A healthy microbiota is defined by high diversity and an ability to resist change under physiological stress. In contrast, microbiota associated with disease is defined by lower species diversity, fewer beneficial microbes and/or the presence of pathobionts.

Clinical Consequences of Diet-Induced Dysbiosis
by Yee Kwan Chan et al.

Key insights
Various disease states are associated with alterations in the balance between beneficial and harmful bacteria that reside in the intestine. This dysbiosis has far-reaching effects on local and systemic immunity, and underpins the pathogenesis of disorders such as inflammatory bowel disease, colorectal cancer, diabetes, atherosclerosis and nonalcoholic fatty liver disease. Interventions that target the microbial profile of the gut have tremendous potential for addressing these disorders.

Current knowledge
There is a complex tripartite relationship between diet, microbes and the gut epithelium. Beyond the postnatal period, long-term dietary patterns have a strong influence on the composition of gut microbes. For example, regular red meat consumption favors a Bacteroides-rich microflora, whereas Prevotella species tends to dominate in vegetarians. A high-fat diet may induce dysbiosis through the actions of bile, which could affect the growth of some microbes. An examination of the digestive process may offer greater insight into the mechanisms through which diet can influence dysbiosis and disease.

Practical implications
Not surprisingly, diet and gut microbes are two critical factors in the pathogenesis of gastrointestinal diseases. Intestinal dysbiosis has also been linked to systemic conditions such as metabolic and cardiac disorders. Although diet is a tempting intervention, our understanding of how to manipulate diet to promote a healthy microbiota is still in its early days. Bacteriotherapy provides a novel approach for restoring healthy homeostasis through the gut microbes. This is achieved through the use of various interventions, including the removal of pathogenic bacteria with antibiotics, supplementation with prebiotics and/or probiotics, and most recently, introduction of a new healthy microbial ecosystem by transplanting fecal bacteria from a healthy donor.

Recommended reading
Clinical Consequences of Diet-Induced Dysbiosis

Yee Kwan Chan  Mehrbod Estaki  Deanna L. Gibson
Department of Biology, University of British Columbia Okanagan, Kelowna, B.C., Canada

Key Messages
- An undesirable alteration of the microbiota resulting in an imbalance between protective and harmful bacteria is termed dysbiosis.
- Dietary patterns alter the intestinal microbiota ecologically and functionally and this results in physiological consequences to the host.
- Dysbiosis has been implicated in many human disease conditions including local gastrointestinal and systemic diseases.
- Restoration and maintenance of a healthy gut microbiota may be an effective, inexpensive and safe remedy to diseases associated with dysbiosis.

Colonization and Diversity of Gut Microbes
Humans have co-evolved with vast amounts of microorganisms that inhabit the body. The average human being harbors 10 times more bacterial cells than their own cell numbers. These microbes colonize the skin, nasal and oral cavity, urogenital and gastrointestinal tract (GIT). Among all sites, the GIT is the most densely populated area with the colon alone harboring over $10^{10} - 10^{12}$ colony-forming units per gram of feces, or 70% of all microbes in the human body [1].

Colonization and Diversity of Gut Microbes

Key Words
Intestinal microbiota · Dysbiosis · Nutrition · Inflammation · Disease susceptibility · Bacteriotherapy

Abstract
Various disease states are associated with an imbalance of protective and pathogenic bacteria in the gut, termed dysbiosis. Current evidence reveals that dietary factors affect the microbial ecosystem in the gut. Changes to community structure of the intestinal microbiota are not without consequence considering the wide effects that the microbes have on both local and systemic immunity. The goal of this review is to give insight into the importance of gut microbiota in disease development and the possible therapeutic interventions in clinical settings. We introduce the complex tripartite relationship between diet, microbes and the gut epithelium. This is followed by a summary of clinical evidence of diet-induced dysbiosis as a contributing factor in the development of gastrointestinal diseases like inflammatory bowel disease, irritable bowel syndrome and colorectal cancer, as well as systemic diseases like obesity, diabetes, atherosclerosis and nonalcoholic fatty liver disease. Finally, the current dietary and microbial interventions to promote a healthy microbial profile will be reviewed.

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Key Messages

- An undesirable alteration of the microbiota resulting in an imbalance between protective and harmful bacteria is termed dysbiosis.
- Dietary patterns alter the intestinal microbiota ecologically and functionally and this results in physiological consequences to the host.
- Dysbiosis has been implicated in many human disease conditions including local gastrointestinal and systemic diseases.
- Restoration and maintenance of a healthy gut microbiota may be an effective, inexpensive and safe remedy to diseases associated with dysbiosis.
While it has been thought that a fetus is sterile in utero, there is some evidence that microbial DNA and potentially even microbes are exposed to the fetus and fetal gut through the placenta [discussed by Luoto et al. in this issue]. During birth, microbial colonization of the GIT occurs and develops rapidly thereafter with maternal and environmental microbes. Colonization does not appear to be random but preprogrammed; yet, the mode of infant delivery, antibiotic exposure, nutrition and other extrinsic factors influence microbial ecology (fig. 1). Microbial diversity increases during the first few years of life and then stabilizes by 2–4 years of age resembling that of an adult [2]. Most of these bacteria associate with the intestinal mucosal surface and maintain their specific niches over time as indigenous populations. Newly introduced bacteria either pass through the GIT in the stool or compete with indigenous bacteria to create their niche. While there is evidence that the intestinal microbiota is relatively stable throughout life, extrinsic factors such as stress, alcohol consumption, exercise and dietary choices do change the ecology and function of the microbiota in adults. We do not yet understand how dynamic the ecology of the microbiota is, so microbial changes may only be transient and reversible, but more research is required to understand this plasticity.

Humans carry 500–1,000 bacterial species in the GIT of which the majority belongs in only two phyla: the Firmicutes and Bacteroidetes (>90%). Other phyla present to a lesser extent include: Actinobacteria, Proteobacteria, Fusobacteria, Spirochaetae and Verrucomicrobia. While the dominating phyla are relatively constant between individuals, diversity increases along the taxonomic line with each individual harboring over a hundred unique species. Three distinct clusters of gut microbiota have been identified in humans. These ‘enterotypes’ are mainly driven by species composition and are not geographical, age or gender specific [3]. An undesirable alteration of the microbiota resulting in an imbalance between protective and harmful bacteria is termed dysbiosis and may cluster as a specific entero-
In support of this, enterotypes have been shown to associate with chronic ailments such as colonic inflammation [3], symptomatic atherosclerosis [4] and nonalcoholic steatohepatitis [5]. Factors such as nutrient load, macro- and micronutrients induce changes to the ecology and functionality of the gut microbiota, and long-term dietary patterns can alter the original enterotype [6]. Identifying dietary factors that promote beneficial microbes and prevent pathobiont intrusion may be an important tactic in the prevention of dysbiosis-associated diseases.

**The GIT, Microbes and Diet**

The gut microbial ecosystem has tremendous influence on the overall health status of the human host. The microbiota lies at the interface of the internal and external environment in the gut forming a tripartite relationship with the intestinal epithelial cells and dietary antigens (fig. 2). Due to this conspicuous location, the microbiota is able to liaise with both the intestinal mucosal surface and the luminal environment that contain partially digested food. Dietary antigens interact with both the microbes and the intestinal epithelium. Microbes impart physiological changes to the host by interacting with the

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**Fig. 2.** GIT under homeostatic and dysbiotic conditions. The intestinal microbiota lies strategically at the interface of the internal and external environment of the gut. It plays several important biological roles including: aiding in digestion and absorption of nutrients from partially digested food, production of SCFA – a primary energy source for intestinal epithelial cells (IECs), stimulating immune responses by releasing ligands, and protection against enteropathogens by production of antimicrobial peptides (AMPs). In addition, commensal bacteria also work as a protective barrier against pathobionts through competition for space and food. The highly selective permeable monolayer made up of IECs and adjacent tight junctions acts as the only barrier separating the microbe-rich lumen side from the sterile submucosal area. Damage to this layer or loss of the tight junctions’ integrity in a diseased state allows for increased passing of microorganisms and their immune-stimulating molecules such as MAMPs, i.e. lipopolysaccharide, to the submucosa where ultimately they may enter circulation, induce pro-inflammatory signaling and recruit leukocytes.

Goblet cells found within the IEC layer replenish the mucus layer covering the epithelium by releasing large glycoprotein polymers such as mucin. The secretion of mucus droplets by the goblet cells is regulated by the microbiota, thus dysbiosis plays a key role in disruption of the mucus layer. Dietary antigens (dark grey triangles) can interact with the microbiota and IECs inducing biological responses in both. After the IEC layer, antigen-presenting cells (APC) act as the next line of cellular defense. APCs, which include dendritic cells (DC), M1 and M2 type macrophages, are part of the innate immune response which protects the host against invading pathobionts. Typically, under dysbiotic conditions, overactivation of the innate immune response leads to higher than normal expressions of activated M1 to M2 type macrophages which increase pro-inflammatory events. Regulatory T cells (Treg) regulate the adaptive immune response by maintaining tolerance to self-antigens and suppressing overactivation of the immune responses. Insufficient Treg expression can lead to increased levels of Th1 and Th17 facilitating chronic inflammatory responses.
intestinal epithelial cells via innate immune receptors [discussed by Walker in this issue]. The intestines contain the largest mass of lymphoid tissue in the body: the gut-associated lymphoid tissue (GALT). The GALT relays signals from the mucosal surface to the rest of the body through various immune cells and immune receptors including innate toll-like receptors (TLRs) and NOD-like receptors (NLRs). The intestinal microbiota plays crucial roles in the GIT development, systemic immunity and colonic homeostasis. Gut microbiota can modulate the function and responsiveness of intestinal immune cells, like T regulatory cells, to bacterial products. This is required to regulate mechanisms that keep both mucosal and systemic immunity in balance, allowing for mucosal surfaces to tolerate harmless bacteria, yet adequately respond to invading pathogens. Production of short-chain fatty acid (SCFA) by gut microbes also plays an important role in regulating homeostasis in the gut. For example, butyrate produced by colonic microbes is not only the main energy source for colonocytes, but also inhibits intestinal cell proliferation which can reduce colitis symptoms [7]. Given the vital relationship between microbes and intestinal health, a normal functioning microbiota is crucial to maintaining a balance of local and systemic immunity. As discussed below, in the absence of a healthy microbiota, immune disorders may arise. Identifying dietary factors that control the intestinal microbial ecology and their role in enteric disease susceptibility could provide insight into the functioning of the microbiota in healthy and diseased individuals. Yet, due to the vast diversity of dietary antigens and gut microbes, we are challenged to define the exact interactions between microbes, dietary antigens and epithelium and their consequences to the host.

Dietary antigens can interact with both the microbiota and the intestinal mucosa, initiating biological reactions in the host. Food contains numerous compounds that shape the chemistry of the gut as well as the whole body. For example, dietary antigens are absorbed through the intestine which results in metabolites in the circulating fluids like blood and lymph [8]. The association of specific metabolites in the body with dominant bacterial taxa in infants suggests that the chemical composition of the diet can define the gut microbial ecology [9]. While dietary factors can directly affect the functionality of intestinal epithelial cells and the underlying immune cells [10], dietary antigens also alter the intestinal ecosystem by enabling certain microbial populations to proliferate and dampening the dominance of others (reviewed by Brown et al. [11]). The consequences of dysbiosis are not innocent, but detrimental when pathobionts (any disease-causing microorganism) become prominent in the microbial communities. To support this idea, oral microbes sequenced from ancient teeth found in skeletons from various periods of time have become increasingly cariogenic dominant, or rich in microbes that promote dental disease [12]. These microbial changes have occurred during the two greatest dietary shifts in human evolution: the transition from the hunter-gatherer ‘Paleolithic’ period to the carbohydrate-rich farming ‘Neolithic’ period (~10,000 years ago) and the initiation of the industrialized period characterized by processed foods (~160 years ago). These findings support the notion that diet induces dysbiosis which alters the health of the host.

Evidence suggests that dietary factors alter intestinal ecology in both rodent models (reviewed by Brown et al. [11]) and in humans, and the changed ecology is associated with clinical consequences (table 1). Neonatal nutrition is critical in the initial development of microbial ecology [13]. For example, formula-fed infants have higher levels of pathobionts like Enterobacteriaceae and less beneficial microbes like *Bifidobacteria* spp. compared to breastfed infants [14]. Interestingly, infants fed cow’s milk but not infant formula supplemented with fish oil had increased *Bifidobacteria* spp. [15] suggesting that postnatal nutrition could be used to target specific changes in microbial diversity. Beyond the postnatal period, long-term dietary choices are strongly associated with the gut microbiota composition [6]. In humans, diets that include regular red meat consumption tend to favor a predominantly *Bacteroides*-rich gut ecosystem [16], while *Prevotella* species dominate in vegetarians [17]. European children are deficient in Bacteroidetes and enriched with Enterobacteriaceae compared to rural African children who consume diets rich in fiber [18]. This study may be an important key to understanding the increase in noncommunicable diseases in European children. While it is generally agreed that high-fat diets promote dysbiosis, recent evidence from our laboratory suggests that the specific type of dietary fatty acid as opposed to total calories from fat appears to be important. For example, diets rich in ome-

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_Diet, Microbes and Human Health_
Table 1. Summary of studies showing that dietary factors change microbial profiles in humans and the associated clinical consequences

<table>
<thead>
<tr>
<th>Dietary factor implicated</th>
<th>Specific diet</th>
<th>Sample size</th>
<th>Location of microbes analyzed in host</th>
<th>Bacterial population altered</th>
<th>Method of bacterial detection</th>
<th>Associated host effect</th>
<th>Ref. PubMed accession No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat</td>
<td>high fat (shortening) and high sugar</td>
<td>1 man, 15 mice</td>
<td>feces of men</td>
<td>↑ Clostridium innocuum, Catenobacterium mitsuikai, Enterococcus spp., ↓ Bacteroides spp.</td>
<td>multiplex amplicon pyrosequencing</td>
<td>↑ obesity when transplanted into mouse</td>
<td>20368178</td>
</tr>
<tr>
<td></td>
<td>fish oil-supplemented infant formula versus cow’s milk</td>
<td>65</td>
<td>feces of 10-month-old infants</td>
<td>consumption of cow’s milk and infant formula resulted in different microbial patterns; fish oil supplementation affects the microbial pattern of the cow’s milk group only</td>
<td>DGGE</td>
<td>not examined</td>
<td>17460496</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>increased carbohydrate-rich foods</td>
<td>34</td>
<td>mouth of ancient skeletons</td>
<td>cariogenic-dominant</td>
<td>454 pyrosequencing</td>
<td>↑ dental disease</td>
<td>23416520</td>
</tr>
<tr>
<td></td>
<td>diets high in resistant starch compared to non-starch polysaccharides and low carbohydrate</td>
<td>14</td>
<td>feces of overweight men</td>
<td>↑ Firmicutes, Eubacterium rectale, Roseburia, Ruminococcus bromii (R-ruminococi)</td>
<td>qPCR</td>
<td>↑ digestibility of starch</td>
<td>20686513</td>
</tr>
<tr>
<td></td>
<td>dietary fiber-rich diets found in rural Africa compared to Western European diets</td>
<td>29</td>
<td>fecal microbiota of children aged 1–6 years</td>
<td>↑ Bacteroidetes, ↑ Firmicutes, ↑ Prevotella and Xylanibacter, ↑ Enterobacteriaceae</td>
<td>454 pyrosequencing</td>
<td>↑ bacterial genes for cellulose and xylan hydrolysis, ↑ SCFAs</td>
<td>20679230</td>
</tr>
<tr>
<td></td>
<td>inulin and Brussels sprouts</td>
<td>1 man, 48 rats</td>
<td>feces</td>
<td>↑ Bifidobacterium and Lactobacillus</td>
<td>TTGE</td>
<td>↑ cecal butyrate and acetate when transplanted into rats</td>
<td>15975167</td>
</tr>
<tr>
<td></td>
<td>kiwi fruit</td>
<td>10</td>
<td>feces</td>
<td>↑ Bifidobacterium and Bacteroides-Prevotella-Porphyromonas group</td>
<td>qPCR</td>
<td>↑ microbial glycosidases and SCFAs</td>
<td>22576129</td>
</tr>
<tr>
<td></td>
<td>sucrose-free chocolates + maltitol + bulking agents (polydextrose and resistant starch)</td>
<td>40</td>
<td>feces</td>
<td>↑ Bifidobacterium and Lactobacillus</td>
<td>FISH</td>
<td>↑ SCFAs propionate and butyrate</td>
<td>20370946</td>
</tr>
<tr>
<td></td>
<td>bread enriched with arabinoxylan-oligosaccharides</td>
<td>40</td>
<td>feces</td>
<td>↑ Bifidobacterium and Lactobacillus</td>
<td>FISH</td>
<td>↑ butyrate; ↓ isovalerate and fatty acids associated with protein fermentation</td>
<td>22657950</td>
</tr>
<tr>
<td>Protein</td>
<td>vegetarian</td>
<td>29</td>
<td>feces</td>
<td>↑ in overall bacterial DNA, ↑ the amount and changing the diversity of Clostridium cluster IV</td>
<td>DGGE, qPCR</td>
<td>not examined</td>
<td>19641302</td>
</tr>
<tr>
<td></td>
<td>high red-meat diet</td>
<td>24 mice</td>
<td>feces</td>
<td>↑ Bacteroides spp.</td>
<td>qPCR</td>
<td>no functional changes observed when transplanted into mouse</td>
<td>23239972</td>
</tr>
<tr>
<td></td>
<td>gluten-free diet</td>
<td>10</td>
<td>feces</td>
<td>↑ Bifidobacterium and Lactobacillus, ↑ Enterobacteriaceae</td>
<td>not mentioned</td>
<td>↑ TNF-α, IFN-γ, IL-8 and IL-10 in peripheral blood mononuclear cells</td>
<td>21327021</td>
</tr>
<tr>
<td>Breastfeeding compared to formula feeding</td>
<td>not reported</td>
<td>feces of 3-month-old infants</td>
<td>↑ Bacteroidetes, ↑ Firmicutes and Verrucomicrobia</td>
<td>454 pyrosequencing</td>
<td>gene networks (inflammation, cell adhesion, barrier function, histamine, etc.) differentially expressed in exfoliated intestinal epithelial cells</td>
<td>22585924</td>
<td></td>
</tr>
<tr>
<td></td>
<td>breastfeeding compared to formula feeding</td>
<td>207</td>
<td>mouth of 3-month-old infants</td>
<td>↑ Lactobacillus spp.</td>
<td>culturing, qPCR</td>
<td>inhibited growth of the cariogenic Streptococcus spp.</td>
<td>22954540</td>
</tr>
<tr>
<td>Other</td>
<td>ready-to-use therapeutic food composed of peanut paste, sugar, vegetable oil and milk fortified with vitamins and minerals</td>
<td>634</td>
<td>feces of Malawian twin pairs over the first 3 years of life</td>
<td>↑ Actinobacteria in kwashiorkor twin compared to healthy twin</td>
<td>multiplex shotgun sequencing</td>
<td>severe acute malnutrition caused when kwashiorkor microbiota transplanted into mouse</td>
<td>23363771</td>
</tr>
<tr>
<td></td>
<td>3 cups of coffee daily for 3 weeks</td>
<td>16</td>
<td>feces</td>
<td>↑ Bifidobacterium spp.</td>
<td>DGGE, FISH</td>
<td>↑ metabolic activity of Bifidobacteria spp.</td>
<td>19217682</td>
</tr>
<tr>
<td></td>
<td>dark chocolate</td>
<td>30</td>
<td>urine</td>
<td>not examined</td>
<td>1H NMR, MS analysis</td>
<td>different energy profiles, hormonal metabolism and gut microbial activity</td>
<td>19810704</td>
</tr>
</tbody>
</table>

DGGE = Denaturing gradient gel electrophoresis; FISH = fluorescence in situ hybridization; 1H NMR = proton nuclear magnetic resonance; MS = mass spectrometry; qPCR = quantitative polymerase chain reaction; TTGE = temporal temperature gradient electrophoresis.
ga-6 polyunsaturated fatty acids (PUFAs) cause blooms of pathobionts, but isocaloric diets supplemented with omega-3 PUFA can reverse such microbial alterations in mice [19, 20].

Diet, Microbes and Human Health

One of the main functions of the microbiota is to break down food to make it available to the host and as a result, the effect of dysbiosis on metabolism has received considerable attention in current research. Humanized mice, or germ-free mice transplanted with human fecal microbiota, are now being used to test the effects of human gut microbiota on mammalian physiology. Using this model, humanized mice fed a ‘Western’ diet high in fat and sugar were shown to have increased adiposity as a result of decreased ratios of Bacteroidetes to Firmicutes in the fecal microbiota [21]. Similarly, the gut microbiome was shown to play an important role in the development of kwashiorkor disease, a severe form of malnutrition [22]. In this study, the fecal microbiota of Malawian twins that were discordant for kwashiorkor was transplanted into mice. When fed a Malawian diet, weight loss and metabolic perturbations were more severe in the mice that received microbiota from the twin that had kwashiorkor compared to those that received microbes from the unaffected twin. Another study elegantly links specific nutrition factors to microbial ecology and the complex biological consequences that occur in the intestinal epithelial cells [23]. This study examined infant fecal microbiota with varying human milk oligosaccharide consumption and found that differences in microbiota modulated major gene networks including signal transduction, inflammation, histamine, cell migration and adhesion. GIT motility is another major function that is affected by the intricate interactions amongst diet and microbes. When humanized mice were fed a diet containing fermentable fructooligosaccharides (FOS), gastrointestinal transit time was altered [24].

Dietary factors alter the microbial ecology in the small intestine where food antigens are primarily digested, as well as the cecum and the distal colon where digestion is not a main function of the host but an important function of the microbes. High-fat feeding induces dysbiosis through the direct antimicrobial activity of bile. Insoluble lipid molecules are broken into small droplets by bile and lipases which become soluble free fatty acids and monoglycerides, which then enter the bloodstream. As shown, bile secreted during high-fat feeding could affect the growth or survival of some microbes [25], although we have found that varying types of fatty acids play more of a role in dysbiosis than high-fat feeding alone [19, 20]. The process of lipid digestion may give more clues as to how microbes could be related to various diseases.

Clinical Evidence for Intestinal Dysbiosis-Associated Diseases

A healthy microbiota is defined by high diversity and an ability to resist change under physiological stress. In contrast, microbiota associated with disease is defined by lower species diversity, fewer beneficial microbes and/or the presence of pathobionts. Given the role of the microbiota in mediating host metabolism and immunity, disruption of the microbiota has been associated with various human diseases of the GIT and systemically throughout the body. Here, we review evidence from recent clinical studies connecting dysbiosis to various diseases, with an emphasis on the involvement of dietary factors.

Intestinal Dysbiosis in Gastrointestinal Diseases

The functional roles of the human GIT include nutrient absorption, waste removal via peristalsis, defense against ingested pathogens and prevention of translocation of food or antigens into the bloodstream. The gut microbiota regulates several of these functions including peristalsis, barrier function and maintaining balanced inflammatory and homeostatic responses. Disruption of the gut microbiota renders the GIT vulnerable to local disease states (fig. 3).

Inflammatory Bowel Diseases

Clinical studies have identified dysbiosis in patients with inflammatory bowel disease (IBD), including both Crohn’s disease (CD) and ulcerative colitis (UC). Studies examining twins have shown enriched Actinobacteria and Proteobacteria and reduced Bacteroidetes in the twins with UC as compared to their healthy siblings [26]. An increase in sulfide-generating Desulfovibrio subspecies and Fusobacterium varium that can invade the epithelium are present in UC patients [27], while anti-in-
Inflammatory-associated *Faecalibacterium prausnitzii* is reduced [28]. A typical trait of human IBD patients is reduced gut microbial biodiversity [29, 30]. For example, patients with CD had reduced levels of *Faecalibacterium* and *Roseburia*, increased *Ruminococcus* [30] and Enterobacteriaceae including adherent-invasive *Escherichia coli* [31]. Excessive milk fat [32] and omega-6 PUFA [19] were shown in rodents to exacerbate IBD through dysbiosis, which is supported by a 30% increased risk for UC by excessive consumption of omega-6 PUFA [33].

**Colorectal Cancer**

The adaptation of African-Americans to Western diets has been shown to increase the incidence of and mortality due to colorectal cancer (CRC) corresponding to altered fecal microbial profiles [34]. CRC patients are shown to have increased levels of certain bacterial species such as *Bacteroides fragilis*, *Enterococcus*, *Escherichia/Shigella*, Klebsiella, *Streptococcus*, Peptostreptococcus, *Roseburia* and decreased abundance in butyrate-producing *Lachnospiraceae* [35]. Growing evidence supports an inverse relationship between dietary fiber, fruit and vegetable intake to CRC development risk. Long-term fiber intake can result in a microbiota enterotype that positively associates with Firmicutes and Proteobacteria and inversely with Bacteroidetes, *Actinobacteria* [6] and *Bifidobacteria* [36]. This may be through improved intestinal barrier function since beneficial microbes improve barrier integrity and this is associated with decreased complications in patients undergoing colectomy [37]. Dietary fiber intake can also reduce the risk of CRC development by promoting a gut microbiota that is enriched by SCFA production [38].

**Irritable Bowel Syndrome**

Diet and gut microbiota are two crucial components implicated in the pathogenesis of irritable bowel syndrome (IBS). Poorly absorbed dietary carbohydrates induce prolonged hydrogen production in the intestines of patients with IBS (Rome III criteria), which is important since the amount of methane produced corresponds with disease symptoms [39]. IBS patients have an altered carbohydrate and protein energy metabolism in the gut, accompanied by changes in the diversity of particular gut bacterial genera [40], where enriched Firmicutes and reduced Bacteroidetes are found to be associated with a distinct subset of IBS patients [41]. Studies conducted in diarrhea-dominated IBS patients show reduced fecal...
aerobic bacteria, *Bifidobacteria* and *Verrucomicrobiun* and an increase in *Lactobacillus*, *Veillonella*, *Prevotella* and *Parasporo* [42, 43]. In addition, the increase in *E. coli* and decrease in *Leptum* and *Bifidobacteria* and bacteria involved in bile acid transformation is accompanied by an increase in fecal bile acids, which acts as an endogenous laxative further exacerbating disease symptoms [44].

*Intestinal Dysbiosis in Systemic Diseases*

In addition to local GIT diseases, intestinal dysbiosis is also associated with systemic diseases such as obesity, diabetes, atherosclerosis and nonalcoholic fatty liver disease (NAFLD) (fig. 3). Indeed, many metabolic diseases are associated with chronic inflammation induced by lipopolysaccharide, a major component of the outer membrane of Gram-negative bacteria. Other causative factors associated with the intestinal microbiota include gut barrier dysfunction, immunomodulation, production of SCFA and other metabolites, as well as changes to metabolic pathways involved in nutrient or energy harvest.

**Obesity**

Current evidence reveals that gut microbes are critical in overall energy harvest influencing obesity [45]. Fat- and carbohydrate-restricted diets lead to increased Bacteroidetes and decreased Firmicutes [46]. Other diets with low carbohydrate/high protein content, resistant starch [47] or high dietary fiber [48] also lead to distinct increases in various bacterial populations. Obese children have a microbiota enriched with Enterobacteriaceae [49], reduced *Bacteroides* and Bacteroidetes to Firmicutes ratio that are negatively correlated with body mass index [50]. Obese children also have increased Desulfovibrio and *Ak kermansia muciniphila* [49] found important for gut barrier dysfunction [51]. Moreover, obese children also have increased SCFAs and more exhaustive substrate utilization implicating that microbes are capable of increased energy harvest [52]. Similarly, obese adolescents had gut microbes that were more engaged in de novo B12 synthesis and butyrate production [53]. Finnish women with metabolic disorders were found to have increased *Eubac- terium rectale-Clostridium coccoides* that efficiently harvest energy and nutrients and positively correlated with several metabolic markers [54].

**Diabetes**

Type 2 diabetes (T2D) is a metabolic disorder defined by insulin resistance, impaired intestinal permeability, endotoxemia and chronic inflammation, all of which are linked to diet-induced dysbiosis [55]. Patients with T2D have been shown to have a fecal microbiota with reduced populations of Firmicutes including microbes from the Clostridia clusters [56]. Recently, a metagenome-wide association study involving 345 Chinese subjects had their fecal microbiota shotgun sequenced and dysbiosis was confirmed in patients with T2D. The results revealed that the patients’ fecal microbiota was enriched with more opportunistic pathogens and less microbes involved in butyrate production. This resulted in increased microbial functions involving sulfate reduction and oxidative stress resistance [57]. Another study found that T2D patients of Chinese origin also displayed a microbiota decreased in *Bifidobacteria* spp. [58], a beneficial microbe often shown to be decreased in rodent models of T2D. Although mounting evidence reveals that intestinal microbes are important in T1D pathogenesis, so far, little evidence has linked dietary factors to disease progression.

**Atherosclerosis**

Recent evidence reveals that gut microbiota participates in atherosclerosis, a chronic inflammatory condition of the arteries with the formation of multiple plaques that restrict blood flow. Various microbial byproducts or so-called microbial-associated molecular patterns (MAMPs) play a pivotal role in atherogenesis [59]. Additionally, the metabolism of dietary phosphatidylcholine and the subsequent generation of cardiovascular disease risk markers are gut microbiota dependent [60]. Specific bacterial phylotypes are present in atherosclerotic plaques that are common to oral or gut samples from patients with atherosclerosis, where the amount of bacterial DNA correlated with the amount of leukocytes found in the atherosclerotic plaque.
nated enterotypes were under- and overexpressed, respectively, in atherosclerotic patients. The disease microbiome was enriched in genes encoding peptidoglycan synthesis but depleted in phytoene dehydrogenase required for metabolism of lipid-soluble antioxidants [4]. Although there are limited clinical studies to date, they present a powerful message to potential therapeutic strategies against atherosclerosis targeted to the gut.

Nonalcoholic Fatty Liver Disease

NAFLD is associated with small intestinal bacterial overgrowth (SIBO) and the resulting effects of increased acetaldehyde, trimethylamine, trimethylamine N-oxide and tumor necrosis factor-α [62]. Given that the gut and liver are connected by the portal venous system, it makes the liver more vulnerable to translocation of bacteria, bacterial products, endotoxin or secreted cytokines. An obesogenic microbiota can alternate liver function by stimulating hepatic triglyceride and modulating systemic lipid metabolism that indirectly impact the storage of fatty acids in the liver [63]. In support of this, SIBO correlates with a leaky gut in humans [64] and hepatic steatosis in obese patients [65]. The severity of NAFLD is associated with chronic endotoxin exposure in humans [66]. Choline deficiency and fatty liver development have also been associated with changes in abundance of γ-Proteobacteria and Erysipelotrichi [67]. The diet-induced change of such bacterial abundance further helps predict the risk of fatty liver development.

Bacteriotherapy to Promote a Healthy Microbial Profile

Diet is considered a modifiable intervention; however, our understanding of how to manipulate diet to promote a healthy microbiota is in its infancy, since the effects of many dietary factors are frequently changed, disputed or simply lack evidence. A novel approach to alter our intestinal microbes is by the use of bacteriotherapy (fig. 4). While bacteriotherapy may be an alternative approach to preventing, treating or even curing ailments, there is a lack of clarity as to its efficacy in humans.
Table 2. Summary of clinical studies using probiotics against dysbiosis-induced diseases

<table>
<thead>
<tr>
<th>Probiotics</th>
<th>Dose, CFU/day</th>
<th>Duration</th>
<th>Sample size</th>
<th>Subject's condition</th>
<th>Gut/fecal microbiota change</th>
<th>Method of bacterial detection</th>
<th>Outcome (generalized)</th>
<th>Ref. PubMed accession No.</th>
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</thead>
<tbody>
<tr>
<td>B. bifidum</td>
<td>$1 \times 10^9$</td>
<td>4 weeks</td>
<td>122</td>
<td>IBS</td>
<td>NA</td>
<td>NA</td>
<td>improved IBS symptoms and QOL</td>
<td>21418261</td>
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<tr>
<td>MIMBb75</td>
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<tr>
<td>VSL#3</td>
<td>$9 \times 10^{11}$</td>
<td>8 weeks</td>
<td>24</td>
<td>IBS, diarrhea predominant</td>
<td>no change</td>
<td>microarray hybridization</td>
<td>no major changes</td>
<td>22247743</td>
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<tr>
<td>L. longum</td>
<td>NA</td>
<td>4 weeks</td>
<td>60</td>
<td>IBS</td>
<td>no change</td>
<td>qPCR</td>
<td>improved IBS symptoms</td>
<td>22837798</td>
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<tr>
<td>L. acidophilus</td>
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<td></td>
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<td></td>
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<tr>
<td>L. plantarum</td>
<td>$1 \times 10^{10}$</td>
<td>6 weeks</td>
<td>28</td>
<td>IBS</td>
<td>no change</td>
<td>direct sequencing, 454 pyrosequencing</td>
<td>aggravated IBS symptoms</td>
<td>22899904</td>
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<td>MF1298</td>
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<tr>
<td>L. casei DG</td>
<td>$1.6 \times 10^9$</td>
<td>8 weeks</td>
<td>26</td>
<td>IBD, mild left-sided UC</td>
<td>↑ Lactobacillus spp., ↑ Enterobacteriaceae</td>
<td>culturing</td>
<td>decreased inflammation</td>
<td>20737210</td>
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<td>(rectal)</td>
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<tr>
<td>L. plantarum</td>
<td>$2.6 \times 10^{14}$</td>
<td>6 days pre- and 10 days postoperatively</td>
<td>100</td>
<td>CRC, undergoing colectomy</td>
<td>↑ Bacterial variety</td>
<td>culturing, DGGE</td>
<td>improved gut permeability, improved recovery from surgery</td>
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<tr>
<td>B. longum</td>
<td>NA</td>
<td>20 days, 40 days, 60 days</td>
<td>297</td>
<td>chronic constipation with hypocaloric diet</td>
<td>NA</td>
<td>no change</td>
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<tr>
<td>B. longum W1 FOS Actilight</td>
<td>NA</td>
<td>24 weeks</td>
<td>66</td>
<td>NASH</td>
<td>NA</td>
<td>NA</td>
<td>reduced inflammation and NASH activity index</td>
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<td>L. casei Shirotu</td>
<td>$1.95 \times 10^{10}$</td>
<td>3 months</td>
<td>28</td>
<td>metabolic syndrome</td>
<td>NA</td>
<td>NA</td>
<td>increased inflammation</td>
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<td>L. salivarius</td>
<td>$1 \times 10^{10}$</td>
<td>12 weeks</td>
<td>50</td>
<td>obesity</td>
<td>similar change in both groups</td>
<td>qPCR</td>
<td>no change in metabolic biomarkers</td>
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<tr>
<td>L. rhamnosus</td>
<td>$1 \times 10^{10}$</td>
<td>4 weeks pre- and 6 weeks post-delivery</td>
<td>159</td>
<td>pregnant</td>
<td>NA</td>
<td>NA</td>
<td>restrained excessive weight gain in offspring during their first years of life</td>
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<tr>
<td>GG</td>
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<tr>
<td>L. plantarum</td>
<td>$2 \times 10^9$</td>
<td>56 weeks</td>
<td>43</td>
<td>healthy</td>
<td>NA</td>
<td>NA</td>
<td>reduced total cholesterol and low-density lipoprotein</td>
<td>16026136</td>
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<tr>
<td>M-74, selenium</td>
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<tr>
<td>E. faecium</td>
<td>$2 \times 10^9$</td>
<td>8 weeks</td>
<td>36</td>
<td>heavy smokers</td>
<td>NA</td>
<td>NA</td>
<td>reduced cardiovascular risk development</td>
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<td>299v</td>
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<tr>
<td>L. plantarum</td>
<td>$1 \times 10^{11}$</td>
<td>4 weeks</td>
<td>16</td>
<td>incipient arteriosclerosis</td>
<td>↑ Lactobacillus spp., ↑ diversity</td>
<td>culturing, T-RFLP</td>
<td>decreased SCFA conc., no change in blood markers</td>
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<tr>
<td>DSM 9843</td>
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CFU = Colony forming units; conc. = concentration; DGGE = denaturing gradient gel electrophoresis; NA = not available; NASH = nonalcoholic steatohepatitis; QOL = quality of life; qPCR = quantitative polymerase chain reaction; REP-PCR = repetitive sequence-based polymerase chain reaction; T-RFLP = terminal restriction fragment length polymorphism.
Probiotics, Prebiotics and Symbiotics

Probiotics are defined as live microorganisms which confer health benefits to the host when taken in adequate quantities. These are discussed by Versalovic in this issue. Prebiotics are nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of beneficial colonic bacteria. A combination of probiotics and prebiotics is termed symbiotics. Probiotics are strain specific and require sufficient dosages and time to exert efficient effects. Various kinds of probiotics have been tested clinically as potential therapeutic agents for both localized and systemic diseases. A recent review of the effects of probiotics on health and disease is shown in table 2. The effects of probiotics in local gastrointestinal diseases are generally positive, although there is usually a lack of evidence that the effects were gut microbiota mediated. While still largely unknown, the effects of probiotics in systemic diseases are more variable.

Antibiotics

It is well documented that antibiotic treatments cause aberrancies in the host microbiota. Though it is generally believed that such changes are normalized within weeks of cessation of antibiotics, recent evidence challenges this notion [68]. For example, significant reduction in diversity of Bacteroides persisted up to 2 years following 7 days of Clindamycin administration [68]. In the context of dysbiosis, antibiotics thus can be viewed as a double-edged sword. They are effective in eradicating pathogens but also nonspecifically reduce microbial diversity enabling opportunistic bacteria to colonize the newly hospitable niches in the gut ecosystem. Such is the case of Clostridium difficile, an opportunistic pathogen which emerged in the 1970s in patients treated with Clindamycin [69]. Another example of antibiotics’ conflicting nature in dysbiosis is their effect on IBD. For instance, the use of ciprofloxacin has been shown clinically to modestly improve symptoms and remission rates of patients with CD [70]; however, antibiotic exposure in childhood has been associated with development of IBD in later years [71]. In a clinical setting, this raises important concern regarding the appropriate use or avoidance of antibiotics. It is important to develop more specific antimicrobial or concurrent therapies to restore or minimize disturbances to the normal microbiota.

Fecal Transplantation

One promising approach for relieving dysbiosis-associated diseases is the re-establishment of normal microbiota via transplantation of a healthy donor’s stool into a symptomatic host, called fecal transplantation (FT) (fig. 4). In clinical settings, FT has emerged as a much more effective and safer procedure than standard antibiotics treatment in the immediate and lasting resolution of recurrent C. difficile. Currently, this procedure suffers from a lack of standardization; however, its success rate being above 95% [72] and seemingly lack of adverse effects has led experts to investigate its use in treatment of other chronic illnesses such as IBD [73] and metabolic syndrome [74]. As our understanding of the essential role that host microbiota plays in disease and immunity increases, the use of microbiota manipulation therapies becomes more sensible. For example, one possible future venue for FT is the use of a patient’s own stored healthy stool to restore their intestinal microbiota following antibiotic treatment or disease onset. Due to its inexpensive nature, FT might be particularly favorable in populations where expensive treatments are not easily accessible.

Conclusions

Interactions between different dietary factors and gut microbes may lead to dysbiosis that exerts distinct immune responses in the host, resulting in higher susceptibility to various gastrointestinal and systemic diseases. Restoration and maintenance of a healthy gut microbiota may be an effective, inexpensive and safe remedy to these diseases.

Acknowledgement

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References

Diet, Microbes and Human Health


15 Diet, Microbes and Human Health


