Chapter 5

Gut Flora: In the Treatment of Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/65073

Abstract

Gut flora is the largest reservoir of human flora. It is an essential factor in certain pathological disorders, including multisystem organ failure, colon cancer and inflammatory bowel diseases and extraintestinal disorders, such as allergy, asthma and even obesity. Prebiotics and probiotics are known to have a role in prevention or treatment of some diseases. Nevertheless, bacteria have been found to be useful for treating disease and thus promoting human health in a safe and natural way.

Keywords: gut flora, cancer, allergy, inflammatory bowel disease, obesity

1. Introduction

The endogenous gastrointestinal microbial flora plays a fundamentally important role in normal health and disease [1]. According to recent advances in microbiome research, the infectious, inflammatory and functional bowel diseases are closely associated with the pathologic changes in gut microbiota. Recent discovery of the fact that disbalance of gut microbiome has a profound impact on the function of the liver through microbiota liver axis [2]. There has been a re-emergence of interest in the relationship between gastrointestinal flora and gut function with the recognition that prebiotics, probiotics and other means of modifying gut flora may function as therapeutic modalities.

2. The normal flora

The human intestine is colonized by millions of bacteria, primarily anaerobic bacteria, comprising approximately 1000 species. The bacterial distribution varies greatly at different

levels of the gastrointestinal tract (GIT) [2] ranging from $<10^3$ colony-forming units/ml (CFU/ml) in the stomach to 10^{11}–10^{12} CFU/ml within the colon, where anaerobes outnumber aerobes by a ratio of 1000:1.

2.1. Types of flora

2.1.1. Commensal flora

The intestinal flora includes Bifidobacteria, Lactobacillus, Propionobacteria, Peptostreptococci and Enterococci. The commensal flora produces antibiotic-like substances that are anti-fungal, anti-viral and reduce pH near the wall of the gut forming a protective barrier, which is uninhabitable for the pathogenic bacteria to colonize [3].

2.1.2. Opportunistic flora

This includes intestinal flora like Bacteroides, Peptococci, Staphylococci, Streptococci, Bacilli, Clostridia, Yeasts, Enterobacteria, Fusobacteria, Eubacteria, Catenobacteria and others. In a healthy person, their numbers are limited and controlled by commensal flora.

2.1.3. Transitional Flora

The flora which enters the body through food and drink constitutes the transitional flora. In a healthy gut microbiome, it does not cause disease however any harm to the commensal flora will enable them to cause the disease.

3. Role of gut flora in the treatment of disease

3.1. Cancer

Indiscriminate use of antibiotics not only makes the problem of antibiotic resistant bacterial strains even worse, but also kills many commensal bacteria that promote homeostasis and protect against carcinogenesis. It has been seen that changes in the bacterial community occur in the gut microbiome of colon cancer patients, with tumors harboring increased bacterial diversity and an abundance of pathogenic bacteria compared to surrounding healthy tissue [4]. Lactobacillus and Bifidobacteria are known to prevent tumor formation by suppressing the growth factors like MyD88 (an adaptor molecule necessary for most toll-like receptors (TLR) signaling) was found to be essential in the development of the carcinomas [5, 6].

A number of *in vitro* and animal studies provide evidence that consuming probiotics suppresses colon rectal cancer. These studies have also proposed multiple pathways by which probiotics could inhibit colon cancer by influencing innate immune pathways and apoptosis, reducing oxidative stress and modulating intestinal bacteria and their metabolism [7]. *Lactobacillus johnsonii* reduced the concentration of *Enterobacters* and modulated immune response in colon rectal cancer patients, whereas *Bifidobacterium longum* did not have any effect.

http://dx.doi.org/10.5772/65073

In another study, *L. casei* suppressed colorectal tumor growth in patients, after 2–4 years of treatment. However, these clinical trials are limited by the small number of subjects and their short duration [8]. Mice experimentally colonized with *Helicobacter hepaticus* and enterotoxigenic *Bacteroides fragilis* exhibit colonic Th17 inflammatory infiltrates that appear to have a beneficial role in human ovarian cancer [9], murine melanoma, pancreatic and colon cancer [10–12]. It has also been found that *Helicobacter pylori* can alter stomach pH and acid reflux, which could protect against Barrett's esophagus and esophageal cancer [13].

4. Probiotics and prebiotics in cancer prevention

Fecal microbiota transplantations (FMT) are effective in maintaining a healthy gut microbiome particularly in patients with severe *Clostridium difficile* infections. A recent study transplanted a culture of six phylogenetically diverse gut microbes into mice. With *C. difficile* infections, this restored a normal microbial community, displaced the *Clostridium difficile* and resolved the disease [14].

Probiotics are live microorganisms present in foods as dietary supplement that confer a health benefit. Lactobacilli in yoghurt improved digestion of dairy products in individuals who are lactose intolerant [15]. Probiotics can be improved upon by supplementing food with bacteria engineered to have more beneficial effect. Oral administration of a strain of *Lactobacillus acidophilus* (having phosphoglycerol transferase gene deleted) to APC floxed mice resulted in the reduction in polyps [16]. A protein elafin produced by engineered strains of *Lactobacillus casie* and *Lactococcus lactis* diminished inflammation in a mouse model of colitis [17]. Another example is a strain of *Lactobacillus gasseri*, which was engineered to overexpress the antioxidant superoxide dismutase and decreased colitis in interleukin (IL)-10 knockout mice [18]. The introduction of genetically engineered organisms to produce and deliver cytokines or other biologically relevant molecules to the mucosa offers further potential to the probiotics.

Prebiotics are the non-digestible food ingredient that beneficially affects the host by stimulating the growth or activity of a genus of bacteria. A number of prebiotics have been implicated in cancer prevention [19]. Prebiotics include dietary fiber sources such as inulin that promote the growth of bifidobacteria. Dietary polyphenols include flavonoids, phenolic acids, lignins present in tea, wine, fruits, nuts and vegetables. Ellagic acid is polyphenol present in certain berries and nuts that is an antioxidant with cancer preventive properties [20]. Epidemiological studies have reported correlations between equol or equol-producing bacteria and diminished breast cancer risk in women and diminished prostate cancer in men in Asian populations [21].

However, further studies are needed to determine whether probiotics can be used as protective agents for the prevention of human colon cancer. It is possible that a microbiota favoring commensal bacteria could alter the immune response to tumors at extraintestinal as well as intestinal sites.

5. Treatment of inflammatory bowel disease and colitis

Bacterial species isolated from inflammatory bowel disease (IBD) patients have shown to be capable of inducing intestinal inflammation (e.g., enterotoxigenic *B. fragilis, Bacteroides vulgates*). Intestinal inflammation was seen in germ-free SCID mice colonized with individual or combinations of strains of *Enterococcus faecalis, Fusobacterium mortiferum, Bacteroides distasonis* and segmented filamentous bacteria (SFB) [22]. SFB also play a role in the development of experimental autoimmune encephalomyelitis (EAE) [23] and Rheumatoid arthritis(RA) [24]. Because of the potentially harmful role of these bacteria, antibiotics are frequently prescribed to treat IBD [25].

A probiotic nonpathogenic strain of *E.coli* has been shown to be effective in patients diagnosed with ulcerative colitis [26]. More recently, a probiotic product called VSL#3 which is a combination of eight probiotics: *Bifidobacterium breve, B. longum, Bifidobacterium infantis, L. acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus bulgaricus* and *Streptococcus thermophilus* have demonstrated efficacy for inducing remission in ulcerative colitis [27].

6. Fecal microbiota transplantation and IBD

The results of fecal microbiota transplantation (FMT) show very promising but discrepant results. A meta-analysis recently conducted by Colman *et al.* showed that 45% of patients achieved clinical remission and reduced some anti-inflammatory drugs after FMT [28–30]. A recently conducted randomized trial in patients with ulcerative colitis showed that the clinical remission was not statistically significant with FMT due to small study numbers but in all the responders a shift in the microbiota composition was observed supporting the role of microbiota manipulation in the treatment of IBD [31, 32].

7. Helminth: induced suppression of IBD

Novel treatment strategies for IBD and celiac disease are being developed using parasitic nematodes particularly *Trichuris* spp. and *Necator americanus* [33, 34].

Studies of the impact of parasite colonization on the human gut microbiota have shed light on the potential role of the gut microbiota in whipworm-mediated suppression of inflammation. The therapeutic ability of *T. trichura* whipworms to improve clinical symptoms of inflammation associated with significant changes in the composition and relative abundance of different gut bacterial species has been shown [35]. A significant decrease in the bacterial phylum cyanobacteria accompanied by an expansion of Bacteroidetes and Tenericutes was seen in Trichuris-infected ICD macques. In another study, the administration of a single dose of *T. suis* ova was able to alter the composition of the gut microbiota of infected pigs with IBD, including a reduction in the abundance of Fibrobacter and Ruminococcus expansion of Campylobacter [36].

Another study involving experimental infection with *Heligmosomoides polygyrus bakeri* in a mouse model of IBD revealed a significant expansion of the bacterial family Lactobacillaceae in the ileum of infected mice, which correlated with disease outcome [37].

8. Therapeutic potential of Hookworms

While heavy burdens of hookworm parasites are associated with pathological effects, experimental infections with small numbers of *N. americanus* are safe and well tolerated. When administered in a mouse model of IBD, hookworm excretory/secretory products protect against inflammation and weight loss [38]. A pilot study done to explore the impact of experimental infections with *N. americanus* on the human gut microbiota has shown increased bacterial richness at 8 weeks post infection in the volunteer subjects [39]. A higher species richness of the gut microbiota has been associated with healthier homeostasis.

9. Role of microbiota in allergic diseases

Allergic disease development has been associated with alterations in the intestinal microbiota. Infants with food allergies were found to exhibit lower lactobacilli and bifidobacteria species while coliforms and *Staphylococcus aureus* were higher [40]. Bifidobacteria was decreased while increase in clostridia was found in infants with atopic dermatitis [41]. Administration of *L. casei* GG to the mothers before and after delivery prevents atopic eczema, which develop later in children at risk [42]. A number of studies have been performed using probiotics to treat the severity of various allergic diseases, including atopic eczema, atopic dermatitis and food allergy in these children [43, 44]. Oral administration of optimal combinations of probiotic Lactobacilli and Bifidobacteria in murine models is able to reduce allergic diseases. This could be due to lower Th2 cytokine secretion on innate exposure [45, 46].

Environmental exposures in early infancy are thus a deciding factor of the composition of gut microbiota which decides the development of immune function in an individual. These differences in immune function link to the development of allergy and asthma [47].

A possible interpretation is that the bacteria ingested or inhaled served as a kind of tolerance inducing adjuvant for allergens ingested or inhaled as reported recently that commensal bacteria protect against food allergen sensitization [48]. The bacteria associated with protection were largely members of the Bacteriodetes and Firmicutes phyla (e.g., Rickenellaceae, Porphyromonadaceae, Lachnospiraceae, Prevotellaceae, etc.).

Several associations exist between commensal microbiota and the development of allergic diseases. In prospective studies, early fecal samples of infants who go on to develop allergies, compared to those who remain healthy, grew less Enterococci, Bifidobacteria, Bacteroides, Clostridia and Staphylococci [49]. Japanese infants developing early allergy have different *bifidobacteria* spp compared to nonallergic infants [50]. In an experimental animal model of food

allergy, the gut microbiota and its stimulatory action on innate immune system by toll-like receptors (TLR), particularly TLR4, have been found. Mice susceptible to food allergies have a mutation in TLR4 blocking its signaling [51].

10. Mode of action of probiotics to treat/prevent allergy

Probiotics have been suggested to act by reducing the permeability of intestine [52]. Probiotics induce low grade inflammation characterized by increases in CRP, total IgA, total IgE and IL-10 levels. They can interact with the host immune system and modify the natural course of allergic disease [53]. Recent data indicate that probiotics could modulate the production of cytokines by monocytes and lymphocytes [54]. The dendritic cells may be stimulated by probiotic bacteria in the intestinal lumen and express TLR-2 and inflammatory cytokines [55]. Therefore, the stimulation of innate immunity may be the cause of the observed inflammatory signs and beneficial clinical effects.

11. Role of microflora in obesity

The microbes occupying the human gut are in direct relation to obesity. The obese have more Firmicutes and fewer Bacteroidetes. The more Bacteroidetes, the more weight loss by an obese person [56]. An opportunistic pathogen isolated from the gut of obese human causing obesity in germ-free mice has been identified [57].

Housing mice with obese microbiota with those of lean microbiota suppresses the obesity factor in the former mice [58]. These data indicate clearly that microbiota can influence metabolic parameters or even obesity [59, 60].

12. Regulation of obesity by gut flora

12.1. Extraction of addition calories from ingested food

The intestinal flora of obese individuals has been suggested to undergo changes that would increase the extraction of calories from nutrients. An animal study, using germ-free mice observed that these mice despite ingesting greater amounts of food than conventionally raised mice, presented a lower amount of body fat [61]. Another study has shown that obese mice had a reduced number of Bacteroides and a proportional increase in Firmicutes when compared to lean mice [62]. They also proposed that flora of obese mice favored a greater capacity of extracting calories from food, as the feces of these mice were observed to have less calories and a greater amount of fermentation end products.

12.2. Induction of subclinical inflammation

A correlation between obesity and intestinal flora has been proposed in type 2 diabetes. The inflammation that leads to diabetes in obesity has been proposed to be triggered by LPS of Gram-negative bacteria, which compose the intestinal flora [63]. Also it has been seen that in humans, individuals with type 2 diabetes presented lower levels of serum lipopolysaccharide than patients with type 2 diabetes by age [64]. Also in animal studies, it has been seen that mice treated with a high fat diet were observed to present a reduction in intestinal permeability and in serum LPS levels, in addition to a decrease in inflammation of adipose tissue and macrophage infiltration, after the modification of gut flora by antibiotics [65].

13. Conclusion

The endogenous gastrointestinal flora plays a fundamentally important role in health and disease. The characterization of this diverse ecosystem fuelled by the recognition of the potential value of probiotics and other means of modifying gut flora can be used as future therapeutic modalities. It may hence be possible to establish profiles of the microbiota in humans based on the bacterial species composition of the enterotypes [66].

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