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Influence of Early Life, Diet, and the Environment on the Microbiome

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Advances in sequencing technology and bioinformatics have greatly enhanced our ability to understand the human microbiome. Over the last decade, a growing body of literature has linked nutrition and the environment to the microbiome and is now thought to be an important contributor to overall health. This paper reviews the literature from the past 10 years to highlight the influence of environmental factors such as diet, early life adversity and stress in shaping and modifying our microbiome towards health and disease. The review shows that many factors such as the mode of delivery, breast milk, stress, diet and medications can greatly influence the development of our gut microbiome and potentially make us more prone to certain diseases. By incorporating environmental factors into models that study the microbiome in the setting of health and disease, may provide a better understanding of disease and potentially new areas of treatment. To highlight this, we will additionally explore the role of the environment and the microbiome in the development of obesity and functional bowel disorders.

Keywords: Gut Microbiome; Environment; Early Life Diet; Stress; Obesity; Irritable Bowel Syndrome.

In the last decade, advances in sequencing technology and bioinformatics have enhanced the ability to understand the human microbiome, and how the environment contributes to shifts in these complex systems over time.[1,2] The human microbiome represents a microbial community that encompasses 10 times more cells and approximately 100 times more genes than contained in the human body alone.[3] Although the major function of the gut microbiome is to aid in the fermentation and energy extraction of indigestible dietary fiber, multiple studies have linked the microbiome to energy homeostasis, immune function, and the development of certain diseases.[4] An increased understanding of the relationship between humans, their microbes, and the environment can help better understand the maintenance of health and the development of disease.[5] This review explores the recent literature related to the influence of environmental factors, such as early life events, diet, pathogens, social factors, and stress, on the complex host-microbe interactions and how these interactions contribute to or are protective against disease. Example disease models, such as obesity and irritable bowel syndrome (IBS), are discussed to highlight how environmental perturbations in the human microbiome contribute to disease.

Environmental Factors

The environment plays a critical part in the composition of the human microbiome (Figure 1). A total of 22%–36% of the interperson microbiome variability is associated with environmental factors and only 1.9%–9% by genetics.[2] Environmental factors start in the early days of life and extend well into adulthood. Next we highlight how environmental factors, such as the mode of delivery, breastfeeding, and introductions of foods, are critical steps in the development of a mature adult microbiome. We later show how such environmental factors as diet, smoking, home life, and stress can induce shifts in the microbiome during the lifespan and make humans more prone to certain diseases.

Early Life Events

Early life events are critical to the development of the human microbiome because they can shape the sequence of microbial community establishment and ultimately the final composition of the mature adult microbiome.[6] This section summarizes how the microbiome matures during the transition from inside the womb, which is a relatively sterile environment, into the external environment after birth when ingestion of milk and solid food are introduced. Microbial community differences during each key early life process are summarized in Table 1.

Prenatal. Studies have suggested that the introduction of microbes can occur as early as during the prenatal period. Although certain intrauterine infections and bacteria from such groups as Burkholderia,

Abbreviations used in this paper: C-section, cesarean section; IBS, irritable bowel syndrome; SCFA, short-chain fatty acid.

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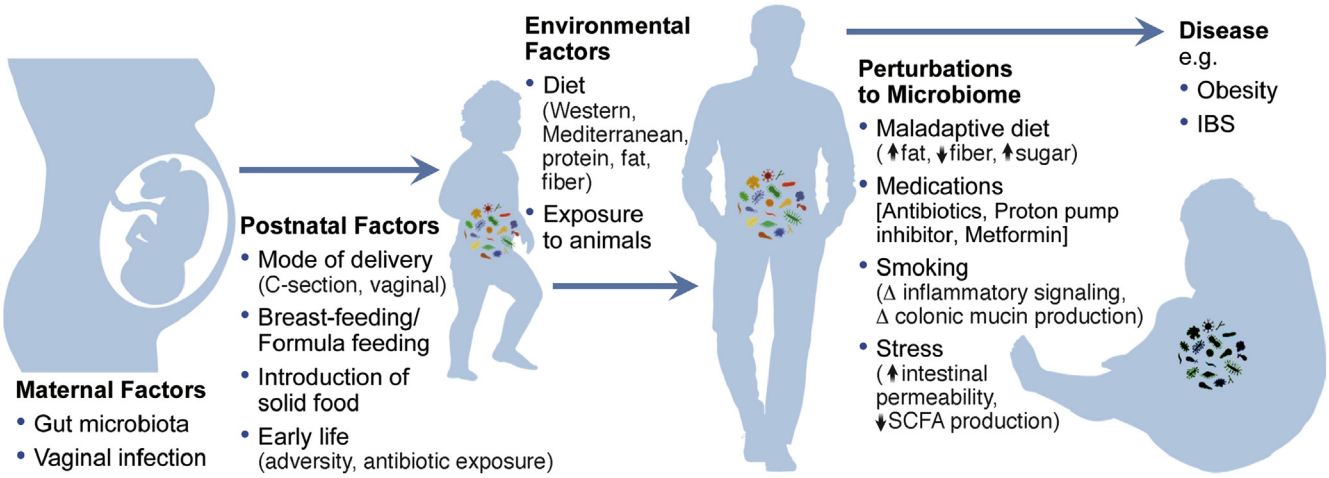

Figure 1. Environmental factors shape and change the microbiome over time and perturbations can lead to disease. Maternal factors: vaginal infections and gut microbiome can lead to bacterial translocation into the uterus. Postnatal factors: mode of delivery, breastfeeding versus formula feeding, introduction of solid food, and early life adversity and antibiotic exposure can shape the developing microbiome in early childhood. Environmental factors across the lifespan: long-term diet and exposure to animals can modify the microbiome throughout childhood and adulthood. Perturbations to the microbiome: medications, such as antibiotics, proton pump inhibitors, and metformin, and a variety of different diets can make individuals more prone to disease, such as inflammatory bowel disease, IBS, and obesity. Stress can lead to changes in the microbiome that affects intestinal permeability and SCFA production. Smoking can cause microbial shifts that change inflammatory signaling and colonic mucin production, all of which can be mechanisms that lead to the development of disease.

Actinomycetales, and Alphaproteobacteria are associated with preterm delivery, it has been shown that a variety of other microbes may be present in the placenta, umbilical cord, amniotic fluid, and meconium of normal pregnancy.[7–9] The maternal microbiome is likely translocated into the uterus via the bloodstream, an idea supported by the detection of labeled *Enterococcus faecium* in the meconium of inoculated pregnant mice.[7] In a recent population-based study, researchers found the most abundant phyla isolated from first-pass meconium were Firmicutes, Proteobacteria, and Bacteriodetes.[10] All bacteria isolated from the umbilical cord blood of healthy neonates belonged to the genus *Enterococcus*, *Streptococcus*, *Staphylococcus*, or *Propionibacterium*.[11] In the placenta, the genus *Bifidobacterium* and *Lactobacillus* were identified.[8]

However, the role and function of these microbes in human health or disease during the prenatal period remains unclear. Because of the possibility of maternal contamination, it is difficult to definitively establish the presence of a prenatal microbiome.[12] Further studies are required to confirm the existence of a viable intrauterine-resident microbiota with the use of adequate controls (such as maternal blood or sampling at a site nearby delivery) to determine if the existence of such a microbiome might affect the future development of the newborn.

Table 1. Microbial Communities Described by Type of Early Life Environmental Factors

Environmental factors	Bacterial community	References
Vaginal delivery vs cesarean section delivery	↑*Lactobacillus* ↑*Prevotella* ↑*Sneathia* ↑*Bifidobacterium* ↑*Bacteroides* ↓*Staphylococcus* ↓*Propionibacterium* ↓*Corynebacterium*	18,19
Breastfeeding vs formula feeding	↑*Bifidobacteria* ↑*Lactobacillus* ↓*Clostridiales* ↓*Proteobacteria*	31,32
Introduction of solid food	↑Lachnospiraceae ↑Ruminococcaceae ↑Bacteroidaceae ↓Lactobacillaceae ↓*Bifidobacterium* ↓Enterococcaceae ↓Enterobacteriaceae	35,36

Delivery. Although the existence of a prenatal microbiome may be controversial, many agree that the first major introduction of a microbial community to a newborn is through delivery.[6] As the newborn is passing through the vaginal canal, it is ultimately introduced to the commensal vaginal and fecal microbiome of the mother.[13] This community of microbes seems to be distinct from the community of nonpregnant women because the vaginal microbiome changes during pregnancy.[14] For example, healthy pregnant women, when compared with nonpregnant women, had lower vaginal bacterial diversity with higher levels of *Lactobacillus*, Clostridiales, Bacteroidales, and Actinomycetales; these levels were associated with gestational age.[15] Beyond the vaginal microbiome, there is also evidence that the community of the maternal gut also changes during the

course of pregnancy. For example, a Finnish cohort of 91 healthy pregnant women demonstrated decreased bacterial diversity as evidenced by increased levels of high-energy-yielding fecal microbiota with increasing gestational age.[16] From the first to the third trimester, the proportion of Proteobacteria, including species of the Enterobacteriaceae family and *Streptococcus* genus, decreased, whereas the proportion of *Faecalibacterium prausnitzii* increased. These changes in the microbiome were independent of prepregnancy body weight, gestational diabetes, diet, and antibiotic use, suggesting that they were caused by the changes of normal pregnancy. These changes in the microbiome have a beneficial role for the mother and neonate by protecting against certain infections, such as *Neisseria gonorrhea* and bacterial vaginosis, and also by permitting greater efficiency for energy harvest to support the growth of the mother and fetus.[16,17]

With these specific pregnancy-related changes effecting the vaginal and fecal microbiome of the mother, it is unsurprising that the mode of delivery also greatly affects how the newborn microbiome develops. The differences seen between cesarean section (C-section) and vaginally delivered babies are drastic. Compared with vaginally born babies, those that are born by C-section without membrane rupture have no vaginal microbes, such as *Lactobacillus*, *Prevotella*, and *Sneathia*. Instead, babies born by C-section are colonized with skin microbes, such as *Staphylococcus*, *Propionibacterium*, and *Corynebacterium*.[18] These babies have a delayed colonization of intestinal microbes, such as *Bacteroides* and *Bifidobacterium*.[19] Although the exact length of time these differences exist is unknown, microbial differences between C-section and vaginally delivered babies have been observed to as far out as 7 years of age.[20] The deficits in the human microbiome associated with C-section deliveries have been implicated in certain childhood autoimmune disease, such as celiac disease, asthma, and type I diabetes.[21] These studies also suggest that restoration of a more "normal" microbiome after C-section deliveries may therefore be beneficial. "Vaginal seeding," or the process by which vaginal fluids are applied to a newborn child delivered by C-section, has been a method used to restore the human microbiome. Although a small pilot study of 4 babies demonstrated the feasibility of restoring the early microbiome of babies born by C-section,[22] the long-term health consequence of such a procedure remains unknown and may even increase the risk of transmittable diseases to the newborn. Therefore, further prospective studies are needed to determine the safety and potential benefits, if any, of these methods used to restore the human microbiome.

Even though the mode of delivery is important to microbial seeding, it may not be the only mode for vertical transmission. Recent human studies have highlighted maternal vertical transmission from multiple different sources, such as the skin, mouth, and gastrointestinal track.[23,24] By examining strain-level data, these studies demonstrated that the direct mother-to-infant transmission changes over time as different floras are introduced through processes, such as skin contact and breastfeeding.[23,24]

Breastfeeding and introduction of solid food. The other major early life events that affect the development and maturation of the newborn microbiome are breastfeeding and the introduction of solid food. Breast milk bacteria, such as *Corynebacterium* and *Rothia*, can seed the infant gut and influence the bacteria that follows, affecting the communities even through adulthood.[25] These early seeding events may be the mechanism by which breast milk can protect children against autoimmune diseases, such as asthma and type 1 diabetes.[26]

Similar to the vaginal microbiome, it has been shown that the microbiome of breast milk also varies with increasing gestational age, and is related to maternal health and mode of delivery.[26,27] The breast milk microbial community is dominated by *Corynebacterium*, *Ralstonia*, *Staphylococcus*, *Streptococcus*, *Serratia*, *Pseudomonas*, *Propionibacterium*, *Sphingomonas*, and Bradyrhizobiaceae.[26] In a study of 107 healthy women who were breastfeeding their infants for the first 30 days of life, the gut microbiome changed in a dose-dependent manner with 27.7% of the mean bacteria being derived from breast milk and 10.3% from areola skin.[26]

Breast milk also contains many important prebiotic compounds, such as human milk oligosaccharides. These sugar polymers are almost exclusively metabolized by the gut microbiome[28] and they can promote the growth of key communities including *Bifidobacterium* spp.[29] Bifidobacteria has been shown to inhibit the growth of pathogenic organisms and improve barrier function in the infant gut.[30] In a mouse model, human milk oligosaccharides were found to be protective in the development of autoimmune disease and obesity.[31,32]

There are clear differences in the composition of the microbiome in infants who are breastfed versus those who are formula fed. Infants who are breastfed have a higher proportion of *Bifidobacterium* and *Lactobacillus* spp, whereas infants who are formula-fed have a higher proportion of Clostridiales and Proteobacteria.[33,34] Formula-fed infants also have lower diversity and richness even after the first year of life as compared with their breastfed counterparts.[33] In a study of 30 preterm infants, breastfeeding was found to be protective against gut immaturity and possibly necrotizing enterocolitis.[35] Several other epidemiologic studies have provided support for the beneficial role of breastfeeding in the development of disease. Formula feeding has been associated with various inflammatory and autoimmune diseases.[36] In contrast, breastfeeding, through its effects on the microbiome, has been associated with a protective role against asthma, autism spectrum disorder, and type 1 diabetes.[26,36]

One of the last major events in early life affecting microbial development is the introduction of solid food. Although breast milk keeps the microbiome in a state that

is characterized by low diversity and *Bifidobacterium* predominance, the introduction of solid food and the cessation of breastfeeding increases adult-associated microbes, such as Lachnospiraceae and Ruminococcaceae.[37] In a Danish study of 330 children between 9 and 36 months of age, Lactobacillaceae, Bifidobacteriaceae, Enterococcaceae, and Enterobacteriaceae decreased, whereas Lachnospiraceae, Ruminococcaceae, and Bacteroidaceae increased during the period when solid foods was being introduced.[38] Another study of 531 children born in 5 different countries showed similar results independent of location, use of antibiotics, mode of delivery, or milk feeding practices, suggesting that these changes were typical of the normal developing microbiome as solid foods are being introduced.[39] This transition is necessary and beneficial. It allows for a microbial community that is better equipped to extract energy and process a diet that is no longer dependent on milk to a diet that is higher in fiber and protein, similar to the diet of a mature adult.

Early life adversity. Recently, researchers are discovering that early life adverse events can manipulate the microbial community in significant ways. In rats, limited nesting stress during postnatal days 2–10 led to a delayed maturation of the hypothalamic-pituitary-adrenal axis that was associated with decreased microbial diversity, an increase of gram-positive cocci, and a reduction of fiber-degrading bacteria.[40] Similar findings were demonstrated in mice and rhesus monkeys when exposed to stress at an early age.[41,42] Finally, in patients with IBS, those that had a microbiome profile distinct from healthy control subjects were more likely to have a history of early adverse events and trauma than those with a microbiome that was more similar to healthy control subjects.[43] Although these studies are predominantly associations, exploring how adverse events and early gut dysbiosis can cause such diseases as IBS is an active research area.

Antibiotic use can also play a significant role during early life. The average U.S. child receives about 1–3 antibiotic courses by the age of 2 years.[44] Several studies have highlighted how antibiotic exposure in children can be associated with an increased risk for obesity, diabetes, allergies, asthma, IBS, and inflammatory bowel disease.[33,45] Children exposed to antibiotics have delayed maturation of their microbiome as compared with their respective control subjects, but whether this is the exact mechanism by which early antibiotics predisposes children to disease is still unclear.[33] In animal models, peripartum antibiotic exposure in the mother can lead to persistent gut dysbiosis in the offspring and colitis in susceptible individuals.[46,47] Although these studies do not provide an exact mechanistic explanation of the effect of antibiotic use on microbiome development or on disease susceptibility, they do highlight that early antibiotic exposure is linked in some way to the normal development of microbial community and to disease development.

Diet

During the early stages of life, breast milk and the introduction of solid food are critical events in the development of the human microbiome. Therefore, it is not surprising that the introduction of diet throughout life has large effects on the human microbiome. The gut microbiota can change within days of a new diet, but to what extent these changes are permanent once the new diet has terminated remains uncertain.[48] In this section, we review the current literature, focusing on popular diets and how the microbiome is connected (summarized in Table 2).

Western diet. The Western diet or standard American diet is a diet characterized by high fat, high sugar, high level of red and processed meat, high levels of refined grains, and a lower level of fiber.[48] Many studies have linked the Western diet to inflammation, diabetes, cardiovascular risks, obesity, and metabolic syndrome.[48,49] Although a Western diet affects many different cell types, such as adipocytes, immune cells, and endocrine cells, there is also a strong link that connects the deleterious effects of a Western diet to shifts in the microbiome.[48] Compared with other indigenous diets, the microbiome on a Western diet is characterized by a significantly lower microbial diversity and species richness.[50] The Western diet microbial composition is classically characterized by an overabundance of the phyla Firmicutes and a decrease in Bacteroidetes.[51] On a genus level, a Western diet shows a decrease in *Bifidobacterium* and *Lactobacillus*, whereas being high in *Enterobacter*.[52] Consequently, the Western diet has been linked to an increase in endotoxemia, a state characterized by decreased intestinal barrier function and increased levels of bacterial lipopolysaccharides and inflammatory signaling.[53,54] Furthermore, a Western diet can possibly lead to permanent microbiome changes that may be responsible for postdieting weight regain or the common concept of yo-yo dieting, which has been linked to higher long-term weight gain, increased obesity-related risk factors, and increased difficulty reducing weight.[55]

Mediterranean diet. In contrast to a Western diet, a Mediterranean diet is considered a healthier diet. It is characterized by a beneficial fatty acid profile; higher intake of fiber, vegetables, and fruits; and with lower intake of sugar and red meat.[56] A recent study demonstrated that out of 153 participants, those who were more adherent to a Mediterranean diet had an increased level of short-chain fatty acids (SCFA), *Prevotella*, and certain Firmicutes, which have all been associated with decreased cardiovascular events.[57] Additionally, they also showed that low adherence to the Mediterranean diet led to decreases in urinary trimethylamine oxide levels, which is associated with higher cardiovascular risk.[57,58] Several studies have shown that consumption of foods encompassing the typical Mediterranean diet improved obesity, inflammation, and lipid profile and were associated with increases in *Lactobacillus*,

Table 2. Influence of Diet on the Gut Microbiome

Diet	Species richness/diversity	Microbes altered	Associated physiological effect	Associated disease state	References
Western diet	↓	↑*Bacteroides* ↑ Enterobacteria ↓ Bifidobacteria ↓ Lactobacilli ↓Eubacteria	Reduced SCFA Higher LPS levels Higher inflammation Decrease gut barrier	Obesity Colon cancer Type 2 diabetes	46–48
Mediterranean diet	↑	↑Bifidobacteria ↑Lactobacilli ↑Eubacteria ↑*Bacteroides* ↑*Prevotella* ↑*Roseburia* ↓*Clostridium*	Increase SCFA Decrease inflammation	Decrease risk of CVD and obesity	46,51,53
Protein					
Plant protein	↑	↑Bifidobacteria ↑Lactobacilli ↓*Bacteroides* ↓*Clostridium perfringes*	Increase SCFAs Increase gut barrier Reduce inflammation		46,56
Animal protein	↑	↑Alistipes ↑Bilophila ↑Clostridia ↓*Roseburia*	Increase TMAO Reduce SCFA Increase amines and sulfides	CVD IBD	46,57,58
Fats					
Unsaturated fats	↑	↑ *Lactobacillus* ↑ Lachnospiraceae ↑ *Streptococcus* ↑ *Akkermansia muciniphila*	Reduce TLR activation Reduce white adipose tissue inflammation	Decrease risk for IBD, obesity, psoriatic arthritis	46,63,64
Saturated fats	↓	↑*Bacteroides* ↑Bilophila ↑*Faecalibacterium prausnitzii*	TLR activation Promote proinflammatory TH1	CVD Obesity Diabetes	46,62
Dietary fiber	↑	↑Lactobacilli ↑Bifidobacteria ↑Clostridia ↑*Prevotella* ↑*Treponema*	SCFA production Anti-inflammatory Anticancer activities	Decrease risk for CVD, obesity, diabetes, colon cancer	46,71

CVD, cardiovascular disease; IBD, inflammatory bowel disease; LPS, lipopolysaccharides; SCFA, short-chain fatty acid; TLR, toll-like receptor; TMAO, trimethylamine N-oxide.

Bifidobacterium, and *Prevotella*, but with decreases in *Clostridium* levels.[52,59]

Protein. Although such diets as the Western diet and the Mediterranean diet have varying compositions of protein, fat, and fiber, studies have found that the gut microbiome can also be affected by these individual components. High protein consumption can have a large effect on human health and the microbiome. Overall, studies have shown that a diet that is high in protein correlates positively with microbial diversity, which is important in intestinal health and barrier function.[60,61] However, not all protein is the same because the source of the protein, whether from animals or plants, can have very different effects on the microbiome.

Diets high in plant-based protein can increase *Bifidobacterium* and *Lactobacillus*, while decreasing pathogenic species, such as *Bacteroides fragilis* and *Clostridium perfringens*.[62] These shifts are associated with higher levels of SCFA and possibly improved gut barrier function.[62] However, diets high in animal protein have consistently been associated with an increase in *Bacteroides*, *Alistipes*, *Bilophila*, and intestinal inflammation.[63,64] Although, diets high in animal protein can have immediate effects associated with weight loss, these shifts can be detrimental to colonic health in the long term.[65] Animal protein is associated with an increased level of microbial-derived toxic metabolites, such as amines and sulfides, within the colon.[66] The proinflammatory state induced by animal protein is one of the potential mechanisms that explained the 3.3-fold increased risk of inflammatory bowel disease in a prospective cohort of 67,581 participants.[63] This observation was corroborated in a recent animal study demonstrating how dietary protein can change the density of the fecal microbiota while increasing intestinal permeability and the severity of dextran sulfate sodium–induced colitis.[67]

Fats. Similar to the changes seen in the microbiome with proteins, fats are also not all equal. A Western diet

that is high in saturated fat and *trans* fat has been linked to obesity and cardiovascular disease, whereas a diet rich in monounsaturated and polyunsaturated fats can be protective.[68] To study this, Fava et al[69] examined 88 subjects at risk for metabolic syndrome and fed them varying amounts and types of fats. They found that diets high in saturated fats led to an increase of *F prausnitzii* and reduced bacterial richness, whereas a diet high in monounsaturated fats did not have any significant shifts in any bacterial genera. In another larger, cross-sectional study with 876 women, Menni et al[70] demonstrated that polyunsaturated fats were associated with an increase in microbial diversity and an increase in members of the Lachnospiraceae family.

Mouse studies have also offered insights regarding differences in microbial composition related to type and amount of fat intake. For example, a recent study found that mice fed lard fat had a higher abundance of *Bacteroides* and *Bilophila*, whereas mice fed fish oil–derived fat had higher levels of *Akkermansia* and *Lactobaccillus*.[71] The mice on a lard fat diet also had higher toll-like receptor activation and white adipose tissue inflammation, in addition to a decrease in insulin sensitivity relative to mice fed on the fish oil–derived fat. Transplantation of the microbiome of the lard fat–fed mice into germ-free mice successfully replicated the donor's inflammatory and metabolic phenotypes, suggesting that these pathways were at least in part mediated by the gut microbiome.[71] Another potential mechanism by which fat intake can affect the host's microbiome is through alterations of the host circadian rhythm.[72] Several recent studies have shown that the microbiome has a diurnal variation in structure and function and that these variations can modify the host circadian clock genes.[73,74] A diet high in saturated fats disturbs normal diurnal microbial patterns leading to host dysregulation of circadian rhythm and metabolism, potentially promoting diet-induced obesity.[72]

Dietary fiber. Unlike protein and fat, the gut microbiome is absolutely necessary for the metabolism of dietary fiber. Carbohydrates, in particular those with dietary fiber, are a principal source of energy for colonic microbes. The recommended daily intake of fiber per day is 25–30 g. The average American only ingests about 15 g per day, highlighting the substantial deficit in fiber intake needed for the healthy function of the colon.[75] Evolutionarily, the human diet was very heavy in dietary fiber as compared with fiber content in the current more modern diets. The diet and microbiome of indigenous populations in Papua New Guinea, Tanzania, and the Amazon rainforest are markedly different from those in the industrialized societies.[76] With the advent of farming and industrialization, modern diets have become heavier in protein and fat while lighter in dietary fiber. This dietary shift has led to a reduction in microbial diversity that has been linked to a higher susceptibility of more Western diseases, such as diabetes, obesity, and inflammatory bowel disease.[76] Several studies have shown fiber to be protective against such diseases as type II diabetes, cardiovascular disease, colon cancer, and obesity.[77,78] One of the main mechanism by which fiber and the microbiome impact health is through the production of SCFAs. SCFAs are the major product of fiber fermentation and represent a major substrate for energy for colonic cells. Acetate, propionate, and butyrate are the major SCFAs, accounting for 90% of the total, with ratios approximating 65:20:15.[79] SCFA can affect gene regulation and colonocyte proliferation and inflammation.[80] In diversion colitis, a disease state characterized by distal inflammation, the role of butyrate enemas as a treatment highlights the importance of SCFA to colonic health. The capacity of SCFA to regulate colonocyte differentiation and apoptosis further underscores its potential to protect against colon cancer.[80] In mouse models of obesity, fiber supplementation prevented inflammation and metabolic syndrome by restoring interleukin-22 production within the colon.[81] Diets high in fiber tend to have higher microbial richness and diversity with an abundance in such genera as *Prevotella* and *Treponema*.[82] These shifts have been linked to a decrease in inflammatory signaling, protection against obesity, and possibly decrease in the presence of colorectal cancer.[82]

Other Environmental Factors

Even though early life events and diet can shape the way the microbiome is formed, there are many other environmental exposures throughout the lifespan into adulthood that can lead to changes in microbial composition and ultimately health (Figure 1).

Pharmaceuticals

One of the most significant ways to affect health and the microbiome is through the use of drugs. Antibiotics are the most well-known class of medications to cause shifts in the microbiome. Although the microbial community mostly returns to its preantibiotic state, studies have suggested that postantibiotic exposure can lead to a new steady state that is different from the original preantibiotic community.[83] This new steady state that emerges after antibiotic exposure increases the host's susceptibility to infection, atopic diseases, and metabolic syndrome.[84] Long-term studies have shown that these effects of antibiotics can be long lasting, as far out as 4 years postexposure.[85] Antibiotics may also expand antibiotic-resistant strains, which can act as a reservoir for resistance genes in the gut microbiome.[86]

The effect of antibiotics on the microbiome is best highlighted by the research regarding *Clostridium difficile*. Changes in the gut microenvironment after the exposure of antibiotics creates a metabolic environment that favors *C difficile* germination and colonization.[87] *C difficile* can be a debilitating disease for patients and

costly to the medical system. Although the mainstay of *C difficile* treatment is further antibiotic therapy, fecal microbiota transplantation has gained substantial credibility for the treatment of recurrent *C difficile*.[88] The first randomized trial of fecal microbiota transplantation demonstrated higher rates of resolution of *C difficile* infection when compared with placebo (81% vs 31%).[89] Since then, several other studies have shown the efficacy and safety of fecal microbiota transplantation for patients with *C difficile*.[88]

Medications other than antibiotics have also been associated with changes in the human microbiome. Proton pump inhibitors and metformin are 2 notable common examples, with more than 100 million users of either medication in the United States alone.[90,91] Through reduced acid production and hence higher luminal pH, proton pump inhibitors have been shown to alter the flora of the stomach in chronic users and increase the incidence of small bacterial overgrowth.[92] In a study examining individuals with type 2 diabetes, Wu et al[93] demonstrated that the introduction of metformin strongly alters the gut microbiome. They further demonstrated that the beneficial effects of metformin can be transferred to germ-free mice through fecal transplantation, providing support that the alteration of the gut microbiome mediates some of metformin's antidiabetic effects.[93] The idea of nonantibiotic drugs effecting the microbiome led Maier et al[94] to screen more than 1000 marketed drugs highlighting that 24% of them could affect bacterial growth. Although these studies demonstrate dramatic effects on the gut microbiome, further research is needed to see how these drugs can affect microbial communities and how these changes are related to drug efficacy.

Family Life

Pets. Other than pharmaceuticals, household pets and animal exposure can also influence the microbiome. In a study of 60 families with or without pets, household members' skin flora was more similar to each other and to their pets than to other households without pets.[95] This highlights the theory that pets play a critical part as a conduit to the environment and their human coinhabitants. Many studies have reported that the exposure during early life to pets or to farm animals is associated with less pediatric allergy.[96,97] The theory is related to the idea that pets and farm animals introduce environmental allergens that sensitize the developing immune system of the child.[98] The fact that these exposures are mediated through microbes is supported by studies that demonstrate how certain bacterial species, such as *Acinetobacter lwofii* and *Lactococcus lactis*, which are isolated from farming communities, can reduce allergic responses in mouse models.[99] In a study of 24 healthy, full-term infants, microbial richness and diversity of fecal samples were higher in infants living with pets.[100] Infants living with pets showed a reduction of Bifidobacteriaceae and an increase in Peptostreptococcaceae. Another study found that *Bifidobacterium longum* levels were higher in fecal samples of infants with pet exposure compared with those without and that the abundance of *B longum* was inversely associated with the onset of wheezy bronchitis. However, the role of animal exposure on the adult gut microbiome still remains unclear.

Smoking. Another important environmental exposure is smoking. Although the link between smoking and disease has been well established, several studies have emerged over the last several years that explore the influence of smoking on the oral, esophageal, and gastric microbiome.[101] Within the mouth, smokers tend to have an increase in anaerobic bacteria leading to shifts in a community that possibly favors pathogenic microbes.[101] In regards to the intestinal microbiome, mouse models and human studies have indicated that smoking can affect microbial composition and intestinal inflammation. A recent study that used side-stream smoke on wild-type C57BL/6 mice demonstrated that smoke can increase the abundance of *Clostridium clostridiforme* and decrease *Lactococcus*, *Ruminococcus albus*, and the family of Enterobacteriacae.[102] These shifts were associated with a change in tight junction proteins and inflammatory signaling.

In humans, smoking has been associated with a decrease in Firmicutes and Actinobacteria, in addition to an increase in Bacteroidetes and Proteobacteria.[103] An observational study demonstrated that after smoking cessation, the levels of Firmicutes and Actinobacteria reversed and microbial diversity increases.[103,104] Similar findings were found in patients with active Crohn's disease. In a study of 103 smoking and nonsmoking patients with active Crohn's disease compared with 66 smoking and nonsmoking healthy control subjects, active smoking was independently associated with higher abundance of *Bacteroides* and *Prevotella*, genera commonly associated with colonic inflammation.[105,106] The exact mechanism on how smoking affects the microbiome is an active area of research; however, it may be linked to alterations of intestinal tight junction, immune signaling, and/or mucin production.[102,107] Whether these changes in the intestinal microbiome mediate some of the deleterious effects of smoking remains unclear.

Stress. In recent years there is growing evidence that there are bidirectional communication pathways between the gut microbiome and the brain, and recent studies have highlighted that this communication takes place through various processes including the vagus nerve, gut hormone signaling, inflammatory processes, and neurotransmitter production, just to name a few.[108,109] Therefore, real or perceived stress can modulate this bidirectional communication in a way that increases dysbiosis and increases an individual's propensity to develop disease.[110,111] For example, stress can trigger the flight or fight response, increasing the production of corticotropin-releasing hormone and

catecholamine production from the central nervous system, which then modulates gut microbiome function.[111,112] However, bottom up processes involving release of microbial products, such as tryptophan or serotonin, during stressful events can contribute to the enteric dysbiosis, increased intestinal permeability, and the release of certain neurotransmitters associated with certain diseases.[113] Studies have also shown that in the absence of stress and during stress-reducing practices, such as meditation, the microbiota increase production of SCFAs and anti-inflammatory processes, further highlighting the negative effects of stress on gut function and health.[111,114] These studies highlight the importance of considering the modulation of the brain-gut-microbiome axis as an effective strategy for the development of treatments for various disorders.

Clinical Implications of Altered Human Microbiome

Although previous sections have shown how environmental exposures, such as diet, stress, pets, and medications, can affect the microbiome, perturbations in the microbiome can also be a potential cause for disease (Figure 1). Although there are many diseases that are associated with microbial dysbiosis, we review the diseases with the best causal relationship between the environment and the microbiome: obesity and IBS.

Obesity

The previous section underscored the notable shifts in the microbiome that occur with a Western diet and a high-fat diet. These diets are tightly linked to obesity and many believe that the microbiome is a key mediator. One of the early seminal papers that linked obesity and diet to the gut microbiome came from Turnbaugh et al in 2006.[115] They used human and mice16s rRNA analyses to highlight how obesity and a high-fat diet were related to an increased ratio of Firmicutes to Bacteroidetes and that colonization of this obesity-related microbial profile could recapitulate the obese phenotype in germ-free mice. Since then, animal studies have shown that gut microbes can influence weight gain and adiposity by affecting host gene expression, metabolic pathways, and the gut-brain axis.[116] Moreover, weight loss interventions have also been associated with distinct shifts in the gut microbiome. A variety of surgical weight loss intervention in humans and in animals have shown distinct and long-lasting microbial profile differences.[117] A study using Roux-en-Y gastric bypass in mice led to a sustained increase in *Escherichia* and *Akkermansia* and that the transfer of fecal material of post–bariatric surgery mice into nonoperated germ-free mice can successfully transfer the lean phenotype.[118] Mechanisms by which microbes can cause host metabolic changes include shifts in SCFA production; changes in energy extraction; decreased gut hormones, such as glucagon-like peptide and peptide YY; and changes in toll-like receptor signaling.[119]

Irritable Bowel Syndrome

Much like obesity, IBS is one of the most common diseases seen by primary care doctors and gastroenterologists. Factors linked to the pathogenesis of IBS include a history of enteric infection, alteration in the gut-brain axis, changes in visceral sensitivity, and modifications in the gut microbiome.[43,120] Studies have linked early life stress and adverse events to microbial shifts that could potentially be the cause of visceral sensitivity and subsequent IBS development.[43,108,121] Patients with IBS generally had less *Lactobacillus*, *Bifidobacterium*, and *F prausnitzii* than healthy control subjects.[113] Although it is unclear which changes are necessary and/or sufficient, studies in germ-free mice transplanted with fecal microbes from patients with IBS cause alterations in gut permeability, motility, visceral perception, and food processing that ultimately triggers IBS symptoms.[122] The treatment of IBS is varied and often personalized, but certain therapeutics for IBS with diarrhea often target the gut microbiota. These include the use of nonsystemic antibiotic rifaximin; dietary modification with a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet; and certain probiotic formulations.[122] Even though these treatments are promising, more research is required to elucidate how alterations in the gut microbiota can affect disease outcome in other subtypes of IBS. This section has highlighted how certain microbial communities can lead to certain end points, such as weight loss and patient symptomology. However, whether these microbial communities lead to similar end points outside of these specific disease states remains unknown and remains an area of active investigation.

Limitations of Current Methods and Future Directions

Obesity and IBS are 2 example diseases that highlight the significant gains microbiome research has undergone in the last decade. Despite those gains, there is still much more research to be done. To date, much of the current research in human samples has been predominantly association studies, with little insight into the underlying mechanisms associated with altered gut microbiome and disease. The limitation of these studies is that they are unable to clearly state if dysbiosis is a cause of disease or merely a by-product. Currently, there is an important shift away from these types of analyses and a move toward investigations to define mechanisms by using germ-free animals and multi'omics analysis.[5] By starting with a multi'omics approach that integrates metabolomics, proteomics, and 16S rRNA analysis, for example,

researchers can more clearly postulate microbial-dependent mechanistic pathways that lead to disease. By recapitulating the disease phenotype through microbial transplantation in germ-free animal models, researchers can then clearly model out the direct causative effects of dysbiosis to disease development. Even though most mechanistic studies have been done in animals, the observations seen in animal models and how they have correlated in humans have provided a deeper understanding of microbial-host signaling and pathogenesis of diseases. Future research may also focus on the interplay between the microbiome and epigenetics. There is an emerging body of literature on the role of transgenerational epigenetic inheritance on health and disease.[123] As reviewed here, stress and the environment play a major role in the development and stability of the microbiome over time. But exactly how these signals can alter host epigenetics, particularly across generations, is an active area of research.

The other current limitation in the field is the lack of standardization across similar studies or even across same disease groups. Currently, there are not any definitive studies on how microbial analysis differ across the various sampling techniques and the many analytical pipelines. For example, it is difficult to compare studies of similar patients if sampling was done using differing methods, such as via fresh or frozen stool collection, endoscopic aspiration, or via mucosal scrapings/biopsy. As the field matures, sample collection and processing need to be standardized to ensure reproducibility and to allow researchers to readily compare outcomes across different studies using different patient groups.

Another major shift involves cheaper sequencing technology to obtain strain-level data. 16S rRNA sequencing is currently the most commonly used method for microbiome analysis.[5] However, 16S rRNA sequencing is only able to obtain species-level resolution. Because of horizontal gene transfer, bacterial genomes of strains even within the same species can be potentially diverse.[124] Although shotgun sequencing is available and able to provide strain-level resolution, it is out of reach for many because of its high costs. But with greater advances in sequencing technology, this cost may be reduced enough for widespread use in the future.[125] Even though there is a long way to go, improvements in sequencing throughput and accuracy, complemented by an upsurge of novel bioinformatics analysis of proteomes, metabolomes, and transcriptomes, has brought the field closer to a better understanding of human disease and treatment.

Conclusions

The microbiome is a complex system at the intersection of environment and health. Although many aspects of the environment can cause shifts in the microbiome, we see through the example of obesity and IBS that the perturbations of this intricate system can also be at the core of disease. Even though longitudinal studies are still required to determine the direct relationship between environmental factors and gut dysbiosis with disease development, improvements in sequencing technology and an ever-growing field of bioinformatics are providing new daily insights on how environment, heath, and microbes are linked. This has implications for not only better understanding the underlying pathophysiology of disease but can also help better develop targeted treatments based on specific microbial molecules.

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