

REVIEW

New insights into therapeutic strategies for gut microbiota modulation in inflammatory diseases

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The interaction between the gut microbiota and the host immune system is very important for balancing and resolving inflammation. The human microbiota begins to form during childbirth; the complex interaction between bacteria and host cells becomes critical for the formation of a healthy or a disease-promoting microbiota. C-section delivery, formula feeding, a high-sugar diet, a high-fat diet and excess hygiene negatively affect the health of the microbiota. Considering that the majority of the global population has experienced at least one of these factors that can lead to inflammatory disease, it is important to understand strategies to modulate the gut microbiota. In this review, we will discuss new insights into gut microbiota modulation as potential strategies to prevent and treat inflammatory diseases. Owing to the great advances in tools for microbial analysis, therapeutic strategies such as prebiotic, probiotic and postbiotic treatment and fecal microbiota transplantation have gained popularity.

Clinical & Translational Immunology (2016) 5, e87; doi:10.1038/cti.2016.38; published online 24 June 2016

The mammalian gastrointestinal tract is populated by a collection of microorganisms, primarily bacteria, that interact with host cells. Until recently, most studies of the microbiota reported impressive numerical data concerning our body constitution: bacteria residing in the human body outnumber human cells by a factor of 10 or more.^{1–3} More recently, it was concluded that the ratio of bacteria to human cells is 1:1.⁴ Although this new information appears less impressive, it does not diminish the biological importance of our microbiome. In the past two decades, several studies have demonstrated the effects of the microbiota on host physiological, metabolic and immunological processes and have revealed that the microbiota is fundamental to host body function.^{2,5–8} This symbiotic relationship is also important for educating the host immune system, allowing immune cells to tolerate abundance of microorganisms in the body. However, when this interaction is disrupted or dysfunctional, it can lead to the development of inflammatory diseases.^{9,10} Thus, it is crucial to identify the factors that can influence microbiota composition and to maintain a healthy microbiota–host interaction.

The human microbiota begins to form during childbirth.¹¹ Breastfeeding and nutrition in early life are critical for the development of the population of healthy and disease-promoting microbes in the newborn host.^{11–14} The term infant's gut microbiota matures over the first 3 years of life, and after 3 years, the gut microbiota composition is similar to that of an adult.¹¹ In addition to birth conditions, breastfeeding,¹² diet,¹⁴ medication¹⁵ and host genetics¹⁶

are involved in intestinal microbiota formation and modulation. Thus, it is very difficult to dissect the contribution of each environmental or host factor to the development of inflammatory diseases. For example, Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), are complex diseases in which both genetic factors and the gut microbiota are involved in disease onset.¹⁷ Genetic analysis has revealed a complex set of polymorphisms that confer varying risk levels, and these loci revealed that impaired handling of commensal microbes and pathogens is a prominent factor in CD development.¹⁸ Thus, understanding how the microbiota composition interacts with host genetics to induce disease may be helpful to the development of effective therapeutic strategies. Considering that host genetic manipulation strategies to prevent or treat diseases are complicated at both the ethical and technological levels,¹⁹ microbiota manipulation appears to be less complicated. Moreover, it is well known that modulation of the gut microbiota can be used as a therapeutic strategy to manage several gastrointestinal disorders. In this regard, several therapeutic approaches have been developed to modulate and restore the gut microbiota. Prebiotics, probiotics, postbiotics and fecal microbiota transplantation (FMT) represent the most widespread treatment options. However, the molecular mechanisms underlying these approaches are still unclear, although these strategies are more effective approaches to prevent inflammatory disorders than gene-target approaches.

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Received 1 March 2016; revised 12 May 2016; accepted 23 May 2016

Antibiotics also modulate the gut microbiota. Although antibiotics are the basis of the treatment of infectious disease, they are known to impair the gut microbiota in association with a consequent increase in susceptibility to microbiota-associated diseases. Additionally, antibiotic treatment has been recognized as a trigger for *Clostridium difficile* infection (CDI).²⁰ On the other hand, an interesting recent study using different regimens of antibiotic therapy demonstrated that different types of antibiotic administration in an experimental model of CDI induced distinct changes in microbiota structure by recovering an intestinal microbiota that was more resistant to CDI.²¹ In addition, a single bacterial species, *C. scindens*, was able to confer resistance to infection by synthesizing *C. difficile*-inhibiting metabolites from host-derived bile salts. This observation suggests an important strategy for selecting and identifying new candidate probiotics. However, given that antibiotic therapy may lead to the development of antibiotic resistance, the use of antibiotics as a new strategy for gut microbiota modulation, despite their effectiveness in the treatment of IBD, should be carefully and more deeply investigated. For this reason, we decided not to extend this review to the truly complex relationship between antibiotics and the gut microbiota.

In the present review, we provide an updated overview of microbiota modulation strategies via diet/prebiotics, probiotics/postbiotics and FMT (Figure 1) and discuss important issues regarding these therapeutic approaches.

UNDERSTANDING THE IMPORTANCE OF MICROBIOTA MODULATION FROM EARLY TO LATE STAGES OF LIFE

Microbiota colonization from birth to childhood is heavily influenced by the mother. Many studies have shown that the delivery mode and breastfeeding can alter the microbial composition in early life.^{11,18,22–24} Moreover, it has been shown that the placenta contains a remarkable microbiota, which could affect the formation of the child's microbiota. Phyla represented in the oral microbiota, such as Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes and Fusobacteria, have been detected in the placenta.²⁵ Interestingly, a hospital case-controlled study showed that pregnant women with periodontal disease had a threefold higher likelihood of preterm delivery than control mothers.²⁶ However, these findings are still controversial, and it is unclear whether a relationship exists between periodontitis and the placental

microbiota. Therefore, additional studies are necessary to understand the role of the placental microbiota and the correlation between the oral microbiota, preterm delivery and child microbiota colonization. In the future, it may be possible to treat oral microbiota dysbiosis by modulating the microbiota to prevent preterm delivery or improve the placental microbial community.

It has been reported that delivery mode also affects intestinal colonization.¹¹ Vaginal delivery puts the child into contact with microorganisms, causing it to have an intestinal bacterial composition similar to that of the mother's vaginal microbiota, containing *Lactobacillus* and *Prevotella* or *Sneathia* spp.²⁷ In contrast, newborns delivered by C-section have a microbial composition similar to that of the mother's skin and the hospital environment.²⁸ Cesarean birth has been associated with several diseases later in life, including obesity, type 1 diabetes and asthma, which could be attributed to microbial colonization.^{11,23} Although still uncommon, the use of products containing probiotics or prebiotics to improve vaginal health is becoming more popular.^{12,29} It is interesting to explore whether it is possible to manipulate the vaginal microbiota to improve a newborn's health. Partial recolonization of the microbiota of babies born via C-section has been performed by swabbing gauze from the mother's vagina onto the newborn's skin within 1 min after delivery.³⁰ This procedure increased the similarity of the babies' microbiomes to those of babies delivered vaginally, at least in the first week of life.³⁰ This study did not provide evidence that this procedure benefited the child in any way, but the results demonstrate a proof of principle that it is possible to alter a newborn's microbiome, and this finding may have valuable clinical applications.

After birth, breastfeeding is very important for intestinal microbiota formation.²⁷ Recent studies have identified and isolated microorganisms in colostrum and breast milk.³¹ A 9-genus 'core' composed of *Streptococcus*, *Staphylococcus*, *Serratia*, *Pseudomonas*, *Corynebacteria*, *Ralstonia*, *Propionibacterium*, *Sphingomonas* and *Bradyrhizobiaceae* has been identified.³¹ This 'core' is likely shared between every subject studied. Therefore, breastfeeding potentially provides probiotics to the newborn gastrointestinal tract. Furthermore, breast milk contains galacto-oligosaccharides, which are resistant fermentable sugars processed by bacteria in the colon. Probiotic bacteria and galacto-oligosaccharides facilitate the development of a

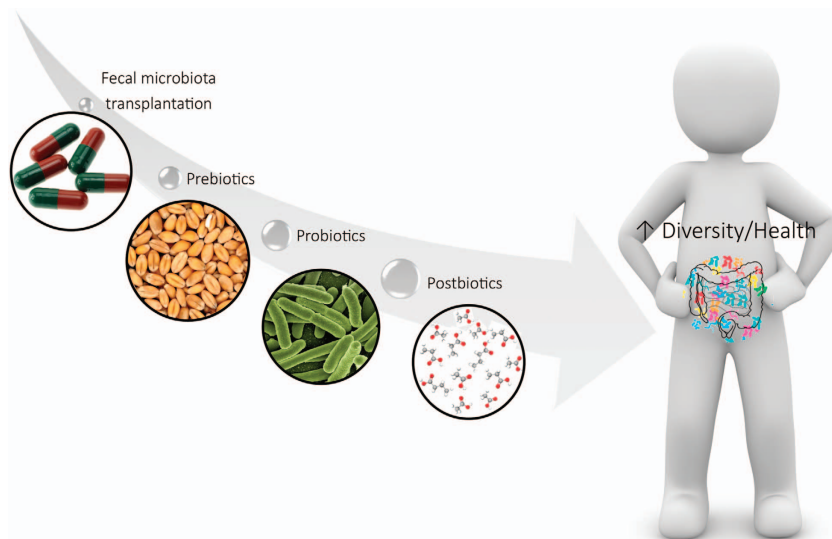


Figure 1 Four mechanisms of modulating the gut microbiota.

more uniform microbiome in children than formula alone.²³ The addition of oligosaccharides to infant formulas represents a new approach to child nutrition, as this strategy allows the colonic microbiota of these children to more closely resemble that of children fed only breast milk.^{23,24} Importantly, a relationship between formula-fed infants and diseases has been identified, and it can be partially attributed to differences in the microbiota.²⁴ It has been found that the breast microbiome is distinct from that of any other human organ and may not be a subset of the overall microbiome. It is unclear how live bacteria reach the mammary glands.³² It has been demonstrated that dendritic cells can send protrusions into the gastrointestinal tract lumen to capture and hold non-pathogenic microbes. This mechanism may not be exclusive to dendritic cells but rather may include other CD18⁺ cells, such as macrophages. Once inside the cell, the bacteria can travel throughout the body and be released into the mammary glands.^{23,32,33} However, it is unclear whether this is the primary pathway by which the bacteria reach the mammary glands. Moreover, it is still unclear whether manipulation of the gut microbiota would also alter the milk microbiota, which would provide benefits to the newborn. In a case-control study, a multi-strain probiotic product was orally administered to pregnant mothers, and the results showed that some species reached the breast milk. However, the authors were unable to determine whether the bacteria found in the breast milk were endogenous or from the product.³⁴ In addition, it has been reported that obesity and overnutrition during pregnancy and lactation can increase the risk of obesity in the offspring.³⁵ It was recently reported that prebiotic intake during pregnancy and lactation attenuates the detrimental nutritional programming of offspring associated with maternal obesity.³⁵ Another study in mice has demonstrated that the nursing mother, not the birth mother, determines the fecal microbiota composition of the offspring.³⁶ In that study, researchers tested cross-feeding of pups within 48 h of birth as a means to permanently shift the microbiota from birth.³⁶ Based on these studies, it is likely possible to treat pregnant women to target the baby.

The microbiota of humans already resembles that of an adult by 3 years of age.²⁸ Factors such as diet changes, antibiotic use and

diseases can temporarily disrupt the microbiota, but the microbiota subsequently regenerates itself.³⁷ This phenomenon confirms the hypotheses that the early stages of life are essential for microbiota formation and that mothers are key elements in establishing the microbiota. Disruption of the child's microbiota at the early stage and/or a mother's microbiota could affect the child later in life.³⁸

The gut microbiome becomes unstable as people age and displays greater interindividual variation among older adults than among younger adults.³⁹ Characteristics specific to this population make the application of probiotics and prebiotics an interesting field. Elderly people frequently use medications, weakening their immune system and affecting the gastrointestinal system.³⁹ Some studies have proposed that postmenopausal women can benefit from the use of probiotics. As women reach climacteric, the abundance of the vaginal microbiota, which is predominantly colonized by *Lactobacilli*, begins to decrease, the vaginal pH increases, making women more susceptible to problems such as bacterial vaginosis and candidiasis.⁴⁰ Another problem that occurs among postmenopausal women is an increased risk of osteoporosis due to a decrease in hormone levels. In a randomized, double-blind, cross-over trial, women between 56 and 64 years old were treated with 5 or 10 g of lactulose or a corresponding placebo for 9 days.⁴¹ Calcium absorption was greater in the treatment group compared with the placebo group. Moreover, a significant correlation between lactulose dose and calcium absorption was found.⁴¹ These results suggest that prebiotics can also be used to prevent bone loss. When determining the optimal time in life to administer pre- and probiotics, it is important to consider that circadian rhythms and gender influence microbiota composition and function.⁴² A diurnal oscillation in the relative abundance of *Bacteroidetes* and *Firmicutes*⁴² has been observed, and this oscillation may affect pro- or prebiotic treatments. In addition, females show more significant microbiota oscillations with circadian rhythms than males. Interestingly, the microbiota of male and female mice diverge after puberty, and this phenomenon may explain why females are more frequently affected by autoimmune disease.⁴²

In conclusion, it is clear that influences in the early stages of life, possibly including gestation, are extremely important in microbiota

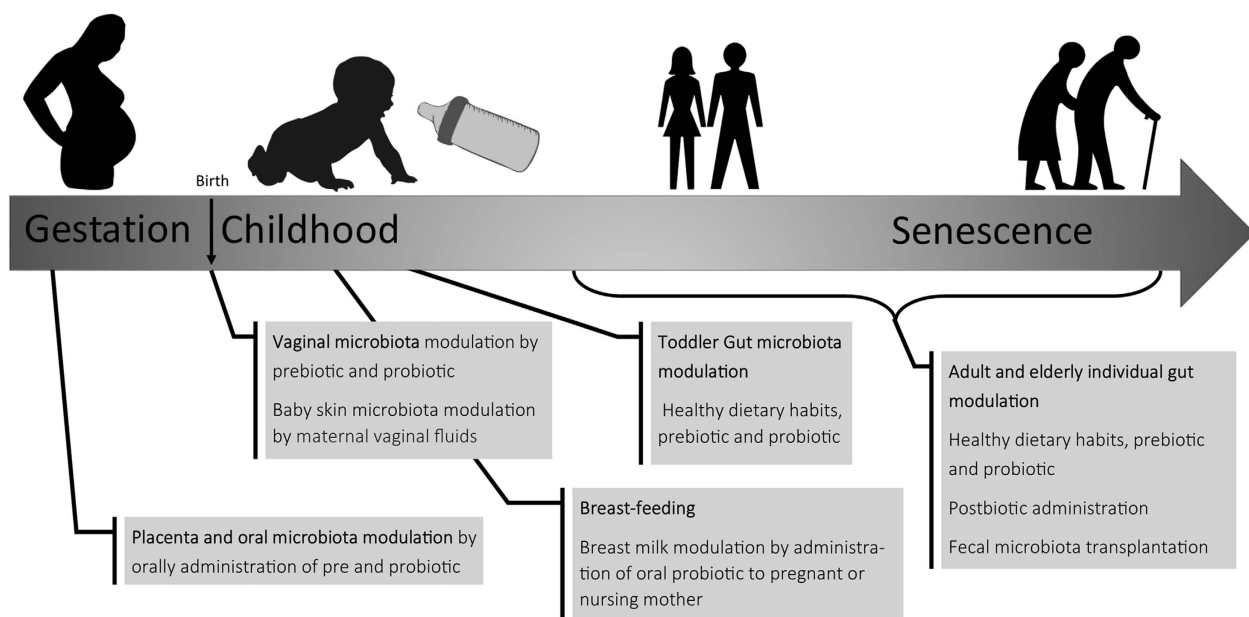


Figure 2 Therapeutic strategies of gut microbiota modulation from early to late stages of life.

formation, making this period a great target for biotherapeutics that may prevent diseases later in life (Figure 2). However, it is also clear that microbiota modulation can occur in any stage of life via different approaches, such as attenuation of inflammation and enhancement of immune system activity, although these interventions become more difficult as age increases.

CURRENT STRATEGIES OF GUT MICROBIOTA MODULATION

Diet/prebiotics

Many complex plant polysaccharides in the human diet cannot be digested by human enzymes owing to insolubility or a lack of human-encoded hydrolytic enzymes. However, some bacteria can degrade them, and consuming polysaccharides is important for bacterial growth; this type of food substrate used by probiotic microorganisms is collectively termed a prebiotic. Within the genomes in the microbiome, there are many genes and operons devoted to degrading and consuming polysaccharides. This ability of bacteria to use our food can explain why dietary habit is a primary environmental factor that influences the amount and diversity of the gut microbiota. In 2010, a comparative study in children from Europe and rural Africa powerfully reported the association between diet and the microbiota.¹⁴ European children who consumed fast food had reduced microbial richness, whereas children from rural Africa ate high-fiber foods, such as cereals, nuts and vegetables, and had a higher proportion of healthy microbes and a lower proportion of obesity-associated gut microbes. The microbiome of rural African children are dominated by *Bacteroidetes* and high levels of short-chain fatty acids (SCFAs).¹⁴ SCFAs are the primary metabolic products of anaerobic bacterial fermentation in the gut and are considered to be anti-inflammatory mediators. Two possible mechanisms involving diet can determine or modulate the microbiota. One possible mechanism involves the substrate available to the microbiota. Individual *Bacteroides* genomes typically possess large numbers of polysaccharide utilization loci, distinct from other bacterial species that use different substrates. In a recent *in vitro* study, researchers supplied two different non-digestible polysaccharides (apple pectin and inulin) to three different human gut microbiota in anaerobic, pH-controlled continuous-flow fermentors.⁴³ Bacterial community analysis showed that supplying apple pectin or inulin resulted in the highly specific enrichment of particular bacterial operational taxonomic units (based on 16S rRNA gene sequences).⁴³ Considering the eight most abundant *Bacteroides* operational taxonomic units detected, six were promoted by pectin and two by inulin. Alternatively, among *Firmicutes*, most species were stimulated by inulin. In addition, community diversity was greater in the pectin-fed fermentors than in the inulin-fed fermentors, most likely because the constitution of pectin is more complex.⁴³ As another example, degradation of xylan (particularly abundant in cereal grains) is not universally shared by *Bacteroidetes* in the human gut; rather, multiple species and even different strains, such as *Bacteroides eggerthii*, *Bacteroides cellulosilyticus*, *Bacteroides intestinalis*, *Bacteroides ovatus* and *Bacteroides xylanisolvens*, have different capacities to degrade xylan.⁴⁴ Thus, specific substrates in the diet confer competitive advantages to bacteria with specific polysaccharide utilization loci. Importantly, specific prebiotics may favor both beneficial and harmful bacteria. For example, inulin stimulated colonization by *Faecalibacterium prausnitzii*, which has anti-inflammatory effects,⁴³ due to butyrate production⁴³ and also promoted the growth of some *Proteobacteria*, including *Sutterella wadsworthensis*, which has been isolated from healthy individuals and individuals with gastrointestinal disease.⁴³ Thus, additional studies are necessary to identify the range of bacteria that may be stimulated by a specific prebiotic.

Another possible mechanism by which fiber can regulate the gut microbiota composition is that metabolic products of anaerobic fermentation, such as SCFAs, can change the gut environment, especially its pH, creating a more acidic environment. It has been shown that pH exerts a strong influence on the microbiota composition. For example, at pH 6.5, Gram-negative *Bacteroides* predominates, but at pH 5.5, Gram-positive *Firmicutes* have an advantage.⁴⁵ Subsequent experiments also showed that pH exerts important control over the competition between bacteria from different phyla or families with varying abilities to consume similar polysaccharides.⁴³ *In vitro* experiments have shown this effect for inulin bacteria fermentors, in which the percentage of *Bacteroidetes* 16S rRNA gene copies was reduced from ~60% at pH 6.9 to ~30% at pH 5.5.⁴⁶ Thus, the pH is considered an important factor in polysaccharide use because it has a strong influence on competition between bacteria. However, we must consider that the *in vitro* studies of pH may differ from the situation *in vivo*, in which the absorption and turnover of fermentation products are very dynamic.⁴⁷

Based on the aforementioned study of European children, it would be interesting to examine whether it is possible to modulate the gut microbiota by providing a polysaccharide-rich diet at schools to prevent inflammatory diseases. There are not sufficient studies to address this question. The ability of a healthy fiber-rich diet to cause a long-lasting microbial shift is not yet clear. It was recently reported that a lack of dietary fiber induces a substantial loss of microbial community diversity and influences the ability of gut bacteria to be transferred from parents to their offspring.⁴⁸ Furthermore, it appears that simply restoring fiber consumption is insufficient to reverse a lack of microbial community diversity once it has been passed to subsequent generations.⁴⁸ In addition, a study in human adults showed that as soon as subjects are taken off their respective diets, the microbial composition returns to the prediet levels within days.⁴⁹ Based on studies showing that low-fiber diets not only deplete complex microbial ecosystems in the gut but also can cause an irreversible loss of diversity in only a few generations, European children may not be capable of restoring their microbial diversity. However, many studies have demonstrated several health benefits of a high-fiber diet during its consumption. Additionally, it has been reported that specific fiber sources can be better for specific disease conditions. For example, diets high in resistant starch have been shown to enhance insulin sensitivity, and this effect may be mediated by bacterial fermentation activity in the colon.⁴⁴ Diets containing resistant starch and non-starch polysaccharides offer potential benefits in preventing colorectal cancer because of the presence of bacteria producing butyrate.⁴⁵

Another important question is whether the same diet elicits similar changes in the gut microbiota of different European children. Although it is known that ~90% of the gut bacteria belong to the *Firmicutes* or *Bacteroidetes* phyla, the species composition is highly variable.⁵⁰ In 2011, a study revealed that changes in the microbiota can be highly specific to the individual; thus, a specific diet cannot exert the same effects on all individuals, and its effects depend on the initial composition of the gut microbiota.⁴⁴ Therefore, before choosing to eat a fiber-enriched diet, it is important to consider interindividual differences in microbiota and understand which anti-inflammatory molecules are stimulated by specific diets.

Next-generation probiotics

Probiotics have been defined as live, natural microorganisms that are given orally to confer health benefits to the host.⁵¹ The most extensively commercialized probiotics used are the *Bifidobacterium*

and *Lactobacillus* bacterial strains, although other microorganisms, such as the yeast *Saccharomyces*, have also been widely commercialized.⁵² Although probiotic treatment has been reported to have several beneficial effects, the molecular mechanisms underlying the action of probiotics remain unclear. Moreover, it has become very clear that different probiotic strains are not equally potent and that their effects are mediated by interactions with the host immune response and within a very complex microbiota ecosystem. Thus, it has been challenging to determine the mechanisms involved in the crosstalk between individual bacterial strains and the host. Understanding the action of probiotics and their effects on the host is useful and important for modulating the gut microbiota and treating a broad range of human diseases. The primary actions related to probiotic use are as follows: anti-microbial effects, enhancement of mucosal barrier integrity and host immunomodulation. In the past few decades, metagenomics and bioinformatics studies have allowed us to understand the complex interrelationship between the microbiota and the host, providing further insight into human health and disease and advancing the development of the next generation of probiotics. Genetically modified probiotic strains have been investigated as a promising and alternative future therapy, particularly for IBD.⁵³ Positive results have been obtained in animal models and human clinical trials using probiotics, especially using recombinant lactic acid bacteria expressing beneficial molecules as a live system delivered to inflammatory sites.^{54–57} The anti-inflammatory effects of the *Lactococcus lactis* strain, which produces 15-lipoxygenase-1, were shown to be effective in preventing intestinal damage and in alleviating trinitrobenzenesulfonic acid-induced colitis in an experimental murine model.⁵⁷ In addition, genetically modified *L. lactis* expressing cytokines, such as human interleukin-10 (IL-10), has been shown to prevent intestinal damage in experimental colitis.^{55,58} Modified *L. lactis* was also used in a clinical trial of CD patients without adverse effects.⁵⁹ Alternatively, new systems, such as the delivery of DNA into eukaryotic cells to induce the production of molecules of interest, have been developed.^{54,60} From these perspectives, the efficiency of using probiotic strains as a delivery system for target molecules represents an important advance in the treatment of inflammatory diseases. However, when considering these strategies, it is important to be aware that genetically modified organisms may impact other microorganisms in the host microbiota, although this issue has not yet been addressed.

Differences in the microbiota profile have been reported to be related to known clinical risk factors for many diseases, such as metabolic diseases, asthma, arthritis and cancer.^{61–64} In this sense, personalized probiotic therapies aiming to manipulate the host microbiota using specific and different strains have gained considerable interest in recent years. If we continue to learn about other gut microorganisms and their roles in human health, we may obtain a complete rationale for selecting the next generation of probiotics. For example, Clostridia clusters IV, XIVa and XVIII and *Faecalibacterium prausnitzii* have emerged as non-traditional probiotics, and their effects have been studied in inflammatory diseases, with promising results.^{65–67} *F. prausnitzii* is a commensal bacterial strain that has been reported to be less abundant in colitis patients.⁶⁸ However, *F. prausnitzii* exhibited an increased capacity to induce IL-10 production, which elicits an important anti-inflammatory response in mouse experimental colitis models.⁶⁵ Most of these effects were linked to the high capacity of this strain to produce metabolites with anti-inflammatory effects, for example, decreasing the infiltration of polymorphonuclear cells into the site of inflammation and reducing the systemic levels of proinflammatory cytokines such as IL-2 and

IL-5 in the host after colitis induction.⁶⁹ *Clostridium butyricum* is another potential non-traditional candidate probiotic that can produce metabolites with anti-inflammatory effects, such as butyrate.⁶⁷ Interestingly, the effectiveness of these ‘new probiotic strains’ appears to originate from their capability to produce metabolites with anti-inflammatory activities. These findings are exciting and reside in the ecological network and in the traditional concept of using whole live probiotic cells to provide health benefits to the host. However, the use of ‘postbiotics’, non-viable bacterial products or metabolites with biological effects on the host has also evolved as an effective alternative method to increase the potential and functionality of each probiotic strain and has opened a new opportunity to search for and investigate the potential uses of microbiota-derived products as novel therapies for many inflammatory diseases.

Postbiotics

Postbiotics have recently been proposed as ‘non-viable’ bacterial products or metabolic byproducts from probiotic microorganisms that promote biological activity in the host.⁷⁰ The use of postbiotics is derived from the concept that in most cases, the effect of administered probiotics was more evident when the bacteria were still alive. Even probiotic bacterial culture supernatant was able to provide immunomodulatory effects to the host. This finding suggests that the beneficial effects of probiotics are dependent on the metabolic activity of the bacteria, although heat-killed probiotics may also act as postbiotics. Heat-killed microorganisms retain important bacterial structures that can still exert biological effects on the host immune system and can therefore also be a useful therapy for inflammatory diseases.^{71,72} A recent study showed that the beneficial effects of *Bifidobacterium longum* for lung inflammation after infection, observed as increased levels of the anti-inflammatory cytokine IL-10 and reduced infiltration of inflammatory cells into the lungs of mice under treatment with the probiotic, were greater from treatment with live bacteria than with heat-killed bacteria.⁷² Unsurprisingly, the combinatorial effects of metabolites and other biological molecules together with live microorganisms may be more powerful. In this regard, the generation of probiotics with engineered changes in their metabolic pathways, aiming to enhance metabolite production to favor host health, is a formidable challenge and a potential therapy for inflammatory diseases. Nevertheless, with advances in the understanding of the microbiota–host metabolism axis, the use of postbiotic molecules has become a prominent strategy for treating many inflammatory diseases, as these molecules mimic the useful therapeutic effects of probiotics while avoiding the risk of administering live microorganisms to a host with an impaired immune system. For instance, metabolites are considered pivotal mediators of host–microbiota communication,⁷³ and many bacterial metabolites can also manipulate host metabolism. The microbial metabolic products SCFAs, including acetate, butyrate and propionate, have been shown to elicit several modulatory effects on the host.^{74,75} Many commensal bacteria produce SCFAs, and these metabolites have shown promising results in several studies using mouse models of inflammatory diseases, such as colitis,⁶¹ arthritis,⁷⁶ asthma,⁷⁷ gout⁷⁸ and pneumonia.⁷² The pathways modulating these beneficial inflammatory effects alter cytokine release and cell recruitment to and survival at the site of inflammation to induce proresolutive activities. However, these mechanisms are dependent on the cell type and the host target site.

A recent study has shown that the tryptophan produced by commensal *Lactobacillus* induces an inflammatory response that limits pathogen colonization in the intestinal mucosa by upregulating the host cytokine IL-22, an unique cytokine produced by immune cells

that acts on epithelial cells and that is important in maintaining mucosal barrier function and in promoting host defense, especially in association with the proinflammatory cytokine IL-17.^{79,80} Furthermore, other metabolites released by the microbiota as organic acids, such as taurine, histamine and spermine, alter the intestinal microbiota through inflammasome-dependent host signaling.⁸¹ The results of these studies emphasize the complex interactions between host and microbiota-modulated metabolites, constituting an exciting area of future research. However, based on our understanding of the microbiota–host metabolism axis, the use of postbiotics to improve human health remains an exciting therapeutic option for preventing and treating inflammatory disease and represents one of the greatest challenges in this field.

FMT

FMT is a promising strategy for the treatment of inflammatory diseases, especially diseases associated with microbiota dysbiosis. FMT involves the administration of distal gut microbiota-containing fecal material from a healthy person (donor) to a patient with an altered gut microbiota that is causing disease. The modulation of the gut microbiota by FMT primarily follows the probiotic principle, but instead of treating the patient with specific strains, a community of microorganisms is used. In 1958, the first study using feces as a therapy was documented in humans for the treatment of pseudomembranous colitis.⁸² Since then, FMT has gained increasing attention, especially for the treatment of CDI; *C. difficile* is the pathogenic bacterium responsible for pseudomembranous colitis. FMT has been shown to be one of the most effective available treatments for recurrent CDI. Further studies, including large case series and randomized controlled trials, have confirmed the efficacy of FMT for CDI.⁸³ In addition, another recent randomized controlled trial evaluated the efficacy of FMT administered via duodenal infusion and found significantly higher eradication rates (81%) of vancomycin-induced diarrhea for FMT administered via duodenal infusion than for the control treatment.⁸⁴ Based on this study, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) approved the use of FMT for diarrhea recurrence after antibiotic-associated diarrhea.⁸⁵

IBD is not completely understood, but a key feature of IBD is an inappropriate inflammatory response to the intestinal microbiota in genetically susceptible individuals. In addition, it is known that IBD patients have greater microbiota instability and lower abundance of Firmicutes than healthy subjects.⁸⁶ An increased abundance of Actinobacteria and Enterobacteriaceae has also been reported,⁸⁷ and these findings suggest that dysbiosis is associated with IBD development. Therefore, microbiota modulation strategies have been introduced as alternative IBD therapies. Several antibiotics and probiotics have been tested in IBD as strategies to restore the microbiota.^{88,89} However, based on previous data, the European Crohn's and Colitis Organization (ECCO) guidelines suggest the use of antibiotics only for specific conditions, such as septic complications, symptoms attributable to bacterial overgrowth or *C. difficile* superinfection in UC, to avoid antibiotic resistance.⁹⁰ Probiotics have also been tested in IBD treatment, but there are no conclusive data concerning their efficacy. The *Escherichia coli* Nissle 1917 strain has been shown to be effective,^{91–93} and it is the only probiotic suggested in the ECCO guidelines. These findings demonstrated that at least for IBD therapy, alternative microbiota modulation strategies should be studied. The efficacy of FMT in IBD patients has been inconsistent. This variability may be because patient cohorts differ in disease severity and the route of fecal infusion. However, a systematic review

evaluated the efficacy and safety profile of FMT in recurrent CDI patients and found that 87% of 536 subjects experienced resolution of diarrhea.⁹⁴ Nevertheless, several reasons for the differences in the success of FMT via distinct routes have been hypothesized. In addition, the composition of the donor microbiota is a relevant key factor in determining treatment efficacy. Microbiota replacement via FMT in CDI patients was shown to produce a microbiota similar to that of the donor 2 weeks post-transplantation, as determined by 16S rRNA profiling.⁹⁵ Indeed, microbiota modulation strategies for the donor before FMT may further benefit the recipient. However, little is known about the mechanisms underlying FMT therapy. Indeed, FMT has been shown to be more effective than treatment with a 'synthetic microbial mixture', which was characterized as transplantation with a microorganism community that could be controlled and tested for the presence of viruses or pathogens.⁹⁶ Possible explanations for this difference include bacterial quantity and quality, as well as their postbiotic ability.

There are many issues and important points that remain unclear and are worth mentioning when evaluating FMT, such as the likelihood of side effects, including the following: bacterial stability and translocation, genetic factors of individual recipients that may influence the success of FMT and bacterial colonization, or transplant rejection similar to organ transplantation. Further studies are necessary to optimize and improve this technique and expand the use of FMT to not only IBD and CDI but also a range of microbiota-associated inflammatory diseases.

CONCLUDING REMARKS

The use of microbiota modulation to improve health is becoming a powerful strategy of inflammatory disease therapy, and microbiota intervention strategies can be designed using several approaches, including prebiotics, probiotics, postbiotics and FMT. The recent decades of research in the microbiome and immunology fields have revealed the importance of the interindividual variability in gut microbiota composition in promoting health and causing disease. The complexity of microbiota–host crosstalk is still not fully appreciated, as many host factors, including genetic factors, metabolism, environmental exposure, and microorganism composition and function, could affect these interactions. This is an exciting area of research for the rational design of microbiota-modulating interventions for several diseases. As we continue to learn about the relationships between the microbiota and the host, we can identify potential targets and answer several open questions related to the time of treatment, host aging, the appropriate strategy, the optimal strain, personalized prevention or therapy, different inflammatory diseases and the use of 'live' or 'dead' microorganisms.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was funded by São Paulo Research Foundation (FAPESP), project number 2012/50410-8, and The National Council for Scientific and Technological Development (CNPq), project number 486037/2012-6 to CMF. ATV was supported by a fellowship from CNPq, Brazil.

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