune system modulation and protection against pathogens. Moreover, it has been linked to numerous health conditions, including digestive disorders, metabolic diseases, mental health, and immune-related conditions. Qin et al. (2010) used metagenomic sequencing to characterize the genetic diversity of the human gut microbiome. Their work underscores the complexity of the gut microbiome and its importance in human health and physiology [1]. Understanding the gut microbiome's role is pivotal for advancing healthcare and disease prevention strategies.

1.1. Historical Context and Growing Research Interest

1.1.1. Historical Context

Van Leeuwenhoek (1683) was among the first to observe microorganisms in the human gut using primitive microscopes. However, the importance of these microbes was not fully appreciated at the time. The development of the germ theory of disease by Pasteur and Koch in the 19th century emphasized the role of microorganisms in causing illness (Pasteur, 1861; Koch, 1882). This laid the foundation for understanding the potential impact of gut microbiota on health. The discovery and widespread use of antibiotics in the mid-20th century revolutionized the treatment of infectious diseases but raised concerns about their long-term effects on gut microbiota (Fleming, 1929). The advent of advanced DNA sequencing technologies, such as next-generation sequencing, in the late 20th and early 21st centuries, enabled comprehensive and accurate characterization of gut microbiota (Loman & Pallen, 2015).

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1.1.2. Growing Research Interest:

Several factors have fueled the growing research interest in the gut microbiome:

- **Technological Advancements:** The advent of high-throughput DNA sequencing technologies, such as next-generation sequencing (NGS), has enabled the comprehensive analysis of microbial communities in the gut. This technological leap has allowed researchers to uncover the vast diversity of microorganisms inhabiting the gut. Ley et al. (2006) highlights the role of NGS in advancing microbiome research and understanding the gut microbiome's significance [2].
- **Link to Human Health:** The gut microbiome has been associated with a wide range of human health conditions. These include its involvement in digestive disorders (e.g., irritable bowel syndrome), metabolic diseases (e.g., obesity, diabetes), mental health disorders (e.g., depression, anxiety), and immune-related conditions (e.g., inflammatory bowel disease). Clemente et al. (2012) reviewed the role of the gut microbiome in various diseases and emphasize its significance in human health [3].
- **Therapeutic Potential:** The gut microbiome has become a target for therapeutic interventions. Strategies like probiotics, prebiotics, fecal microbiota transplantation (FMT), and microbial-based drugs offer promising avenues for treating and preventing a range of diseases. Paramsothy et al. (2019) have discussed the therapeutic potential of FMT in treating ulcerative colitis, highlighting the translational aspects of microbiome research [4].
- **Multidisciplinary Approach:** Research on the gut microbiome has attracted scientists from diverse disciplines, including microbiology, immunology, genetics, nutrition, and medicine. This multidisciplinary collaboration has enriched the field and expanded research horizons. Huttenhower et al. (2012) underscores the collaborative nature of microbiome research and its implications for various scientific disciplines [5].

2. Composition and Diversity of the Gut Microbiome

The gut microbiome, a complex ecosystem of trillions of microorganisms, primarily bacteria, also includes viruses, fungi, and archaea in the human gastrointestinal tract. Its composition and diversity are crucial for understanding its role in health and disease. Mainly composed of various bacteria, with specific dominant phyla like Firmicutes and Bacteroidetes, the gut microbiome is incredibly individualized, varying across individuals. Beyond bacteria, it comprises a virome and mycobiome, predominantly bacteriophages and fungi like *Candida* and *Saccharomyces*. Research by Claesson et al. (2011); Hannigan et al. (2018) & Minot et al. (2011) delves into these components, showcasing their interactions and diversity [6,7,8]. The hallmark of a healthy microbiome is its diversity, with higher diversity linked to better health outcomes, as evidenced by studies by Lozupone et al. (2012) demonstrating its association with conditions like obesity and inflammatory bowel disease [9].

2.1. Factors Influencing Composition and Diversity

Several factors shape the composition and diversity of the gut microbiome, including genetics, diet, age, and environmental exposures. Genetics can determine an individual's predisposition to certain bacterial strains, while diet plays a crucial role in shaping the microbiome's composition. Yatsunenko et al. (2012) identified significant associations between dietary patterns and gut microbiota composition [10]. Goodrich, J. K., et al. (2014) stress the significance of understanding the composition and diversity of the gut microbiome which provides a foundation for investigating its functional roles and its involvement in various health conditions [11]. As research in this field continues to evolve, it offers promising avenues for personalized healthcare and therapeutic interventions.

2.2. Microbial diversity and variability across individuals

The gut microbiome, which consists of trillions of microorganisms, including bacteria, viruses, fungi, and archaea, plays a critical role in human health. One striking aspect of the gut microbiome is its remarkable diversity and the significant variability observed across individuals.

2.2.1. Gut Microbial Diversity

- **Taxonomic Diversity:** The gut microbiome is taxonomically diverse, with thousands of species. Bacteroidetes and Firmicutes are the dominant phyla, but many others, including Actinobacteria, Proteobacteria, and Verrucomicrobia, contribute to the overall diversity [12].
- **Functional Diversity:** Beyond taxonomic diversity, the gut microbiome is functionally diverse, with different species contributing to a wide range of metabolic and biochemical processes. For example, various bacteria are involved in fiber degradation, short-chain fatty acid production, and vitamin synthesis [13].

- **Temporal Dynamics:** The gut microbiome is not static; it changes over time in response to diet, lifestyle, and other factors. These temporal dynamics contribute to its overall diversity [14].

2.2.2. Variability across Individuals

- **Interpersonal Variation:** Studies have shown that the gut microbiome varies significantly from one person to another. Each individual's microbiome is unique, with a distinct composition of microbial species [15].

2.2.3. Factors Influencing Variability

- **Diet:** Dietary habits strongly influence gut microbial composition. For example, a high-fiber diet is associated with a more diverse microbiome, while diets rich in processed foods are associated with reduced diversity [16].
- **Genetics:** Genetics also play a role in shaping an individual's gut microbiome, although it is a complex interplay between genes and environmental factors [17].
- **Environment:** Factors like geography, lifestyle, and exposure to environmental microorganisms can impact gut microbial diversity [18].
- **Medications:** The use of antibiotics, as well as other medications, can disrupt the gut microbiome and lead to changes in its diversity [19].

2.2.4. The Role of Resident vs. Transient Microbes in the Gut Microbiome

The gut microbiome is a dynamic ecosystem inhabited by a diverse array of microorganisms. Within this complex community, microbes can be broadly categorized into two main groups: resident and transient microbes. Understanding the roles of these two groups is crucial for comprehending the stability, functionality, and resilience of the gut microbiome.

- **Resident microbes:** Resident microbes are those microorganisms that establish long-term or even permanent colonization in the gut. They are typically adapted to the gut environment and play essential roles in maintaining gut homeostasis. Resident microbes are relatively stable over time and are often inherited from the mother during childbirth or established early in life. Arrieta et al. (2014) investigated the development of the infant gut microbiome and its long-lasting effects [20]. They form a core microbiota that is consistent within individuals. They are involved in critical metabolic processes, such as fermentation of dietary fibers, production of short-chain fatty acids (SCFAs), and metabolism of complex carbohydrates. Resident microbes interact with the gut-associated lymphoid tissue (GALT) and play a pivotal role in immune system development and regulation, helping to maintain a balanced immune response. They competitively inhibit the growth of pathogenic microbes, helping to protect against gastrointestinal infections. Kamada et al. (2013) explored how resident bacteria influence host immune responses and protect against pathogens [21].
- **Transient Microbes:** Transient microbes, as the name suggests, are temporary inhabitants of the gut. David et al. (2014) studied the rapid response of transient microbes to dietary changes and their impact on host metabolism [22]. They may be introduced through diet, environmental exposure, or other factors but do not become long-term residents. Transient microbes can exhibit significant variability in composition and abundance, depending on diet, travel, and environmental exposures. They can respond rapidly to changes in diet, reflecting dietary choices and adaptations. Although transient, these microbes can still contribute to various metabolic processes and may participate in the breakdown of specific dietary components. Transient microbes can introduce additional diversity to the gut microbiome, which can have both positive and negative effects on gut health. Wu et al. (2011) explored the variability of transient microbes in individuals and populations [23].

3. Factors Shaping the Gut Microbiome

The composition and functioning of the gut microbiome are influenced by a multitude of factors, including genetics and host-related variables, diet and nutrition, early life influences and environmental factors. Understanding how these factors interact with the gut microbiome is crucial for unraveling the complexity of this ecosystem and its implications for human health.

3.1. Genetics Factors in Shaping the Gut Microbiome

According to Goodrich, J. K., et al. (2016) genetic factors play a significant role in shaping an individual's gut microbiome. These genetic factors can influence the composition of the microbiome, including the types of bacteria present and their relative abundances. Studies in twins have demonstrated that genetically related individuals tend to have more similar gut microbiomes than unrelated individuals [24]. As per the study of Jostins, L., et al. (2012) genetic variations in genes related to the immune system can impact how the immune system interacts with the gut microbiome. For example, mutations in genes associated with immune function can influence the gut's inflammatory response and susceptibility to inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis [25].

3.2. Host Factors Influencing the Gut Microbiome

The gut microbiome, shaped by genetic, physiological, dietary, and environmental factors, plays a pivotal role in human health. Yatsunenko et al. (2012) examined 531 individuals across various regions and age groups, noting that age-related changes in the gut microbiome are influenced by physiological development and dietary habits. For instance, infants' gut microbiomes significantly differ from those of adults. Moreover, the microbiome's diversity and stability tend to increase with age, showcasing the dynamic relationship between the microbiome and the host's development. Understanding these associations is crucial for advancing our comprehension of human health and disease [25].

De Filippo, C., et al. (2010) emphasizes the profound influence of diet on the gut microbiome. They advocate for preserving the diverse microbiota seen in ancient rural communities like those in Burkina Faso to understand the health benefits linked to specific dietary practices. Nutrients in the diet mold the gut's microbial composition and activities. Fiber-rich diets encourage the growth of beneficial bacteria that produce short-chain fatty acids, essential for health [26].

Dethlefsen et al. (2008) shed light on the complex relationship between antibiotics and the human gut microbiota, illustrating the potential impact and the microbiota's resilience post-disturbance. They highlight the need for more research into how the gut's microbial community rebounds. Antibiotics, while effective in treating infections, can upset the gut's balance by selectively targeting bacteria, causing short and potentially long-term changes in its composition [27].

In 2012, Costello et al. explored three significant scenarios of human microbiome assembly, each reflecting distinct ecological contexts. The study analyzed the initial colonization during infancy, the reassembly post-antibiotic disruption, and the response to invasive pathogens introducing new microbial species [28]. Applying ecological theory to these scenarios offered profound insights into the dynamics of the human microbiome. Understanding how these communities assemble enables researchers and healthcare professionals to devise more informed strategies for sustaining this vital ecosystem. This knowledge presents the potential to maintain the microbiota's health-associated services, ultimately contributing to improved human health outcomes.

3.3. Diet and Nutrition Impact on the Gut Microbiome

Diet and nutrition are among the most influential external factors that shape the composition and functionality of the gut microbiome. The complex interplay between dietary components and the gut microbiome has profound implications for human health and disease. Diets rich in dietary fiber, such as fruits, vegetables, and whole grains, promote the growth of fiber degrading bacteria like *Bifidobacteria* and *Prevotella*. These bacteria ferment dietary fiber to produce beneficial short-chain fatty acids (SCFAs), including butyrate, which contribute to gut health and reduce inflammation [29]. According to Wu, G. D., et al. (2011) high-protein and high-fat diets can influence the gut microbiome by favoring the growth of certain microbial species, such as *Bacteroides*, which specialize in metabolizing proteins and fats. This shift in microbial composition can have both positive and negative effects on health [30].

3.3.1. Dietary Components

Specific dietary components, such as polyphenols found in fruits and vegetables and polyunsaturated fatty acids (PUFAs) in fish and nuts, can exert beneficial effects on the gut microbiome. Polyphenols act as prebiotics, supporting the growth of beneficial bacteria, while PUFAs can modulate the gut microbial composition in a favorable way [31,32].

3.3.2. Nutritional Impact on Gut Microbiome Functionality

- **Production of Metabolites:** The gut microbiome plays a pivotal role in the production of essential metabolites, including vitamins (e.g., B vitamins and vitamin K), neurotransmitters (e.g., serotonin), and various metabolic byproducts. Adequate nutrition is required to support the microbial synthesis of these vital compounds.
- **Energy Harvesting:** The gut microbiome helps extract energy from dietary components that would otherwise be indigestible by the host. This process has implications for energy balance and weight management [33].
- **Immune Regulation:** Diet and nutrition can influence the gut microbiome's impact on the host's immune system. A well-balanced microbiome is essential for maintaining a balanced immune response and preventing chronic inflammation [34].

3.4. Early Life Influences on the Gut Microbiome: Birth Mode and Breastfeeding

The gut microbiome is established early in life and undergoes dynamic changes during infancy. Two crucial early life influences on the gut microbiome are the mode of birth and breastfeeding. These factors play significant roles in shaping the microbial composition and functionality of the infant gut, with profound implications for lifelong health.

3.4.1. Birth Mode

- **Vaginal Birth (Microbial Seeding):** Infants born vaginally acquire their initial microbial communities primarily from the mother's birth canal and perineum. This process, known as microbial seeding, exposes the newborn to a diverse array of maternal microbes. Babies born via vaginal delivery typically exhibit a gut microbiome resembling their mother's vaginal microbiota, which is rich in beneficial bacteria like Lactobacillus and Prevotella [35].
- **Cesarean Section (C-Section):** Infants born via cesarean section, on the other hand, miss out on the vaginal seeding process and tend to have a gut microbiome that mirrors the skin and hospital environment, often with a lower diversity of beneficial bacteria [36].

3.4.2. Breastfeeding

- **Breast Milk as Prebiotic:** Breast milk is a rich source of prebiotics, including human milk oligosaccharides (HMOs), which cannot be digested by the infant but serve as nourishment for specific beneficial bacteria in the gut, such as *Bifidobacterium* and *Lactobacillus*. Breast milk also contains immunoglobulins, antimicrobial peptides, and other bioactive components that support the development of a healthy gut microbiome and protect against infections [37].
- **Formula Feeding:** Infants who are formula-fed have a different gut microbial composition compared to breastfed infants. Their microbiome may include a higher proportion of potentially pathogenic bacteria and lower levels of beneficial bacteria [38].
- Early life influences on the gut microbiome have long-lasting consequences for health. A well-balanced, diverse gut microbiome established in infancy is associated with a reduced risk of various health issues, including allergies, asthma, autoimmune diseases, and obesity. Disturbances in the early microbiome, such as C-section birth or lack of breastfeeding, may increase susceptibility to these conditions [39, 40].

3.5. Environmental factors

Environmental factors, including exposure to antibiotics and stress, can disrupt the gut microbiome. Antibiotics are essential for treating bacterial infections, but they can have unintended consequences on the gut microbiome. When antibiotics are used, they not only target the harmful bacteria causing the infection but can also impact the beneficial bacteria residing in the gut. This can lead to a decrease in the diversity and abundance of these beneficial microbes, which are crucial for various aspects of health, including digestion and the immune system [41]. Stress is a psychological and physiological response to challenging situations. It can affect the gut microbiome through the gut-brain axis, a bidirectional communication system between the central nervous system and the gut. Stress can lead to alterations in the composition of the gut microbiota, potentially contributing to gastrointestinal issues such as irritable bowel syndrome (IBS). Both antibiotics and stress can have a significant impact on the gut microbiome, and these disruptions may have implications for an individual's overall health. The balance of the gut microbiome is essential for various physiological functions, and understanding how these environmental factors influence it is crucial for maintaining gut health and well-being [42].

4. Functional Roles of the Gut Microbiome

The gut microbiome, a complex ecosystem of microorganisms residing in the gastrointestinal tract, plays a crucial role in maintaining human health and well-being. It has multifaceted functional roles that extend beyond digestion and metabolism.

4.1. Metabolic Functions

Fermentation and SCFA Production: The gut microbiome ferments undigested dietary components, particularly complex carbohydrates, producing short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. SCFAs serve as an energy source for colonocytes, help regulate host metabolism, and contribute to gut health [43,44]. Gut microbes modify bile acids, influencing their bioavailability and, consequently, lipid metabolism. This interaction plays a role in cholesterol regulation and lipid homeostasis [45].

4.2. Nutrient Absorption and Synthesis

Certain gut microbes synthesize essential vitamins, such as B vitamins (e.g., folate and B12) and vitamin K, contributing to the host's nutritional status. Gut bacteria can metabolize amino acids, affecting the absorption and utilization of dietary proteins. This has implications for nitrogen balance and overall protein metabolism [46].

4.3. Immune System Modulation

The gut microbiome plays a pivotal role in training and modulating the host's immune system. It helps distinguish between pathogens and commensal microorganisms, promoting immune tolerance to harmless microbes while mounting appropriate immune responses to invaders [47]. A balanced gut microbiome helps regulate immune responses, preventing chronic inflammation associated with autoimmune diseases and inflammatory disorders [48].

4.4. Protection against Pathogens

Beneficial gut bacteria compete with pathogens for resources and adhesion sites in the gut, reducing the likelihood of pathogen colonization and infection [49]. Some gut microbes produce antimicrobial compounds (e.g., bacteriocins) that inhibit the growth of harmful bacteria [50].

4.5. Neurological and Psychological Impact

Emerging research suggests that the gut microbiome communicates bidirectionally with the central nervous system through the gut-brain axis. It can influence mood, behaviour, and neurological conditions [51]. Certain gut bacteria produce neurotransmitters like serotonin and gamma-aminobutyric acid (GABA), which can affect mood and cognitive function [52].

4.6. Metabolism of Xenobiotics

Gut microbes can metabolize and detoxify xenobiotics, including drugs, environmental toxins, and dietary compounds. This detoxification process influences drug efficacy and toxicity [53].

4.7. Gut Barrier Integrity

Some gut bacteria can degrade and utilize mucin, the protective layer of the gut lining. This interaction can influence gut barrier integrity and susceptibility to inflammatory bowel diseases [54].

4.8. Synthesis of Secondary Metabolites

Gut microbes metabolize dietary polyphenols into bioactive compounds with antioxidant and anti-inflammatory properties. This metabolic activity may contribute to the health benefits of polyphenol-rich diets [55]. Some gut bacteria are involved in sulfate reduction, a process that can affect the host's mucosal defense mechanisms and contribute to inflammatory bowel diseases [56].

5. Gut Microbiome and Health

5.1. Gastrointestinal disorders

Research over the past decade has unveiled the profound influence of the gut microbiome on various aspects of health, ranging from digestion to immunity and beyond. The gut microbiome plays a central role in digestion by breaking down complex carbohydrates and fibers that human enzymes cannot digest. It produces enzymes that aid in the digestion of food and the absorption of nutrients, contributing to overall digestive health. Imbalances in the gut microbiome can lead to gastrointestinal issues such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) [57].

5.2. Metabolic conditions

Besten et al. (2013) & Canfora et al. (2017) studies shows that the gut microbiome influences host metabolism by fermenting dietary fibers and producing short-chain fatty acids (SCFAs). SCFAs, particularly butyrate, have been associated with improved insulin sensitivity, reduced inflammation, and a decreased risk of metabolic disorders like type 2 diabetes and obesity [58,59]. Belkaid & Hand (2014) found that a well-balanced gut microbiome helps regulate the immune system. It trains the immune system to distinguish between harmful pathogens and beneficial microbes, promoting immune tolerance [60]. Dysbiosis, an imbalance in the gut microbiome, has been linked to autoimmune diseases, allergies, and immune-related disorders.

5.3. Mental and Cardiovascular Health

Cryan and Dinan (2012) & Sarkar et al. (2016) studies show the relationship of the gut-brain axis, a bidirectional communication system between the gut and the brain. The gut microbiome can influence mood, behavior, and neurological conditions such as depression and anxiety. It produces neurotransmitters and bioactive compounds that can affect brain function and mental health [61,62]. Research studies by Kamada et al. (2013) & Bonfrate et al. (2013) found that beneficial gut bacteria compete with pathogens for resources and adhesion sites in the gut, reducing the risk of pathogen colonization and infection. The gut microbiome also produces antimicrobial compounds that inhibit the growth of harmful bacteria [63,64]. Wang et al. (2011) suggested that the gut microbiome may influence cardiovascular health. It can metabolize dietary compounds like choline and carnitine into trimethylamine (TMA), which is then converted into trimethylamine-N-oxide (TMAO) [65]. Elevated TMAO levels have been linked to an increased risk of heart disease.

5.4. Response to Medications and Aging

Wilson & Nicholson (2017) study show that the gut microbiome can influence how individuals respond to medications. It may metabolize drugs, affecting their efficacy and toxicity [66]. This has implications for personalized medicine and drug development. According to O'Toole & Jeffery (2015), the composition and diversity of the gut microbiome change with age. Maintaining a healthy gut microbiome in later life may be associated with healthier aging and longevity [67].

6. Therapeutic Interventions and Manipulation of the Gut Microbiome

Emerging research has unveiled various strategies for intervening in the gut microbiome to improve health and treat a range of conditions. The gut microbiome, a complex community of microorganisms residing in the gastrointestinal tract, is a dynamic entity that can be modified and manipulated for therapeutic purposes.

6.1. Probiotics

Probiotics are live microorganisms, typically beneficial bacteria, that when administered in adequate amounts, confer health benefits to the host. They are widely used to restore and maintain a balanced gut microbiome. Probiotics have been explored for conditions such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and antibiotic-associated diarrhea [68, 69].

6.2. Prebiotics

Prebiotics are non-digestible dietary fibers that promote the growth and activity of beneficial gut bacteria. They serve as food for probiotics and indigenous commensal bacteria. Incorporating prebiotics into the diet can stimulate the growth of beneficial microbes and improve gut health [70].

6.3. Synbiotics

Synbiotics are a combination of probiotics (live beneficial microorganisms) and prebiotics (non-digestible substances that promote the growth of beneficial microorganisms) working together to improve gut health and overall well-being. The synergy between these components helps maintain a balanced gut microbiota, supporting various health benefits.

6.4. Fecal Microbiota Transplantation (FMT)

FMT involves the transfer of fecal material from a healthy donor to a recipient's gastrointestinal tract to restore a balanced microbiome. FMT has shown remarkable success in treating recurrent *Clostridium difficile* infections and it is being explored for other conditions such as inflammatory bowel disease and irritable bowel syndrome [71,72].

6.5. Microbial-Based Therapies

Researchers are developing therapies using specific strains of bacteria or microbial consortia to target various health conditions. These therapies, sometimes referred to as "next-generation probiotics," are designed to have specific functions in the gut, such as producing therapeutic compounds or suppressing harmful microbes [73].

7. Challenges and Future Directions in Gut Microbiome Research

Gut microbiome research has made significant strides in recent years, shedding light on its pivotal role in human health and disease. However, several challenges persist, and ongoing efforts are needed to fully understand and harness the potential of this complex microbial ecosystem.

7.1. Challenges in Gut Microbiome Research

- **Inter-individual Variability:** The gut microbiome varies significantly among individuals, making it challenging to define a "normal" or "healthy" microbiome. Understanding this variability and its implications for health and disease remains a major challenge. Zhernakova et al. (2016) highlight the substantial inter-individual variation in the gut microbiome and its genetic determinants [74].
- **Causality and Mechanistic Understanding:** Lynch and Pedersen (2016) discuss the challenges of inferring causality in microbiome-host interactions and propose a framework for addressing these challenges [75] Establishing causal relationships between the gut microbiome and various diseases or health outcomes is complex. Many associations have been identified, but mechanistic insights are often lacking.
- **Microbiome-Host Interactions:** Belkaid & Harrison (2017) provide insights into the dynamic interactions between the microbiome and the host immune system [76]. Understanding the intricate interactions between the gut microbiome and host physiology is a major challenge. Deciphering how the microbiome influences host metabolism, immunity, and other functions requires innovative approaches.
- **Longitudinal Studies:** Falony et al. (2016) emphasize the importance of longitudinal studies in unraveling the dynamics of the gut microbiome [77]. Many microbiome studies are cross-sectional, limiting our ability to capture dynamic changes over time. Longitudinal studies are essential for understanding the development of the microbiome and its role in health and disease progression.
- **Functional Characterization**: Franzosa et al. (2018) discuss approaches and challenges in species-level functional profiling of metagenomes. While advances in metagenomics have provided insights into microbial composition, functional characterization of the gut microbiome remains challenging [78]. Understanding what functions specific microbial species perform is crucial.

7.2. Future Directions in Gut Microbiome Research

- **Precision Medicine and Personalized Interventions:** Knights et al. (2018) emphasize the potential of precision medicine in microbiome research, paving the way for personalized healthcare approaches [79]. The gut microbiome holds promise for personalized medicine. Tailoring interventions based on an individual's microbiome profile may optimize treatment outcomes for various diseases.
- **Microbiome-Based Therapeutics:** Mimee et al. (2016) discuss the engineering of microbes for therapeutic purposes and the potential of microbiome-based therapeutics [80]. Developing microbiome-based therapies, including next-generation probiotics and microbial-based drugs, is an emerging field. These therapies have the potential to target specific diseases or dysbiosis.
- **Multi-Omics Integration:** Heintz-Buschart et al. (2018) explored the integration of multi-omics data as a future direction in microbiome research. Integrating multi-omics data (e.g., metagenomics, metatranscriptomics, and metabolomics) can provide a holistic understanding of the gut microbiome and its functional roles in health and disease [81].
- **Microbiome and Environmental Factors:** David et al. (2014) highlights the role of diet in shaping the gut microbiome and its implications for health [82]. Investigating the impact of environmental factors, such as diet, lifestyle, and exposure to pollutants, on the gut microbiome will be crucial in understanding disease etiology and developing preventive strategies.
- **Therapeutic Manipulation of the Microbiome:** Paramsothy et al. (2019) discuss the potential of FMT and other microbiome-based therapies in clinical practice. Refining therapeutic interventions to manipulate the gut microbiome for disease prevention and treatment will continue to be a focus of research. This includes optimizing fecal microbiota transplantation (FMT) protocols and exploring novel approaches.

8. Conclusion

In conclusion, research on the gut microbiome has yielded a wealth of knowledge about the complex microbial communities residing within our gastrointestinal tract. These discoveries have significant implications for human health and disease. The human gut is home to a vast array of microbial species, collectively known as the gut microbiome. This diversity varies between individuals, with thousands of different species identified. Microbial diversity is associated with a healthy gut and plays a role in maintaining overall well-being. Reduced diversity has been linked to various health issues, including inflammatory bowel disease (IBD) and obesity. The gut-brain axis is a bidirectional communication system connecting the gut and the central nervous system. The gut microbiome can influence brain function and behavior. This connection has implications for mental health, with emerging evidence suggesting a link between the gut microbiome and conditions such as depression, anxiety, and even neurodegenerative diseases. The gut microbiome plays a vital role in training and modulating the immune system. It helps differentiate between harmful pathogens and beneficial microbes, promoting immune tolerance. Diet significantly influences the composition and function of the gut microbiome. High-fiber diets promote the growth of beneficial bacteria, while diets rich in processed foods can lead to dysbiosis. Dietary interventions can be used to modulate the gut microbiome and improve health outcomes. Prebiotics and probiotics are among the strategies employed to enhance microbial balance. Early life events, such as birth mode and breastfeeding, have a profound impact on the development of an infant's gut microbiome. Establishing a healthy gut microbiome in early life is critical for immune development and may influence the risk of allergies, asthma, and autoimmune diseases later in life. Dysbiosis of the gut microbiome has been associated with various diseases, including inflammatory bowel disease (IBD), obesity, diabetes, and cardiovascular disease. Understanding these associations opens avenues for microbiome-based diagnostics and therapies. Fecal microbiota transplantation (FMT) is one emerging treatment for conditions like recurrent *Clostridium difficile* infections. Researchers are developing therapeutic interventions to manipulate the gut microbiome, including probiotics, prebiotics, FMT, and microbial-based drugs. These interventions have the potential to treat a range of conditions, from gastrointestinal disorders to metabolic diseases. They represent a growing field of microbiome-based therapeutics. Environmental factors, such as exposure to pollutants and antibiotics, can disrupt the gut microbiome and impact human health. Awareness of these environmental influences can guide public health policies and individual choices to protect and promote gut microbiome health. The findings in gut microbiome research have transformative implications for healthcare and beyond. Personalized medicine, precision nutrition, and microbiome-based therapies are emerging as promising strategies for improving human health. Continued research into the gut microbiome's roles and therapeutic potential will undoubtedly shape the future of medicine and wellness.

References

[1] Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature [Internet]. 2010b Mar 1, 464(7285):59–65. Available from: https://doi.org/10.1038/nature08821

[2] Ley RE, Hamady M, Lozupone C, Turnbaugh PJ, Ramey RR, Bircher J, et al. Evolution of mammals and their gut microbes. Science [Internet]. 2008b Jun 20, 320(5883):1647–51. Available from: https://doi.org/10.1126/science.1155725

[3] Clemente JC, Ursell LK, Parfrey LW, Knight R. The Impact of the gut microbiota on Human Health: An Integrative view. Cell [Internet]. 2012 Mar 1, 148(6):1258–70. Available from: https://doi.org/10.1016/j.cell.2012.01.035

[4] Paramsothy S, Kamm MA, Kaakoush NO, Walsh A, Van Den Bogaerde J, Samuel DB, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. The Lancet [Internet]. 2017 Mar 1, 389(10075):1218–28. Available from: https://doi.org/10.1016/s0140-6736(17)30182-4

[5] Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, Chinwalla AT, et al. Structure, function and diversity of the healthy human microbiome. Nature [Internet]. 2012b Jun 1, 486(7402):207–14. Available from: https://doi.org/10.1038/nature11234

[6] Claesson MJ, O'Sullivan Ó, Wang Q, Nikkilä J, Marchesi JR, Smidt H, et al. Comparative analysis of pyrosequencing and a phylogenetic microarray for exploring microbial community structures in the human distal intestine. PLOS ONE [Internet]. 2009 Aug 20, 4(8):e6669. Available from: https://doi.org/10.1371/journal.pone.0006669

[7] Hannigan GD, Meisel JS, Tyldsley AS, Zheng Q, Hodkinson BP, SanMiguel AJ, et al. The Human Skin Double-Stranded DNA Virome: Topographical and Temporal Diversity, Genetic Enrichment, and Dynamic Associations with the Host Microbiome. MBio [Internet]. 2015 Oct 30, 6(5). Available from: https://doi.org/10.1128/mbio.01578-15

[8] Minot SS, Sinha R, Chen J, Li H, Keilbaugh SA, Wu GD, et al. The human gut virome: Inter-individual variation and dynamic response to diet. Genome Research [Internet]. 2011 Aug 31, 21(10):1616–25. Available from: https://doi.org/10.1101/gr.122705.111

[9] Lozupone C, Stombaugh J, Gordon JI, Jansson J, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature [Internet]. 2012 Sep 1, 489(7415):220–30. Available from: https://doi.org/10.1038/nature11550

[10] Yatsunenko T, Rey FE, Manary MJ, Trehan I, Domínguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature [Internet]. 2012 May 9, 486(7402):222–7. Available from: https://doi.org/10.1038/nature11053

[11] Goodrich JK, Davenport E, Beaumont M, Jackson MA, Knight R, Ober C, et al. Genetic Determinants of the gut microbiome in UK twins. Cell Host & Microbe [Internet]. 2016 May 1, 19(5):731–43. Available from: https://doi.org/10.1016/j.chom.2016.04.017

[12] Eckburg PB, Bik EM, Bernstein ÇN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. Science [Internet]. 2005 Jun 10, 308(5728):1635–8. Available from: https://doi.org/10.1126/science.1110591

[13] Lloyd-Price J, Mahurkar A, Rahnavard A, Crabtree J, Orvis J, Hall AB, et al. Strains, functions and dynamics in the expanded Human Microbiome Project. Nature [Internet]. 2017 Sep 20, 550(7674):61–6. Available from: https://doi.org/10.1038/nature23889

[14] David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature [Internet]. 2013 Dec 11, 505(7484):559–63. Available from: https://doi.org/10.1038/nature12820

[15] Huttenhower C, Gevers D, Knight R, Abubucker S, Badger JH, Chinwalla AT, et al. Structure, function and diversity of the healthy human microbiome. Nature [Internet]. 2012c Jun 1, 486(7402):207–14. Available from: https://doi.org/10.1038/nature11234

[16] Sonnenburg JL, Bäckhed F. Diet–microbiota interactions as moderators of human metabolism. Nature [Internet]. 2016 Jul 6, 535(7610):56–64. Available from: https://doi.org/10.1038/nature18846

[17] Goodrich JK, Waters JL, Poole AC, Sutter JL, Koren O, Blekhman R, et al. Human genetics shape the gut microbiome. Cell [Internet]. 2014 Nov 1, 159(4):789–99. Available from: https://doi.org/10.1016/j.cell.2014.09.053

[18] Yatsunenko T, Rey FE, Manary MJ, Trehan I, Domínguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature [Internet]. 2012b May 9, 486(7402):222–7. Available from: https://doi.org/10.1038/nature11053

[19] Ramírez JA, Guarner F, Fernández L, Maruy A, Sdepanian VL, Cohen H. Antibiotics as major disruptors of gut microbiota. Frontiers in Cellular and Infection Microbiology [Internet]. 2020 Nov 24, 10. Available from: https://doi.org/10.3389/fcimb.2020.572912

[20] Arrieta M, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Science Translational Medicine [Internet]. 2015b Sep 30, 7(307). Available from: https://doi.org/10.1126/scitranslmed.aab2271

[21] Kamada N, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. Nature Reviews Immunology [Internet]. 2013b Apr 25, 13(5):321–35. Available from: https://doi.org/10.1038/nri3430

[22] David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature [Internet]. 2013b Dec 11, 505(7484):559–63. Available from: https://doi.org/10.1038/nature12820

[23] Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes. Science [Internet]. 2011 Oct 7, 334(6052):105–8. Available from: https://doi.org/10.1126/science.1208344

[24] Goodrich JK, Davenport E, Waters JL, Clark AG, Ley RE. Cross-species comparisons of host genetic associations with the microbiome. Science [Internet]. 2016b Apr 29, 352(6285):532–5. Available from: https://doi.org/10.1126/science.aad9379

[25] Yatsunenko T, Rey FE, Manary MJ, Trehan I, Domínguez-Bello MG, Contreras M, et al. Human gut microbiome viewed across age and geography. Nature [Internet]. 2012c May 9, 486(7402):222–7. Available from: https://doi.org/10.1038/nature11053

[26] De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proceedings of the National Academy of Sciences of the United States of America [Internet]. 2010 Aug 2, 107(33):14691–6. Available from: https://doi.org/10.1073/pnas.1005963107

[27] Dethlefsen L, Huse SM, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by Deep 16S RRNA sequencing. PLOS Biology [Internet]. 2008 Nov 18, 6(11):e280. Available from: https://doi.org/10.1371/journal.pbio.0060280

[28] Costello EK, Stagaman K, Dethlefsen L, Bohannan BJM, Relman DA. The application of ecological theory toward an understanding of the human microbiome. Science [Internet]. 2012 Jun 8, 336(6086):1255–62. Available from: https://doi.org/10.1126/science.1224203

[29] David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature [Internet]. 2013c Dec 11, 505(7484):559–63. Available from: https://doi.org/10.1038/nature12820

[30] Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes. Science [Internet]. 2011b Oct 7, 334(6052):105–8. Available from: https://doi.org/10.1126/science.1208344

[31] Tzounis X, Vulevic J, Kuhnle G, George T, Leonczak J, Gibson GR, et al. Flavanol monomer-induced changes to the human faecal microflora. British Journal of Nutrition [Internet]. 2007 Nov 1, 99(4):782–92. Available from: https://doi.org/10.1017/s0007114507853384

[32] Costantini L, Molinari R, Farinon B, Merendino N. Impact of omega-3 fatty acids on the gut microbiota. International Journal of Molecular Sciences [Internet]. 2017 Dec 7, 18(12):2645. Available from: https://doi.org/10.3390/ijms18122645

[33] Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature [Internet]. 2006 Dec 1, 444(7122):1027–31. Available from: https://doi.org/10.1038/nature05414

[34] Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell [Internet]. 2014c Mar 1, 157(1):121–41. Available from: https://doi.org/10.1016/j.cell.2014.03.011

[35] Domínguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proceedings of the National Academy of Sciences of the United States of America [Internet]. 2010b Jun 21, 107(26):11971–5. Available from: https://doi.org/10.1073/pnas.1002601107

[36] Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, Li H, et al. Antibiotics, birth mode, and diet shape microbiome maturation during early life. Science Translational Medicine [Internet]. 2016b Jun 15, 8(343). Available from: https://doi.org/10.1126/scitranslmed.aad7121

[37] Lawson MA, O'Neill I, Kujawska M, Javvadi SG, Wijeyesekera A, Flegg Z, et al. Breast milk-derived human milk oligosaccharides promote Bifidobacterium interactions within a single ecosystem. The ISME Journal [Internet]. 2019b Nov 18, 14(2):635–48. Available from: https://doi.org/10.1038/s41396-019-0553-2

[38] Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, Kovatcheva-Datchary P, et al. Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. Cell Host & Microbe [Internet]. 2015b May 1, 17(5):690–703. Available from: https://doi.org/10.1016/j.chom.2015.04.004

[39] Arumugam M, Raes J, Pelletier É, Paslier DL, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. Nature [Internet]. 2011b Apr 20, 473(7346):174–80. Available from: https://doi.org/10.1038/nature09944

[40] Arrieta M, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Science Translational Medicine [Internet]. 2015c Sep 30, 7(307). Available from: https://doi.org/10.1126/scitranslmed.aab2271

[41] Cho I, Yamanishi S, Cox LM, Methé BA, Zavadil J, Li K, et al. Antibiotics in early life alter the murine colonic microbiome and adiposity. Nature [Internet]. 2012 Aug 1, 488(7413):621–6. Available from: https://doi.org/10.1038/nature11400

[42] Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. J Physiol Pharmacol. 2011, 62(6):591–9.

[43] Louis P, Flint HJ. Diversity, metabolism and microbial ecology of butyrate-producing bacteria from the human large intestine. Fems Microbiology Letters [Internet]. 2009b May 1, 294(1):1–8. Available from: https://doi.org/10.1111/j.1574-6968.2009.01514.x

[44] Besten GD, Van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. Journal of Lipid Research [Internet]. 2013c Sep 1, 54(9):2325–40. Available from: https://doi.org/10.1194/jlr.r036012

[45] Joyce SA, Gahan CGM. The gut microbiota and the metabolic health of the host. Current Opinion in Gastroenterology [Internet]. 2014b Mar 1, 30(2):120–7. Available from: https://doi.org/10.1097/mog.0000000000000039

[46] Degnan PH, Ochman H. Illumina-based analysis of microbial community diversity. The ISME Journal [Internet]. 2011b Jun 16, 6(1):183–94. Available from: https://doi.org/10.1038/ismej.2011.74

[47] Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell [Internet]. 2014d Mar 1, 157(1):121–41. Available from: https://doi.org/10.1016/j.cell.2014.03.011

[48] Honda K, Littman DR. The microbiome in infectious disease and inflammation. Annual Review of Immunology [Internet]. 2012c Apr 23, 30(1):759–95. Available from: https://doi.org/10.1146/annurev-immunol-020711-074937

[49] Kamada N, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. Nature Reviews Immunology [Internet]. 2013c Apr 25, 13(5):321–35. Available from: https://doi.org/10.1038/nri3430

[50] Bonfrate L, Tack J, Grattagliano I, Cuomo R, Portincasa P. Microbiota in health and irritable bowel syndrome: current knowledge, perspectives and therapeutic options. Scandinavian Journal of Gastroenterology [Internet]. 2013b Aug 22, 48(9):995–1009. Available from: https://doi.org/10.3109/00365521.2013.799220

[51] Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nature Reviews Neuroscience [Internet]. 2012b Sep 12, 13(10):701–12. Available from: https://doi.org/10.1038/nrn3346

[52] Yano JM, Yu K, Donaldson GP, Shastri GG, Ann P, Ma L, et al. Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. Cell [Internet]. 2015b Apr 1, 161(2):264–76. Available from: https://doi.org/10.1016/j.cell.2015.02.047

[53] Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Translational Research [Internet]. 2017b Jan 1, 179:204–22. Available from: https://doi.org/10.1016/j.trsl.2016.08.002

[54] Johansson M, Phillipson M, Petersson J, Velcich A, Holm L, Hansson GC. The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. Proceedings of the National Academy of Sciences of the United States of America [Internet]. 2008b Sep 30, 105(39):15064–9. Available from: https://doi.org/10.1073/pnas.0803124105

[55] Cardona F, Andrés-Lacueva C, Tulipani S, Tinahones FJ, Queipo-Ortuño MI. Benefits of polyphenols on gut microbiota and implications in human health. Journal of Nutritional Biochemistry [Internet]. 2013b Aug 1, 24(8):1415–22. Available from: https://doi.org/10.1016/j.jnutbio.2013.05.001

[56] Gibson GR, Roberfroid M. Dietary modulation of the human colonic microbiota: Introducing the concept of prebiotics. Journal of Nutrition [Internet]. 1995b Jun 1, 125(6):1401–12. Available from: https://doi.org/10.1093/jn/125.6.1401

[57] Quigley EM. Gut bacteria in health and disease. Gastroenterology & hepatology. 2013 Sep, 9(9):560.

[58] Besten GD, Van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. Journal of Lipid Research [Internet]. 2013d Sep 1, 54(9):2325–40. Available from: https://doi.org/10.1194/jlr.r036012

[59] Canfora EE, Van Der Beek CM, Jocken JWE, Goossens GH, Holst JJ, Damink SWMO, et al. Colonic infusions of short-chain fatty acid mixtures promote energy metabolism in overweight/obese men: a randomized crossover trial. Scientific Reports [Internet]. 2017 May 24, 7(1). Available from: https://doi.org/10.1038/s41598-017-02546-x

[60] Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. Cell [Internet]. 2014d Mar 1, 157(1):121–41. Available from: https://doi.org/10.1016/j.cell.2014.03.011

[61] Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nature Reviews Neuroscience [Internet]. 2012c Sep 12, 13(10):701–12. Available from: https://doi.org/10.1038/nrn3346

[62] Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the manipulation of Bacteria–Gut–Brain signals. Trends in Neurosciences [Internet]. 2016 Nov 1, 39(11):763–81. Available from: https://doi.org/10.1016/j.tins.2016.09.002

[63] Kamada N, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. Nature Reviews Immunology [Internet]. 2013c Apr 25, 13(5):321–35. Available from: https://doi.org/10.1038/nri3430

[64] Bonfrate L, Tack J, Grattagliano I, Cuomo R, Portincasa P. Microbiota in health and irritable bowel syndrome: current knowledge, perspectives and therapeutic options. Scandinavian Journal of Gastroenterology [Internet]. 2013b Aug 22, 48(9):995–1009. Available from: https://doi.org/10.3109/00365521.2013.799220

[65] Wang Z, Klipfell E, Bennett BJ, Koeth RA, Levison BS, DuGar B, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature [Internet]. 2011 Apr 1, 472(7341):57–63. Available from: https://doi.org/10.1038/nature09922

[66] Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Translational Research [Internet]. 2017c Jan 1, 179:204–22. Available from: https://doi.org/10.1016/j.trsl.2016.08.002

[67] O'Toole PW, Jeffery IB. Gut microbiota and aging. Science [Internet]. 2015 Dec 4, 350(6265):1214–5. Available from: https://doi.org/10.1126/science.aac8469

[68] Hill C, Guarner F, Reid G, Gibson GR, Merenstein D, Pot B, et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nature Reviews Gastroenterology & Hepatology [Internet]. 2014 Jun 10, 11(8):506–14. Available from: https://doi.org/10.1038/nrgastro.2014.66

[69] McFarland LV. Use of probiotics to correct dysbiosis of normal microbiota following disease or disruptive events: a systematic review. BMJ Open [Internet]. 2014 Aug 25, 4(8):e005047. Available from: https://doi.org/10.1136/bmjopen-2014-005047

[70] Gibson GR, Hutkins RW, Sanders ME, Prescott SL, Reimer RA, Salminen S, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nature Reviews Gastroenterology & Hepatology [Internet]. 2017 Jun 14, 14(8):491–502. Available from: https://doi.org/10.1038/nrgastro.2017.75

[71] Van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, De Vos WM, et al. Duodenal Infusion of Donor Feces for RecurrentClostridium difficile. The New England Journal of Medicine [Internet]. 2013 Jan 31, 368(5):407–15. Available from: https://doi.org/10.1056/nejmoa1205037

[72] Paramsothy S, Kamm MA, Kaakoush NO, Walsh A, Van Den Bogaerde J, Samuel DB, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. The Lancet [Internet]. 2017b Mar 1, 389(10075):1218–28. Available from: https://doi.org/10.1016/s0140-6736(17)30182-4

[73] Bober JR, Beisel CL, Nair NU. Synthetic biology approaches to engineer probiotics and members of the human microbiota for biomedical applications. Annual Review of Biomedical Engineering [Internet]. 2018 Jun 4, 20(1):277–300. Available from: https://doi.org/10.1146/annurev-bioeng-062117-121019

[74] Zhernakova A, Kurilshikov A, Bonder MJ, Tigchelaar EF, Schirmer M, Vatanen T, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. Science [Internet]. 2016 Apr 29, 352(6285):565–9. Available from: https://doi.org/10.1126/science.aad3369

[75] Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. The New England Journal of Medicine [Internet]. 2016 Dec 15, 375(24):2369–79. Available from: https://doi.org/10.1056/nejmra1600266

[76] Belkaid Y, Harrison OJ. Homeostatic immunity and the microbiota. Immunity [Internet]. 2017 Apr 1, 46(4):562–76. Available from: https://doi.org/10.1016/j.immuni.2017.04.008

[77] Falony G, Joossens M, Vieira-Silva S, Wang J, Darzi Y, Faust K, et al. Population-level analysis of gut microbiome variation. Science [Internet]. 2016 Apr 29, 352(6285):560–4. Available from: https://doi.org/10.1126/science.aad3503

[78] Franzosa EA, McIver LJ, Rahnavard A, Thompson LR, Schirmer M, Weingart G, et al. Species-level functional profiling of metagenomes and metatranscriptomes. Nature Methods [Internet]. 2018 Oct 30, 15(11):962–8. Available from: https://doi.org/10.1038/s41592-018-0176-y

[79] Knight R, Vrbanac A, Taylor BC, Aksenov AA, Callewaert C, Debelius JW, et al. Best practices for analysing microbiomes. Nature Reviews Microbiology [Internet]. 2018 May 23, 16(7):410–22. Available from: https://doi.org/10.1038/s41579-018-0029-9

[80] Bober JR, Beisel CL, Nair NU. Synthetic biology approaches to engineer probiotics and members of the human microbiota for biomedical applications. Annual Review of Biomedical Engineering [Internet]. 2018b Jun 4, 20(1):277–300. Available from: https://doi.org/10.1146/annurev-bioeng-062117-121019

[81] Heintz-Buschart A, May P, Laczny CC, Lebrun L, Bellora C, Krishna A, et al. Integrated multi-omics of the human gut microbiome in a case study of familial type 1 diabetes. Nature Microbiology [Internet]. 2016 Oct 10, 2(1). Available from: https://doi.org/10.1038/nmicrobiol.2016.180

[82] David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature [Internet]. 2013d Dec 11, 505(7484):559–63. Available from: https://doi.org/10.1038/nature12820

[83] Paramsothy S, Kamm MA, Kaakoush NO, Walsh A, Van Den Bogaerde J, Samuel DB, et al. Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. The Lancet [Internet]. 2017b Mar 1, 389(10075):1218–28. Available from: https://doi.org/10.1016/s0140-6736(17)30182-4