# The Human Microbiome: History and Future

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**ABSTRACT -** Microorganisms, or the microbiota, residing in and on the human body have been a scientific curiosity for centuries. Today, although our understanding of the human microbiome is still unfolding, there can be little doubt that the microbiome plays an important role in human health and disease. The interactions between the microbiome and host immune system affect both human health and disease. For example, the composition of the microbiota at one week of life has been associated with the frequency and number of respiratory infections over the first year of life. This brief review indicates that more studies are required using current and new technologies to develop a better understanding of the role the human microbiome plays in human health.

## Brief History of the human microbiome

Microorganisms, or the microbiota, residing in and on the human body have been of scientific interest for centuries. A report emerged as early as the mid-1880s that microorganisms are part of the human system, when Theodor Escherich, an Austrian pediatrician, observed a bacterium (*Escherichia coli*) in the intestinal flora of healthy children and children with diarrheal disease. More microorganisms were isolated from the human body over the perusing years, including in 1898 when *Veillonella parvula* was found in the oral, digestive, urinary, and upper respiratory tracts, and again in the 1900s when bifidobacteria were reported in the intestinal flora. Throughout the 20th century, microorganisms continued to be isolated from nasal passages, oral cavities, skin, the gastrointestinal tract, and the urogenital tract and characterized as part of the human microbiota.

Human dreams often give rise to new science. The concept of the human microbiome and microbiome research is a 21st-century scientific frontier born out of such a dream. The word 'microbiome' was coined in 2001 when Lederberg and McCray (1) published their monumental paper. They defined the human "microbiome" as "the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space'' (1). Around the same time, Relman and Falkow (2) published their ''second human genome project'' (3) that ''would entail a comprehensive inventory of microbial genes and genomes at the four major sites of microbial colonization in the human body: mouth, gut, vagina, and skin.'' A year later Relman (4) advocated that the ''characterization of the microbiome would be accomplished through random shotgun sequencing procedures, targeted large-insert clone sequencing, and assessments of intra- and inter-individual variation by using high-density microarrays.'' Further Relman (4) argued that a ''study of host genome-wide expression analysis,'' would lead to important "'insights into the role of the endogenous flora in health and disease.'' Excellent documentation of the history of microbiome development is provided by Prescott (5).

A healthy human body carries millions of microorganisms (6). Together these organisms form a system called the microbiome. The genomes that constitute the human microbiome represent a diverse array of organisms that includes bacteria, archaea, fungi, protozoans, and nonliving viruses, residing mostly in the gastrointestinal tract (7). Bacteria are the most numerous members of the human microbiome: the bacterial population is estimated at 75 to 200 trillion individual organisms, while the entire human body consists of roughly 50 to 100 trillion somatic cells (8). This microbial imbalance suggests that the human body is a collection of human and microbial cells and genes and thus a blend of human and microbial traits. The

diversity of the human gut microbiome increases from birth through childhood and remains relatively stable during adult life and then begins to decline with age (9). Recent Reyman et al (10) have shown that the microbiota composition at one week of a baby's life is associated with the number and frequency of respiratory infections over the first year of life, again demonstrating how significant the human microbiome is in health and disease (11).

The interest of the biomedical community in the human microbiome has increased dramatically in recent years. The microbiome is a dynamic living system. It is affected by changes in its environment. When the normal environment of a microbiome is disturbed by external factors, potentially harmful adverse health effects can occur (6). Environmental factors (diet, new microbes, medication or antibiotics, foreign chemicals, and infection) have been shown to alter the microbiome, potentially leading to a pro-inflammatory state. Antibiotics severely affect the human gut microbiome creating an imbalance including increased numbers of antibiotic-resistant bacteria (12). Such chronic alterations in the human gut play a major role in the development of adverse health effects (13). Recent studies have identified potential agents that can protect the human gut microbiome from such adverse health effects caused by antibiotic treatment (12), supporting the important observation that microbes play an important role in human health and disease (14). The dysfunction of the microbiome is associated with obesity, diabetes, liver and renal diseases, cancer, and cardiovascular diseases (13, 15, 16).

Knowledge of the human microbiome expanded rapidly after 2007, the year the Human Microbiome Project (HMP)—an international effort to characterize the microbial communities in the human body and to identify each microorganism's role in health and disease—was launched. The decreasing cost of whole-genome sequencing technology, which allows organisms to be identified from samples without the need for culturing in the laboratory facilitated the process of comparing DNA sequences of microorganisms isolated from different parts of the human body and different people. As a result, nearly 200 different bacterial species of the human microbiota have been characterized. The benefits of the gut microbiome are many and diverse with new information being generated almost daily. Importantly, in a healthy human, these organisms coexist with the host peacefully (14).

The impact of the gut microbiome on human health and disease is of public interest. The interaction between the diet, and the microbiome and their effect on the host organism is an important and expanding area of research. This rapidly developing area of research has attracted worldwide attention. In a time frame of approximately the last two decades, microbiome research has seen remarkable growth (14, 16,17, 18). This mini-review presents some of its history and reflects on the future of the human microbiome.

**Human microbiome and host metabolism**

The human microbiome plays an important role in host metabolism and physiology (19). Recent studies suggest a critical relationship between the human microbiome and host metabolism (20, 21). The interactions of the microbiome and host metabolism play a critical role in human health and disease. Change in the gut microbiome affects human health leading to disease conditions (14, 21).

Microbiome development is affected by environmental factors. Diet and environmental chemicals such as bisphenols, phthalates, heavy metals, and pesticides can significantly alter the human gut microbiome (20). Metabolism of environmental chemicals by enzymes from the host's microbiota affects the toxicity of that chemical to the host (22). Such interactions between the human microbiome and host metabolism appear to be an important factor associated with human disease and toxicity, and more than likely play a role in nonclinical testing of drug candidates.

It has been shown that there is a relationship between gut bacteria and host metabolism (23). Catron et al (24) have reported that host microbiota transforms bisphenol A and mediates its health effects. The insecticide carbamate aldicarb alters gut microbiome development and affects brain metabolism in mice (19). Dietary exposure to methylmercury causes dysfunction of the gut microbiome and changes the metabolomes in the mouse brain (25). Dietary exposure to the pesticide chlorpyrifos alters gut microbiota and metabolism in rats associated with neurotoxicity (26). The gut microbiome modulates the toxicity of polybrominated diphenyl ethers by their metabolites (27, 28).

## C-section and the Neonatal Gut Microbiome

Early gut colonization is extremely variable and is influenced by numerous factors. Among these, the mode of birth shapes the early microbial exposure and the immune environment of the neonate. C-section delivery impinges on both the microbiota and the development of the immune system in several ways (29): (1) if labor is lacking, intrauterine immune responses dependent on this process will not occur, affecting the immune environment of the neonate; (2) the lack of exposure to the vaginal and fecal microbes of the mother will alter the type and diversity of the microbes that colonize the gut at birth; (3) the different starting points in terms of microbial exposure and the immune environment will mark the course of microbiota and immune system development, generating multiple feedbacks between the two processes. C-section delivery can impact the lifelong risk of developing immune diseases (29).

For example, Liu and colleagues (2015) characterized the diversity of the intestinal microbiota in Chinese newborn infants delivered vaginally (VD) or by cesarean section (CD) in a cross-sectional study where fecal samples were collected on days 2 and 4 of postnatal life and the fecal microbiota were analyzed. On both days, VD and CD infants did not differ in the richness of the fecal bacterial community; however, the fecal microbiota was significantly different between the groups. In VD infants, *Escherichia coli*, Bacteroides sp, and *Bifidobacterium longum* dominated. In CD infants, Staphylococcus sp, Clostridium sp, Enterobacter sp, and Streptococcus sp were more common. An excellent commentary by Stinson, Payne, and Keelan (30) on the bacterial baptism hypothesis and the impact of cesarean delivery on the infant microbiome was published in 2018 (30).

## Human Microbiome in Health and Disease

The microbiome plays a significant role in both health and disease (31). Within the human body, different types of microbes occupy specific sites and support the function of these organs; for example, bacteria in the gut aid digestion. An important benefit of the gut microbiome is the production of short-chain fatty acids (32). In addition to digestion, microbes also support immune function, metabolism, and reproduction. The evidence continues to mount that metabolic disorders are associated with diseases such as obesity and diabetes. Cani (16), among others, has suggested that the microbiome interacts with host cells, playing a major role in cellular metabolism.

Fecal transplantation (or bacteriotherapy, FMT) is the transfer of stool from a healthy donor into the gastrointestinal tract of another individual. FMT is used to treat *Clostridioides difficile* infection that has occurred multiple times despite adequate antibiotic treatment. The gut microbiome plays an important role in treating irritable bowel syndrome (33, 34). Transplant of fecal microbiota is used for treating irritable bowel syndrome. The quality of the donor stool is a critical factor for this treatment which has been shown to have beneficial effects for at least three months following treatment, but how long this benefit lasts is not well understood.

The gut microbiome interacts with host cells. Improved metabolic health has been reported during a dietary intervention in obesity (35). The host immune system is affected by the microbiome (36). The gut microbiome interacts with immune cells protecting against pathogens [37]. The gut microbiome appears to be associated with some neurodegenerative disorders (16). It has been suggested that the gut microbiota may modulate the outcomes of anticancer immunotherapy and the human gut microbiota may be a potential source of novel therapeutics (16). Changes in gut microbiota have been observed in diseases such as obesity, diabetes, hepatic and renal diseases, and cancer (16). Ferreira et al (38) have suggested the presence of cancer-associated microbiota.

While microbes play an important role in maintaining human health, they are also involved in the development and progression of some cancers and current research suggests that the microbiome can influence patient response to cancer treatments. Much research is focused on understanding how microbes influence health, disease, and response to medical treatments. Some cancer treatments are dependent on inflammation and microbiome mediated inflammation can enhance the efficacy of these therapies.

## The Microbiome and Cancer

Microbiota and the host form complex symbiotic relationships that confer benefits to the host. However, defects in the regulatory circuits of the host that control bacterial sensing and homeostasis, or alterations of the microbiome, through environmental changes, may

disturb this symbiotic relationship and promote disease. Epidemiological studies have suggested that certain microbes played a role in cancer, supporting a link between the human microbiome and various types of cancer (39). However, we are only beginning to understand the science that links the human microbiome and cancer development (40). Increasing evidence indicates a role for the bacterial microbiota in carcinogenesis. A short review of some of the evidence which suggests microbes play a significant role in specific cancers follows.

### *Stomach Cancer*

*Helicobacter pylori*, a spiral-shaped bacterium, provides one of the clearest links between a microbe and cancer development (https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/h-pylori-fact-sheet). *H. pylori* infections are spread by contaminated food and mouth-to-mouth contact. The U.S. Centers for Disease Control and Prevention estimates two-thirds of the world population carries the bacterium. Because *H. pylori* burrows into the mucous layer of the gut, the effectiveness of the host's immune system to clear the bacterium is compromised. Although *H. pylori* infections do not cause illness in most individuals, infected individuals are eight times more likely to develop gastric cancer than non-infected individuals. Long-term inflammation triggered by *H. pylori* infection appears to be involved in cancer development.

### *Breast Cancer*

Hieken et. al. (41) identified microbes living in breast tissue; shortly thereafter, Pevsner-Fisher and colleagues (42) begin to explore the implications of breast tissue microbiomes. Several groups have reported that breast tissue affected by benign and malignant disease had different populations of bacteria (41, 42). It is unclear if the differences in the microbiomes *cause* the development of tumors or is a result of the disease. Mice with a predisposition to developing cancer that were infected with *Helicobacter hepaticus* had an increased mammary gland tumor burden and inflammation compared to uninfected mice (41). These results suggest that *H. hepaticus* can contribute to cancer progression by promoting inflammation.

### *Skin Cancer*

The skin microbiome is diverse and differs by anatomical location (42). The skin microbiome can play a protective or harmful role in cancer development (42, 43). Mice treated with antibiotics had an increased risk of melanoma and shorter average survival times, suggesting the microbiome plays a protective role (42, 43). There also is evidence that the protein flagella of some bacteria promote chronic inflammation, leading to tissue damage and ultimately skin cancer. Genetically modified mice that were unable to respond to bacterial flagella protein were protected against artificially induced cancer, which indicates the inflammatory response to gut bacteria may drive the development of certain skin cancers (43).

### *Colorectal Cancer*

In healthy individuals, *Fusobacterium nucleatum* is commonly found in the oral cavity (44). It has also been found in colorectal adenomas and advanced-stage colorectal cancer (44). *F. nucleatum* induces an inflammatory response and activation of cancer-promoting genes, thereby increasing the rate of proliferation in colorectal cells (44). The gut microbiota metabolites appear to modulate human colon cancer cells (45)

### *Cervical, Anal, and Oral Cancers*

Viruses are responsible for many cases of mouth and throat cancers with approximately 15% of all human cancers being attributed to viruses (46). Although the human papillomavirus (HPV) is responsible for most cases of anal and cervical cancer (46), interestingly, in healthy individuals, papillomaviruses are a common part of the skin and mucosal microbiotas (47).

### *Future of human microbiome*

Our understanding of the human gut microbiome is limited but is evolving as new genomic technologies such a DNA sequencing become more readily available. The microbiome affects host metabolism, but the hows are only now beginning to be understood. Because of the critical role played by the microbiome in host metabolism, it has been suggested that the microbiome may be a potential source of novel therapeutics (12, 16). Detailed characterization of the human gut microbiome is possible because of developments in genomic

technologies. It is possible now to determine the structure and function of microbiomes and the roles individual organisms play in human health and disease (16). The mechanisms of these interactions are being researched globally. There can be no doubt that this is a developing area of research. More recently, it has been shown that microbiomes produce different results under different conditions and at different sites (16, 48). Much remains to be unraveled.

## CONCLUSIONS

Our current understanding of the human microbiome, which plays an important role in human health and disease, is limited. Significant progress, however, has been made in the last two decades. This mini-review indicates that more studies are required using current and new technologies to develop a greater understanding of the role the human microbiome plays in human health and disease and drug development. A Nature "Editorial" advocated for "fully integrated multidisciplinary collaborations" "to convert knowledge of the microbiome into clinical applications" (49).

**CONFLICT ON INTEREST**: None.

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