Supplement Article

Potential role of the intestinal microbiota in programming health and disease

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The composition of the microbiota varies according to prenatal events, delivery methods, infant feeding, infant care environment, and antibiotic use. Postnatal gut function and immune development are largely influenced by the intestinal microbiota. Emerging evidence has shown that early microbiota colonization may influence the occurrence of later diseases (microbial programming). The vast majority of microbial species (commensals) give rise to symbiotic host–bacterial interactions that are fundamental for human health. However, changes in the composition of the gut microbiota (dysbiosis) may be associated with several clinical conditions, including obesity and metabolic diseases, autoimmune diseases and allergy, acute and chronic intestinal inflammation, irritable bowel syndrome (IBS), allergic gastroenteritis (e.g., eosinophilic gastroenteritis and allergic IBS), and necrotizing enterocolitis. Based on recent advances, modulation of gut microbiota with probiotics, prebiotics, or fermented dairy products has been suggested as a treatment of, or prevention for, different disorders such as IBS, infectious diarrhea, allergic disease, and necrotizing enterocolitis.

INTRODUCTION

The microbial communities hosted by the human gut comprise a new, fascinating, and promising area for understanding the development of gut functions and some health disorders and diseases, as well as their treatment and prevention. The microbial communities, previously called the "intestinal microflora," are composed of approximately 10^{14} bacteria, which represent approximately 10 times the number of cells in the human body.[1,2] These bacterial communities have been forged over millennia of co-evolution with humans to achieve a symbiotic relationship that leads to physiological homeostasis. Although the terms "microbiota" and "microbiome" are often used interchangeably, microbiota refers to the organisms that comprise the microbial community, whereas the microbiome refers to the collective genomes of the microbes, which are composed of bacteria, bacteriophages, fungi, protozoa, and viruses that live inside and on the human body. The microbiota is now considered a human organ, with its own functions, i.e., modulating expression of genes involved in mucosal barrier fortification, angiogenesis, and postnatal intestinal maturation.[3,4] The intestinal microbiota is involved in normal digestion and affects energy harvest from the diet and energy storage in the host, fermenting unavailable energy substrates such as fiber to short-chain fatty acids (SCFAs).[3,4]

The diversity of gut microbiota has been revealed by the application of high-throughput sequencing of the microbial ribosomal RNA or DNA (metagenome).[4] This has clearly shown that the microbiota is represented by more than 1500 microbial species. Metagenomic analyses and 16 S rRNA gene sequencing have shown that

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Firmicutes and *Bacteroidetes* are the 2 dominant bacterial phyla in most individuals. Other phyla include *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia*.[4] More recently, groups of bacterial families have been classified into enterotypes on the basis of their functions. For example, classification may be based on metabolism of dietary components and ability to handle drugs. The classification should help to further understanding of the role of enteric microbiota in health and disease.[5] Aging is associated with changes in diversity of noncultured species, with a greater proportion of *Bacteroides* species, a distinct abundance of *Clostridium* clusters, an increased enterobacteria population, and a lower number of bifidobacteria.[6,7]

From birth, the normal gut microbiota contributes to the development of gut function, educates the immune system, contributes to the regulation and maintenance of intestinal barrier function, provides protection against infection, and promotes tolerance of foods. The vast majority of microbial species give rise to symbiotic host–bacteria interactions that are fundamental for human health. Disruption of the establishment of a stable normal gut microbiota may be associated with, or even contribute to, the pathogenesis of disease. Unfavorable changes in the composition of gut microbiota, referred to as dysbiosis, may be associated with several clinical conditions such as nosocomial infection, necrotizing enterocolitis (NEC) in premature infants, inflammatory bowel disease (IBD), obesity, autoimmune diseases, and allergies.

This review aims to highlight factors that influence the gut microbiota soon after birth and the potential harmful effects that occur later in life. Indeed, the intestinal microbiome may be influenced by the environment, resulting in modification of the risk profile for childhood and adult diseases. Due to the association between dysbiosis and disease, an emerging concept is so-called "microbial programming," which is analogous to, or even a component of, "metabolic programming."

FACTORS THAT INFLUENCE INTESTINAL MICROBIAL COLONIZATION

The important role of the resident microflora in human health has gained increased recognition over the past few decades. However, it is not possible to define a "normal microbiome," as healthy individuals can harbor different microbial consortia. It is important to consider the functional capability or the genetic potential of the microbiome (e.g., the bacterial metagenome).[4,5]

Originally, the intestine was thought to be sterile during fetal life. However, the finding of microbial DNA in meconium of preterm and term infants offers the opportunity to further explore the intra-amniotic microbial milieu of newly born infants.[8] Studies have contributed to the characterization of the uterine microbiome, specifically that present in amniotic fluid, fetal membranes, and placenta.[9,10] When present in the uterine compartment, some bacteria such as *Ureaplasma* spp. and *Fusobacterium* spp. appear to be the most significantly associated with negative pregnancy outcomes (e.g., prematurity).[9] Upon delivery, the neonate is exposed to microbes from a variety of sources, including maternal vaginal, fecal, and skin bacteria. Initial colonization of the infant gut is highly influenced by the mother's vaginal and fecal bacterial communities, which include facultative anaerobes such as streptococci and enterobacteriaceae. Indeed, the first and most important phase of normal colonization occurs when the newborn fetus passes through the birth canal and ingests maternal vaginal and colonic microorganisms. These bacteria further proliferate when oral feeding is initiated. After 48 h, the number of bacteria is already as high as approximately 10^4–10^6 colony-forming units per milliliter of intestinal contents. Many factors may influence this process, including gestational length (preterm or full-term), mode of delivery (vaginal or cesarean section), infant diet (breastfeeding or formula), birth environment of neonatal intensive care unit, and use of drugs such as antibiotics and proton pump inhibitors[11–13] (Figure 1).

Infants delivered by cesarean section have a reduced number of bacteria compared with vaginally delivered infants, and colonization by bifidobacteria can be delayed by up to 6 months.[12] The microbiota of vaginally delivered infants mirrors the mother's vaginal and intestinal microbiota. These infants exhibit bacterial communities composed of prominent genera such as *Lactobacillus*, *Prevotella*, *Escherichia*, *Bacteroides*, and *Bifidobacterium*. Biasucci et al.[12] reported that after delivery by cesarean section, the intestinal microbiota is characterized by an absence of bifidobacteria. Vaginally delivered neonates, even if they showed individual microbial profiles, were characterized by predominant groups such as *Bifidobacterium longum* and *Bifidobacterium catenulatum*.[12] By using multiplexed 16 S rRNA gene pyrosequencing to characterize bacterial communities from mothers and their newborns, Dominguez-Bello et al.[14] found that in direct contrast to the highly differentiated communities of their mothers, neonates harbored bacterial communities that were undifferentiated across multiple body habitats, regardless of delivery mode. The results show that vaginally delivered infants acquired bacterial communities resembling their own mother's vaginal microbiota, dominated by *Lactobacillus*, *Prevotella*, and *Sneathia* spp.; cesarean section-delivered infants harbored bacterial communities similar to those found on the skin surface, dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* spp.

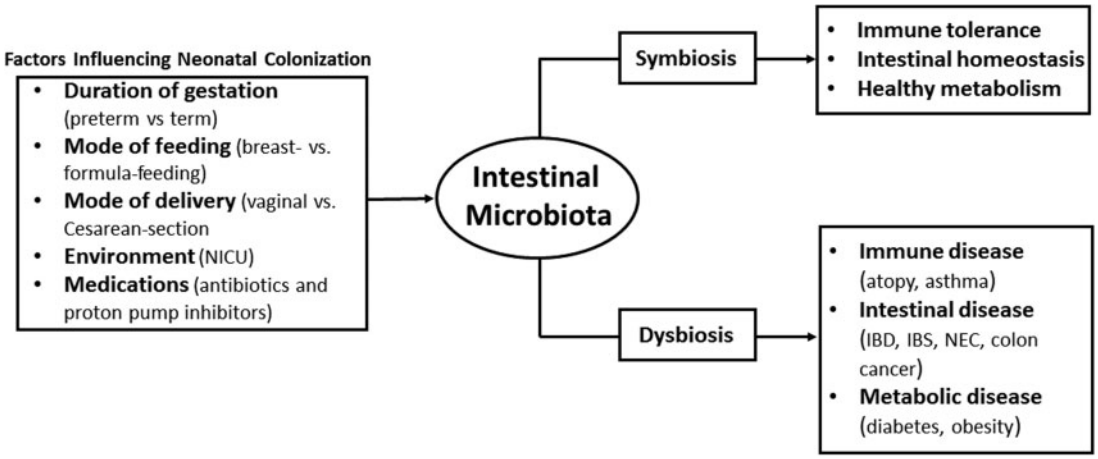

Figure 1 **Illustration of possible programming by the intestinal microbiota.** Abbreviations: IBD, irritable bowel disease; IBS, irritable bowel syndrome; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit

The pattern of bacterial colonization in the preterm infant differs from that in the healthy, full-term neonatal gut.[15] This "abnormal" colonization, mostly due to the routine use of sterile formula and antibiotics in neonatal intensive care units, could have a central role in feeding intolerance and in the development of NEC, a severe disease that primarily affects premature infants and often leads to death or extensive bowel resection (short bowel syndrome).[16]

The nature of oral feeding may influence the short-term composition of an infant's gut microbiota.[17] Human milk contains beneficial factors for the intestinal microbiota, such as human milk oligosaccharides (HMOs).[18] They function as prebiotics by stimulating the growth of *Bifidobacterium* and *Lactobacillus* spp., thereby selectively altering the microbial composition of the intestine.[18] It is likely that evolutionary selective pressure has equipped *Bifidobacterium infantis* with multiple enzymes for deconstructing human milk glycans. As a result, this subspecies is able to outcompete other bifidobacteria as well as other commensals and pathogens in the gut lumen of healthy, breastfed infants.[18] In formula-fed infants, enterococci, *Bacteroides* spp., and clostridia predominate.[19] In breastfed infants aged 1 month, there is a direct association between the levels of secretory immunoglobulin-A (IgA) in intestinal secretions and the number of bifidobacteria in the gut. Moreover, the level of the inflammatory cytokine interleukin-6 (IL-6) in intestinal secretions is inversely related to the number of *Bacteroides fragilis* organisms in the gut at 1 month of age.[20] Excessive inflammation in infancy may cause an increased risk of age-related gastroenteritis. It is suggested that HMOs not only stimulate *B. infantis* proliferation, they also activate important genes involved in the pro- and anti-inflammatory balance within the intestinal mucosa.[21,22] These observations provide additional evidence of the beneficial effects of breastfeeding for the newborn infant. In addition to HMOs, human milk contains other glycans with antimicrobial and prebiotic activity that are thought to have beneficial effects for the infant.[23] Moreover, there is accumulating evidence that human milk is not sterile but contains maternal-derived bacterial molecular motifs that are thought to influence the newborn's immune system development.[24] This procedure, referred to as "bacterial imprinting," requires further study.[24] However, comparative studies in infants fed infant formula have not carefully documented their effects on gut microbiota or health-promoting bacteria. Colonizing bacteria exist in a symbiotic relationship with the host, and immunologic homeostasis exists, protecting the infant from diseases. There is increasing evidence that the microbiome does not reach its adult composition until 2–3 years of age.[25] Finally, host defenses can be improved by feeding breast milk, which helps the immature intestinal mucosal immune system to develop and respond appropriately to highly variable bacterial colonization and food antigen loads. Later in life, the type of food consumed influences the intestinal microbiota profile.[26] In that regard, SCFAs, play a central role. SCFAs are organic fatty acids produced in the distal gut by bacterial fermentation of macrofibrous material that escapes digestion in the upper gastrointestinal (GI) tract and enters the colon. SCFAs are central to the physiology and metabolism of the colon. Resident bacteria can also metabolize dietary carcinogens, synthesize vitamins, and assist in the absorption of various molecules. Most of the SCFAs present in the colon (90%–95%) consist of acetate (60%), propionate (25%), and butyrate (15%). Butyrate is considered a major energy source for the colonic epithelium. SCFAs have been associated with improvement of metabolic functions in type 2 diabetes mellitus, including the control of blood glucose levels, insulin resistance, and Glucagon-like peptide

(GLP)-1 secretion.[27] These effects result from the different tissues that express SCFA receptors and, thus, become capable of responding to the beneficial effects induced by these molecules.[27]

Antibiotic usage changes gut microbiota. For example, administration of broad-spectrum antibiotics significantly reduced the relative abundance of *Bacteroidetes*, with a concurrent increase in *Firmicutes*.[28] Rapid reduction in microbial diversity is often observed after ingestion of antibiotics in infants aged <1 year, and complete recovery of the initial bacterial composition is not always achieved.[29] The understanding of the dynamics and mechanisms that underlie functional changes in the microbiome in response to antibiotic treatments remains limited. The response depends on the type of antibiotics, length of dosing, and baseline microbiome. A recent study provides an extensive description of gut microbiota responses to follow-up β-lactam therapy.[30] The results demonstrate that antibiotics that target specific pathogenic infections and diseases may alter gut microbial ecology and interactions with host metabolism to a much greater degree than previously assumed.[30]

Interestingly, it was found that in very low birth weight infants the meconium is not sterile and is less diverse from birth in infants who develop late-onset sepsis.[31] Prolonged use of antibiotics, which is common in preterm infants, profoundly decreased microbial diversity and promoted the growth of predominant pathogens such as *Clostridium*, *Klebsiella*, and *Veillonella* spp., which have been associated with neonatal sepsis. The authors suggested that there may be a "healthy microbiome" present in extremely premature neonates that may ameliorate risk of sepsis.[31] More research is needed to determine whether altered antibiotics, probiotics, or other novel therapies can reestablish a healthy microbiome in neonates. It was recently shown that disruption of the microbiota during maturation with low-dose antibiotic exposure can alter host metabolism and adiposity in mice.[32] By using low-dose penicillin delivered from birth in a mouse model, Cox et al.[32] demonstrated metabolic alterations and changes in ileal expression of genes involved in immunity. Administration of low-dose penicillin, even limited to early life, sufficiently perturbs the microbiota so as to modify body composition, indicating that microbiota interactions in infancy may be critical determinants of long-term host metabolic effects.

ROLES OF MICROBIOTA IN GUT FUNCTION DEVELOPMENT

Microbial colonization of the intestine is thought to play a particularly important role in postnatal development of the GI, metabolic, and immune systems. For example, Hooper et al.[33] reported that a single bacterial species, *Bacteroides thetaiotaomicron*, a prominent component of the normal mouse and human intestinal microbiome, modulates the expression of genes involved in several important intestinal functions, including nutrient absorption, mucosal barrier fortification, xenobiotic metabolism, angiogenesis, and postnatal intestinal maturation. Collectively, the gut microbiota also influences tissue regeneration, permeability of the epithelium, vascularization of the gut, and tissue homeostasis. More recently, Rakoff-Nahoum et al.[34] investigated changes in global intestinal gene expression through postnatal developmental transitions in wild-type mice. By using myeloid differentiation factor 88/TIR-domain-containing adapter-inducing interferon-β double-knockout mice, they reported profound alterations in small and large intestinal transcriptomes accompanying both weaning and puberty in wild-type mice. They defined the role of Toll-like receptors and IL-1 receptor family member signaling in postnatal gene expression programs and select ontogeny-specific phenotypes such as vascular and smooth muscle development and neonatal epithelial and mast cell homeostasis.[34]

The relationship between the gut microbiota and changes in GI motility has been investigated. For example, bacterial metabolites such as SCFAs and deconjugated bile salts have been shown to generate potent motor responses.[35] A study in mice showed that colonized mice had a faster intestinal transit time than germ-free mice.[36]

The gut microbiota protects against pathogens by competing for nutrients and receptors, by producing antimicrobial compounds, and by stimulating a multiple-cell signaling process that can limit the release of virulence factors.[37] Studies in germ-free mice have shown structural abnormalities such as reduced intestinal surface area and decreased epithelial cell turnover compared with colonized mice.[38] The gut microbiota also influences the development of the intestinal barrier and its functions.

The microbiota exerts many roles in the development of the gut immune system, especially by achieving appropriate programming of mucosal immunity. The roles of the gut microbiota include modulating development of the intestinal mucous layer and lymphoid structures, immune-cell differentiation, and production of immune mediators. Intestinal microbiota exert positive stimulatory effects on the intestinal innate and adaptive immune systems.[39] The intestine is an important immune organ, harboring approximately 60% of total immunoglobulins, $>10^6$ lymphocytes/g tissue, and the largest pool of immune-competent cells of the body within the intestinal mucosa. For instance, in response to

intestinal colonization, the number of T lymphocytes and plasmocytes within the intestinal lamina propria is clearly augmented. Whereas IgA-producing cells are virtually absent in germ-free mice, high IgA levels are detectable within the mucosa upon bacterial colonization.[40]

The innate immune system must discriminate between pathogens and harmless commensal bacteria of the intestinal microbiota. Pathogen recognition receptors such as Toll-like receptors and nucleotide-binding oligomerization domain receptors allow for recognition of a restricted number of bacterial motifs (either microbe-associated molecular patterns or, in the case of pathogens, pathogen-associated molecular patterns).[41] Both types of pathogen recognition receptors are naturally expressed by intestinal epithelial and antigen-presenting cells such as dendritic cells or macrophages, which enable them to easily sense any bacterial motifs. To avoid a permanent and unwanted stimulation of the innate immune system, the intestinal epithelial barrier is protected by a highly viscous microfilm, which prevents close contact between commensal bacteria and intestinal epithelial cells. However, upon contact, the enterocyte is able to send "alarm signals" in the form of chemokines or cytokines to the mucosal adaptive immune system and, at the same time, to secrete bactericidic peptides into the lumen.[42] This mechanism might be altered in some patients with IBD. Proinflammatory signals of enterocytes or antigen-presenting cells within the intestinal mucosa result in a rapid upregulation of homing the receptors on endothelial cells and the chemoattraction of inflammatory cells to the site of infection.

Intestinal mucosal barrier function can be defined as the capacity of the intestine to host the commensal bacteria and molecules, while preserving the ability to absorb nutrients and prevent the invasion of host tissues by resident bacteria. The dense communities of bacteria in the intestine are separated from body tissues by a monolayer of intestinal epithelial cells. The assembly of the multiple components of the intestinal barrier is initiated during fetal development and continues during early postnatal life. Thus, the intestinal barrier has not completely developed soon after birth, particularly in preterm infants. The central element is the epithelial layer, which physically separates the lumen and the internal milieu and is in charge of vectorial transport of ions, nutrients, and other substances. The secretion of mucus-forming mucins, sIgA, and antimicrobial peptides reinforces the mucosal barrier on the extra-epithelial side, while a variety of immune cells contributes to mucosal defense on the inner side. Thus, the mucosal barrier is physical, biochemical, and immune in nature. In addition, the microbiota may be viewed as part of this system because of the mutual influence that occurs between the host and the luminal microorganisms.

Alteration of the mucosal barrier function with accompanying increased permeability and/or bacterial translocation has been linked with a variety of conditions, including metabolic disorders (type 2 diabetes mellitus, insulin resistance, obesity) and IBD.[43] Genetic and environmental factors may converge to evoke a defective function of the barrier, which may, in turn, lead to overt inflammation of the intestine as a result of an exacerbated immune reaction toward the microbiota. IBD may be both precipitated and treated by either stimulation or downregulation of the different elements of the mucosal barrier, with the outcome depending on timing, the cell type affected, and other factors. Fermentation products of commensal bacteria have been shown to enhance the intestinal barrier function by facilitating the assembly of tight junctions through the activation of adenosine mono-phosphate (AMP)-activated protein kinase.[44] On the other hand, the deletion of all detectable commensal gut microbiota by a 4-week oral administration of 4 antibiotics (vancomycin, neomycin, metronidazole, and ampicillin) leads to more severe intestinal mucosal injury in a dextran–sulfate–sodium-induced mouse colitis model.[45] Early treatments with broad-spectrum antibiotics have been shown to alter the GI tract gene expression profile and intestinal barrier development.[46] This underlines the importance of normal bacterial colonization in the development and maintenance of the intestinal barrier. Antibiotic therapy between birth and age 5 years might increase the risk of Crohn's disease by disrupting the pattern of gut colonization.[47] A recent metaanalysis confirmed that antibiotic use is associated with increased risk of new-onset Crohn's disease, but not ulcerative colitis.[48]

EPIDEMIOLOGICAL EVIDENCE OF LINKS BETWEEN BACTERIAL COLONIZATION AND DISEASES

Epidemiological studies have suggested, or even established, an association between the mode of delivery or the use of antibiotics and the occurrence of health disorders or diseases. The use of cesarean section delivery has markedly increased in the past 2 decades in a large number of middle- and high-income countries in the world, reaching an unprecedented level of 50.1% in Brazil in 2009.[49,50] Although these operations can be lifesaving, both for mother and child, there is concern that increasing rates also may have short- and long-term deleterious effects. Studies suggested that children delivered by cesarean section could have increased risk later in life of atopy and allergies,[51] asthma,[52] and type 1 diabetes.[53] The main explanation for possible increased risk is that the lack of contact at birth with maternal vaginal and intestinal bacteria could make these

children more susceptible later in life to a number of diseases because of changes in the development of the immune system.[54]

Several authors have studied the risks of metabolic disorders and obesity linked to cesarean section. In a study by Huh et al.,[55] women were recruited during early pregnancy, and their children were followed after birth. Body mass index (BMI) z-score, obesity (BMI for age and sex ≥95th percentile), and sum of triceps + subscapular skinfold thicknesses were assessed at age 3 years in 1255 children. Among them, 284 children (22.6%) were delivered by cesarean section. At age 3 years, 15.7% of children delivered by cesarean section were obese compared with 7.5% of children born vaginally. In multivariable logistic and linear regression models adjusting for maternal prepregnancy BMI, birth weight, and other covariates, birth by cesarean section was associated with a higher odds of obesity at age 3 years (odds ratio [OR], 2.10; 95% confidence interval [CI], 1.36–3.23) and higher mean BMI z-score (0.20 units; 95% CI, 0.07–0.33). A study performed in Germany confirmed this trend of cesarean section to promote overweight and obesity,[56] as did Blustein et al. in the United Kingdom.[57] In 3 birth cohorts in Brazil, cesarean section did not lead to a significant increased risk of obesity during childhood, adolescence, or early adulthood.[49] Further studies are needed to confirm these findings and to explore mechanisms that underlie this association. Expectant mothers who choose cesarean delivery in the absence of an obstetrical or medical indication should be aware that their children might have a higher risk for obesity.[58]

The mode of delivery has been shown experimentally to shape gut colonization pattern and modulate regulatory immunity in mice.[59] Cesarean section has been considered a factor that contributes to IBD, especially Crohn's disease.[60,61] A metaanalysis of 9 studies evaluated the potential association between cesarean section and the development of IBD.[60] The pooled data from the 6 included studies indicated that cesarean section was a risk factor for Crohn's disease (95% CI, 1.12–1.70; $P = 0.003$). A positive association between cesarean section and pediatric Crohn's disease (95% CI, 1.06–1.35; $P = 0.005$) was observed. However, results from the 4 included studies for ulcerative colitis indicated the rate of cesarean section in ulcerative colitis patients was not higher than that in control patients (95% CI, 0.87–1.32; $P = 0.54$). Results of this metaanalysis support the hypothesis that cesarean section is associated with the risk of Crohn's disease, but not of ulcerative colitis. The overall rate of cesarean section in IBD patients was similar with that of controls. Another study aimed to investigate the relationship between mode of delivery and risk of IBD.[61] Seven eligible studies were included; 4 were of a retrospective cohort design and 3 were case-control studies. The total number of children born by cesarean section in the metaanalysis was 1354, and 11c355 were delivered vaginally. The proportion of IBD in the cesarean section group was 0.249% compared with 0.322% in the vaginal delivery group. The pooled OR for developing IBD when delivered by cesarean section was 1.00 (95% CI, 0.75–1.33). This analysis observed no significant difference in risk of IBD in offspring delivered by cesarean section compared with those born vaginally. The effect of cesarean section on IBD incidence in the age span 0–35 years was studied from a register-based national cohort study of 2.1 million individuals in Denmark born between 1973 and 2008. Cesarean section was associated with moderately increased risk of IBD at age 0–14 years (incidence rate ratio, 1.29; 95% CI, 1.11–1.49), regardless of parental disposition to IBD.[62] It is difficult to come to a conclusion regarding cesarean section as a risk factor for Crohn's disease. The possible impact of increasing cesarean section practices on the overall burden of IBD in childhood is likely to be small and probably associated with other factors yet to be identified.

MODULATION OF INTESTINAL MICROBIOTA, GUT IMMUNE SYSTEM, AND HUMAN DISEASE BY PROBIOTICS

The administration of live microorganisms via food has a long history of practice. Today, both food and medicinal products containing live bacteria aim to modulate the intestinal microbiota. The term "probiotic" has been defined as "living micro-organisms which, upon ingestion in sufficient numbers, exert health benefits beyond basic nutrition." Probiotics are live, viable bacteria or other microorganisms such as yeasts that have a clearly identifiable positive effect on health and disease.[63] Nonviable bacteria or bacterial substrates are not considered to be probiotics. The most commonly used and studied species of probiotics belong to the genera *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*.[64] A wide variety of probiotic products and strains exist, and it is important to consider the term "probiotics" as a generic term for a range of microorganisms endowed with different properties and effects. The term "probiotics" is comparable to the term "antibiotics," which covers many different classes of drugs endowed with differing antibiotic activities. Thus, different antibiotics have different indications. If the term "probiotics" is used in a manner analogous to "antibiotics," it may prevent confusion with respect to the specific properties of probiotics. Some probiotics are used to prevent or treat infections, while others are of value in the prophylaxis

or treatment of allergic and inflammatory disorders. No single probiotic may achieve all clinical benefits. Probiotics have beneficial effects in the prevention and treatment of human disorders, as evidenced by clinical trials. The use of probiotic approaches is particularly helpful in young pediatric patients, since infants are particularly vulnerable to diseases and infancy is characterized by the delicate process of intestinal mucosa maturation and interaction with gut microbiota.[65]

Clinical benefits of probiotics depend on strain selection, dose and duration of administration, preservation in the GI tract, and, perhaps, combinations of probiotics.[66] Depending on the clinical setting, probiotics can be administered as drugs or combined with food such as yogurt and dairy products. Clinical benefits have been achieved using yogurt and dairy products. Interestingly, over a century ago, Élie Metchnikoff theorized that health could be enhanced and that senility could be delayed by manipulating the intestinal microbiome with host-friendly bacteria found in yogurt.[67] His theory flourished for a time, then drifted to the fringe of medical practice, only to reemerge in the mid-1990s as a concept worthy of mainstream medical attention.[68]

Over the last decade, new areas have opened in the use of probiotics in infants and children for treating or preventing infectious and antibiotic-associated diarrhea.[64–66] For allergy, current results of clinical trials are controversial and dependent on the clinical status of children and the probiotic strains used.[69] The use of probiotics to prevent NEC in very low birth weight infants is providing important and promising results.[69] However, controversies remain for a variety of reasons, including the following: the methodologies of metaanalysis involving different probiotic mixtures yield results that are debatable; the mechanisms by which probiotics are active are poorly understood; and in spite of their beneficial effects, probiotics, as live bacteria, make neonatologists anxious, especially regarding the safety of their use in very premature infants.[70] Nevertheless, one should consider the current results as well as hypotheses that might explain nonstrain-specific probiotic effects, such as providing a microbiological barrier against environmental pathogens and improved intestinal permeability from probiotics themselves or from their secreted products, thus protecting against the translocation of harmful bacteria. Moreover, a recent longitudinal analysis of the premature infant intestinal microbiome prior to NEC underlines the importance of microbial diversity.[71] It also demonstrated the impact of intravenously administered antibiotics on the microbial diversity present in fecal material.[71] Thus, while the provision of live bacteria might increase microbial diversity, these hypotheses need to be explored more extensively.

CONCLUSION

It is now well established that the intestinal microbiota play a major role immediately after birth by promoting intestinal function and by developing the gut immune system.[72–74] Numerous factors may influence early intestinal colonization (prematurity, cesarean section, breastfeeding, antibiotics) and the so-called immune phenotype programming.[75] Epidemiological studies suggest relationships between early colonization and occurrence of later human diseases such as obesity, allergic diseases, IBD, and autoimmune diseases. Causal relationships for many of the associations between the microbiome and disease states have yet to be proven. Understanding the links between the microbiome and human disease may provide prophylactic or therapeutic tools to improve human health. Modulation of intestinal microbiota with probiotics, prebiotics, and fermentation products is promising but requires further study to optimize the ingredients used, as well as the dose and duration, and to identify when in the life cycle they should be introduced.

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