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GUT MICROBIOTA AND HEALTH: A REVIEW WITH FOCUS ON METABOLIC AND IMMUNOLOGICAL DISORDERS AND MICROBIAL REMEDIATION

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Understanding and defining health is an important yet fuzzy topic. Despite several attempts, health is not a well-defined concept, therefore we seek to understand health from the perspective of the microbiome. Gut microbiota are an essential component in the modern concept of human health. However, the precise patterns of composition and functional characteristics of a healthy gut microbiome remain ill-defined. Microbial colonization patterns associated with disease states have been documented with the advancement of sequencing technologies. Several prebiotics and probiotics have been reported to restore the normal gut flora after being disrupted by various factors. Fecal microbial transplantation from healthy individuals into recipients suffering from diseases related to gut dysbiosis has also been reported to be effective in restoring the normal makeup of gut microbiota, as shown by its efficacy in treating Clostridium difficile infection, colitis, constipation, irritable bowel syndrome, and neurological conditions such as multiple sclerosis and Parkinson's disease. In this review we attempt to define the parameters of healthy human gut flora and its disruption in diseased conditions, and restoration through administration of prebiotics, probiotics, and fecal microbial transplantation. ***Biomed Rev* 2016; 27: 1-17.**

Key words: microbiota, microbiome, metabolism, autoimmunity, probiotics, fecal microbial transplantation, disease

INTRODUCTION

The meaning of the word health is highly ambiguous and subjective to the user, context, and social setting. Health is usually in reference to either physical or mental health, however, the matter becomes complicated when attempting to establish fixed set of parameters that can be used to define and predict health quantitatively. To date, the best known modern definition for health was put forth during the creation of the Constitution of the World Health Organization (WHO) (1) and entered into force on 7 April 1948. It broadly states that health is "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity". However, many question the suitability of this definition in an era now marked by leaps in the understanding disease at the molecular, individual, and societal levels (2).

A significant obstacle to improving the definition of health

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comes from that fact that "health" is a social construct, widely open to interpretation, and ever changing throughout our natural lives. For instance, a physically fit athlete at the age of 25, an individual living with Down syndrome, and an elderly person at the age of 85 could all be considered "healthy", yet differ immensely in terms of physical and mental capabilities. Where do we draw the line between healthy passion and unhealthy obsessive or addictive behaviour? Furthermore, paradoxically an individual could be considered physically fit and "healthy", yet be considered mentally "unhealthy", and *vice versa*, at the same time. The relative nature of health is made more complex when individual or cultural perception is taken into account. This is readily apparent in the disparity of how individuals, from different cultural backgrounds, view obesity, a disease well-established by the scientific community to confer a myriad of negative physiological effects (3). For example, non-Hispanic white women experience greater social pressure to be thin than African American women (4) with the latter expressing satisfaction with their body image and health at higher mean body mass index (BMI) than that of the former (5).

Abbreviations used

AAD, antibiotic-associated diarrhea
AMPK, adenosine monophosphate-activated protein kinase
BMI, body mass index
CAC, colitis associated cancer
CD, Crohn's disease
CDI, *Clostridium difficile* infection
CRC, colorectal cancer
ETBF, enterotoxigenic *Bacteroides fragilis*
FIAF, fasting-induced adipose factor
FMT, fecal microbial transplantation
GLP-1, glucagon-like peptide 1
HGC, high gene count
IBD, inflammatory bowel disease
IBS, irritable bowel syndrome
IL, interleukin
LGC, low gene count
NOD, non-obese diabetic
OAMD, obesity associated metabolic disorders
OTUs, operational taxonomic units
PKS, polyketide synthase
UC, ulcerative colitis
WHO, World Health Organization

Gray areas will always exist within the concept of health; however, there is ample room to expand our understanding of health by establishing more concrete and predictable parameters at a molecular and cellular level. Deep understanding of our cellular and molecular selves and the underlying mechanisms and systems at hand are very much needed, not only to define health, but also to manipulate and regulate it. In general, a species is defined by its genome and epigenome, but for various organisms including humans, these two concepts alone are not adequate. Another component of the human body is its microbiome, the collective gene functions of all microorganisms inhabiting various sites of the human body. In particular, the human gut is home to an enormous number of microorganisms, approximately 100 trillion bacteria cells, outnumbering human cells by an estimated 10 fold (6). The changes in gut microbial composition have been associated with many infectious and metabolic disorders (Table 1). Identifying the patterns of both healthy gut flora and the gut flora of multiple states of disease will provide another crucial facet in defining the parameters of health, and will help develop methods to maintain or return to a state of desired health. The important terms and their meanings are listed in Box 1.

The gut metagenome (complete set of microbial genes) is 150 times greater than the human genome (7). The adult-like population of microbiota forms at around age 3 (8), shifting from a microbiome that primarily plays a role in lactate digestion, to a more stable population that aids in polysaccharide hydrolysis, vitamin biosynthesis and xenobiotic degradation (9). The gut microbiota consists of a diverse variety of species, including organisms such as bacteria, archaea, eukarya, viruses and endoparasites (10, 11). The healthy human gut is also inhabited by a few select fungal organisms, including different *Candida* yeasts and yeast belonging to the family *Dipodascaceae* (*Galactomyces, Geotrichum, Saprochaete*) (12). The approximate composition of the gut microbiota is 92.9% bacteria, 0.5% eukaryotes, 0.8% archaea and 5.8% viruses (13). Approximately, 1000 bacterial species inhabit the human gut (7). Bacteroidetes and Firmicutes are the most abundant phyla in the human gut (6, 14). Bacteroides are the most abundant and also the most variable genus between different samples (13). Bacterial species richness is higher in healthy individuals and lower in people of poor health, or those with low-grade chronic inflammation (15, 16). Microbial ecosystems that are higher in species richness are more resistant to perturbation from the outside environment (17). Competitive exclusion may prevent a growth bloom in

pathogenic bacteria (18); competitive interactions between species may also help in stabilizing the gut microbiome (19). Gut microbial composition varies significantly in diseased individuals than that of healthy populations. Differential composition of gut microbiota in individuals suffering from illness is correlated with specific metabolic and immunological disorders. In the first part of this review, we discuss the differential composition of gut microbiota in obese, diabetic, *Clostridium difficile* infection (CDI), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) patients with respect to healthy samples. Although we have restricted the scope of our study to diseases related to digestion and metabolism, it should be noted that dysbiosis is pleiotropic, with the capability of driving neurological diseases such as multiple sclerosis and Parkinson's disease (20, 21). Recent developments in gut microbial remediation through prebiotics, probiotics and fecal microbial transplantation (FMT) are reviewed in the latter part of this article

MICROBIAL-LINKED METABOLIC DISORDERS

Obesity and gut microbiota

The prevalence of obesity has doubled globally from 1980 to 2014, with there now being over 600 million obese individuals as estimated by the WHO (22, 23). The known factors contributing to obesity are numerous, including environmental circumstances, life style and diet habits, and genetics (24). Among environmental factors, geography is also thought to highly influence an individual's susceptibility to obesity. This was demonstrated through Kaufman's large scale study comparing obesity and health of black populations in the United States and Caribbean, of African origin, to black populations currently residing in Nigeria and Cameroon. Obesity rates are significantly higher in developed nations (23). Geographical or genetic differences cannot alone explain the sudden increase in obesity rates worldwide. The more plausible explanation for this shift is due to changes in diet and physical activity patterns, which have the potential to alter the gut microbiota (25, 26); this notion is well supported by emerging evidence that has shown both correlative changes in microbiota associated with obesity, and direct causative effects by microbiota that contribute to obesity (17, 27-30). Suzuki *et al* demonstrated the correlation between increased Firmicutes and regions with cold weather, colder climates being associated with higher body mass (Bergmann's rule) (31); a higher ratio of Firmicute bacteria compared to Bacteroides is associated with obesity (28). Following bacterial colonization of germ-free mice, body fat content significantly increases, marked by increased lipoprotein lipase mediated triglyceride storage after microbe mediated inhibition of expression of fasting-induced adipose factor (FIAF) in the intestines (29). It was demonstrated by Backhed *et al* that the gut microbiota are able to induce adipose tissue accumulation through inhibition of phosphorylated adenosine monophosphate-activated protein kinase (AMPK)-dependent fatty acid oxidation, as observed by p-AMPK and acetylCoA carboxylase (Acc) expression levels, as well as carnitine-palmityoyl transferase-1 activity, which were all down-regulated in germ free mice following microbial colonization of the gut (32). Le Chatelier *et al* tried to categorise obese people according to the composition of their gut microbiota. They found a bimodal distribution of microbial gene richness in obese individuals, stratifying individuals as high gene count (HGC) or low gene count (LGC) (33). Individuals with HGC were characterised by higher prevalence of presumed anti-inflammatory species such as *F. prausnitzii*, and an increased production potential of short chain organic acids. In contrast, LGC individuals showed higher relative abundance of potentially pro-inflammatory *Bacteroides* species and genes involved in oxidative stress response (33). Diet-induced weight-loss intervention significantly increased gene richness in the LGC individuals, which was associated with improved metabolic status (34). These findings support the reported link between long-term dietary habits and the structure of the gut microbiota. It also suggests permanent adjustment of the microbiota may be achieved through diet modification. A causal relationship was established between host glucose homoeostasis and gut microbial composition. Fecal microbial transplantation from lean donors to individuals with metabolic syndrome significantly increased insulin sensitivity in the latter (35). The transplant produced an increase in faecal butyrate concentrations, microbial diversity, and the relative abundance of bacteria related to the butyrate-producing *Roseburia intestinalis* (35). Together, these studies produce a body of evidence that the microbiome plays a role in host energy homoeostasis, and the establishment and development of obesity associated metabolic disorders (OAMD). The gut of individuals with OAMD is believed to harbour an inflammation-associated microbiome, with a lower potential for butyrate production and reduced bacterial diversity and/or gene richness. Differences in gut microbial ecology might be an important mediator and a new therapeutic target or a biomarker to predict metabolic dysfunction/obesity in later life.

Box 1. Important terms

Microbiota
The types of microorganisms that are present in a habitat; including bacteria, viruses and eukaryotes.

Microbiome
A collection of different microbes found in a given habitat and their collective gene functions. For example, skin microbiome, gut microbiome *etc*.

Metagenomics
A method which allows us to create catalogues of what the microbiome can do as a single unit based on the collective genes they have.

Dysbiosis
A disturbance or imbalance in a biological system, for example, changes in the types and numbers of bacteria in the gut which may lead to developing different diseases, such as inflammatory bowel disease.

Pathobiont
A commensal organism that can cause disease when specific genetic or environmental conditions are altered in the host.

Prebiotics
A selectively fermented ingredient that results in specific changes in the composition and/or activity of the gut microbiota, thus conferring benefits upon host health.

Probiotics
Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Examples include strains of the genera *Bifid bacterium* and Lactobacillus.

Fecal microbial transplantation
The introduction of gut bacteria from a healthy donor into a patient, through transfer of an infusion of a fecal sample *via* administration through nasal, oral, or rectal tubes.

Diabetes and the gut microbiota

Individuals that have developed type 2 diabetes mellitus or some degree of glucose intolerance, consistently exhibit altered populations of gut microbiota, with certain key species either enriched or supressed (36). A clinical study of diabetic adult males revealed that the proportions of class *Clostridia* and phylum *Firmicutes* were significantly lowered compared to healthy controls, and the ratio of *Bacteroidetes* to *Firmicutes* increased with increasing concentrations of blood glucose (37). Examples of bacteria found to be overall reduced in type 2 diabetes subjects are *Roseburia intestinalis* and *Faecalibacterium prausnitzii*, both butyrate-producing bacteria (38). Not only does the diabetic state of an individual influence the composition of their gut microbiota, but potentially the diabetic state of their mother as well. The meconium obtained from infants born to mothers with type 2 diabetes were enriched with the *Bacteroidetes* and *Parabacteriodes* phyla, as compared to infants born to non-diabetic mothers (39).

It should be noted that there is also some evidence of altered gut microbiota in children suffering from type 1 diabetes compared to healthy controls. Similar to the microbiota of their type 2 diabetic counterparts, the ratio of *Bacteroidetes* to *Firmicutes* increased in type 1 patients compared to healthy controls, with a marked increase in the overall number of *Bacteroidetes*, and the ratio of *Bacteroidetes* to *Firmicutes* positively correlated with blood glucose concentration (40). Also, another similar pattern was observed between type 1 and 2 diabetics, both showing lowered numbers of butyrate-producing bacteria (40, 41). Type 1 patients were observed to have a significant increase in *Veillonella* and *Clostridium* levels, and a robust decrease in the numbers of *Lactobacillus*, *Bifidobacterium, Blautia coccoides*/*Eubacterium rectale* group and *Prevotella* (40).

Additionally, the predisposition to developing type 1 diabetes may actually be dependent on the pre-existing gut microbiota of an individual. Wen *et al* demonstrated that MyD88 (an adapter protein for immune-receptors that recognize microbial stimuli) knock out non-obese diabetic (NOD) mice, which can spontaneously develop type 1 diabetes, do not develop type 1 diabetes when their gut is populated with a microbiota profile matching that of the healthy human gut; however, germ free MyD88-negative NOD mice developed highly progressed type 1 diabetes (42). The resistance to type 1 diabetes found in the first group of MyD88-negative mice could be transferred to wild type NOD mice through fecal transfer, delaying and offsetting the symptoms of type 1 diabetes (43). These findings suggest that microbiota is indeed involved, and microbial dysbiosis may progress type 1 diabetes development, but that gut microbial restoration may alleviate symptoms.

Interestingly, current diabetic treatments may be inadvertently taking advantage of the gut microbiota relationship with glucose metabolism. Metformin's mode of action has long been debated, long thought to interact with either AMPK or the mitochondria to lower blood glucose levels (44). However, a report from 1984 observing the lack of therapeutic effect from intravenous metformin in comparison to oral administration, which has had surprisingly little follow up until recently, brings these primary theories into question (45). A version of metformin with higher bioavailability is less effective than

unmodified metformin which remains in the gut for longer (46). Napolitano *et al* have shown that metformin modified the secretion of entero-endocrine hormones, increasing glucagon-like peptide 1 (GLP-1) expression and activation, and decreasing serum bile acid levels, specifically cholic acid and its conjugates (47), rare examples of carcinogenic endobiotics (48). Together these studies establish the correlation between diabetes and gut microbiota and their modulation to ease glucose intolerance in diabetic patients.

Colorectal cancer and gut microbiota

Colorectal cancer (CRC) is one of the most common fatal malignancies in the world (49). The involvement of gut microbiota in the development of colorectal cancer has been noted for some time (50, 51). Interleukin-10-deficient mice and TCRβ/p53 double knockout mice do not develop colorectal cancer under a germfree environment, providing a rationale for the association between colorectal cancer and gut microbiota (52). Chronic inflammation is known to predispose an individual to cancer, and as such, the presence of IBD increases the risk of colorectal cancer. Another such example would be colitis associated cancer (CAC). A recent study demonstrated that dysbiosis of gut micobiota plays a key role in the pathophysiology of CAC (53). Bacterial diversity is remarkably decreased in the gut microbiota of sporadic colorectal cancer and CAC mice models. When gnotobiotic mice are colonized with feces taken from sporadic colorectal cancer or CAC mice, the incidence and number of tumours are increased in both cases, compared with those colonized with feces of healthy mice. Results from a time-course analysis of the composition of gut microbiota during development of CAC indicated that tumour-bearing mice showed enrichment in operational taxonomic units (OTUs) affiliated with members of the *Bacteroides, Odoribacter,* and *Allobaculum* genera, and decreases in OTUs affiliated with members of the *Prevotellaceae* and *Porphyromonadaceae* families (54). Furthermore, conventionalization (colonization of germfree mice with gut microbiota) with tumour-bearing mice significantly increased colon tumourigenesis compared to those colonized with feces from healthy mice (55). These findings suggest that gut microbiota plays a part in the initiation of colorectal cancer. CAC results from the complex relationship between chronic inflammation and dysbiosis of gut microbiota, which would induce irreversible changes to intestinal epithelial cells. *Bacteroides fragilis* toxin, produced by enterotoxigenic *B. fragilis* (ETBF), induces colorectal cancer by binding to colonic epithelial cells and stimulating cleavage of the cell adhesion molecule E-cadherin, which normally acts as a tumour suppressor protein [56]. Antibody-mediated blockade of interleukin-17 (IL-17), a key cytokine for proinflammatory responses, inhibits ETBF-induced colitis and tumour formation (57). Gut microbiota of IL-10 deficient mice developing spontaneously severe colitis have decreases in bacterial diversity, and increases in the occupancy of *Enterobacteriaceae* (58). Interleukin-10 deficient mice, colonized with either *Escherichia coli* or *Enterococcus faecalis,* develop colon inflammation, but only the mice receiving *E. coli* developed colon tumours. Moreover, it was reported that colibactin, the product of polyketide synthase (PKS) in *E. coli NC101*, cleaved double stranded DNA in colonic epithelial cells and promoted invasive carcinoma in IL-10 deficient mice (59). Because the expression of the *ETBF* toxin gene and *PKS* gene of *E. coli NC101* is higher in patients with colorectal cancer when compared to healthy adults, aberrant proliferation of these bacteria caused by dysbiosis of gut microbiota would induce disruption of epithelial barrier function, and contribute to the underlying mechanisms of CAC development.

To date, human studies examining the effects of dysbiosis with respect to CRC have been limited to small cohorts, with evidence of sampling heterogeneity and limited tumour phenotyping. However, still a small number of specific pathobionts have now been linked with adenomas and CRC, including *Streptococcus gallolyticus* [60], *Enterococcus faecalis* [61] and *B. fragilis* (57). *Escherichia coli* is also overpopulated on CRC mucosa; *E. coli* expresses genes that confer properties relevant to oncological transformation, including M cell translocation, angiogenesis and genotoxicity (62). Enrichment of *Fusobacterium nucleatum* has also been identified in adenoma versus adjacent normal tissue, and is more abundant in stools from CRC and adenoma patients than from healthy controls. *Fusobacterium nucleatum's* FadA, a unique adhesin, allows *E. coli* to adhere to and invade human epithelial cells, eliciting an inflammatory response (63) and stimulating cell proliferation (64). Novel mechanisms from previously un-associated bacteria are also being described to explain how bacterial proteins target proliferating stem-progenitor cells. For example, AvrA, a pathogenic product of Salmonella, has been shown to activate β-catenin signals and enhance colonic tumorigenesis (65). Taken together, it is likely that modulating the gut microbiota will become an effective tool to prevent and combat CRC.

Table 1. *Association between gut microbial dysbiosis and disease*

Disease	Taxonomic changes in disease state microbiota
Obesity	High *Firmicute-Bacteroides* ratio Lower butyrate bacteria related to *Roseburia intestinalis*
Type 2 diabetes	Lower class *Clostridia* and phylum *Firmicutes* High ratio of *Bacteroides-Firmicutes*; +ve correlation with blood glucose concentration Reduced *Roseburia intestinalis* and *Faecalibacterium prausnitzii*
Type 1 diabetes	High ratio of *Bacteroides-Firmicutes*; +ve correlation with blood glucose concentration Increase in Bacteroides populationz Increase in *Veillonella* and *Clostridium* Decrease in *Lactobacillus*, *Bifidobacterium, Blautia coccoides*/*Eubacterium rectale* group and *Prevotella*
Colorectal cancer	Increase in *Bacteroides*, *Odoribacter*, and *Allobaculum* genera Decrease in *Prevotellaceae* and *Porphyromonadaceae* families Increase in *Bacteroides fragilis* and *Bacteroides fragilis* toxin Increase in *Enterobacteriaceae* Increase in *Streptococcus gallolyticus*, *Enterococcus faecalis* and *Bacteroides fragilis* Colorectal cancer mucosa associated *Escherichia coli* and *Fusobacterium nucleatum*
Irritable bowel syndrome	Increased *Clostridium*, *Dorea*, and *Ruminococcus*, Decreased *Bifidobacterium*, *Faecalibacterium* and methanogens Decrease in *Roseburia*, *E. rectale,* H2-consuming bacteria, methanogens and reductive acetogens (C-IBS)
Inflammatory bowel disease	Increased *Actinobacteria* and *Proteobacteria* Increased Candida, Penicillium and Saccharomyces Decreased *Bacteroidetes* and *Lachnospiraceae* <u>Crohn's disease specific changes</u> Increase in *Ruminococcus gnavus* Decrease in *Dialister invisus*, *Faecalibacterium prausnitzii* and *Bifidobacterium adolescentis* <u>Ulcerative colitis specific changes</u> Increased *Escherichia sp*, *Helicobacter sp*, *Campylobacter sp*, and *Pseudomonas aeruginosa* Decreased *Firmicutes* and *Bacteroidetes* Decreased *Clostridium coccoides*, *Clostridium leptum*, *Roseburia*, *Ruminococcus*, *Enterococcus*, *Lactobacillis*, and *Faecalibacterium prausnitzii*
Clostridium difficile infection	Increased *Clostridium difficile*

MICROBIOTA AND GUT INFLAMMATION

Inflammatory bowel syndrome

Irritable bowel syndrome (IBS) is a non-inflammatory condition for which investigators have long been in search of plausible underlying pathogeneses, and it is inevitable that altered composition or function of the gut microbiota will be considered as a potential aetiological factor in at least a subset of patients with IBS. Compared to healthy controls, the collective gut microbiota of IBS patients is characterized by higher populations of *Clostridium*, *Dorea*, and *Ruminococcus*, and a decrease in *Bifidobacterium*, *Faecalibacterium* and methanogens (66). In Constipated-IBS (C-IBS), the numbers of lactate-producing and lactate-utilising bacteria, and the number of H2-consuming populations, methanogens and reductive acetogens, were at least 10-fold lower compared with control subjects. Also, the number of lactate- and H2-utilising sulphate-reducing populations was increased 10 to 100 fold in C-IBS patients compared with healthy subjects. The butyrate-producing *Roseburia*, *E. rectale* group was lower in C-IBS patients than in controls. Constipated-IBS fecal microbiota produced more sulphides and H2, and less butyrate from starch fermentation, compared to healthy control fecal microbiota (67).

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic disorder marked by debilitating inflammation to the gastrointestinal tract, often resulting in recurring symptoms such as severe abdominal pain, gastrointestinal bleeding, and diarrhoea (68). The term IBD is primarily used to describe two distinct conditions with similar symptoms, ulcerative colitis (UC) and Crohn's disease (CD) (69). Little is known of the aetiology of IBD, especially UC, which is marked by phases of relapse and symptom free remission (70). Ulcerative colitis inflammation usually affects the colorectum and is commonly diagnosed in young adults (71). Unlike UC, which is restricted to the colon, CD may affect any portion of the gastrointestinal tract, including the mouth and perianal area (72). Although the root cause of IBD is unclear, it is recognized that the onset of IBD is multifactorial, as immune system alteration and dybiosis of gut flora in genetically susceptible individuals, and environmental factors all play a role. A genetic component contributing to the susceptibility to developing IBD has been demonstrated through large scale genome analyses, which have revealed over 200 genetic loci in humans that are associated with IBD (73). Many of these genes are involved in the regulation of innate immune system functions, such as cytokine release, intestinal

barrier defense and microbial recognition (74). This is supported by a study that observed the loss of immune tolerance by the mucosal immune system in IBD patients (75). Given the established role that immune dysfunction plays in the progression of IBD, primary treatment strategies for both disorders have revolved around the administration of aminosalicylates, corticosteroids, and immune-suppressants (76-78). However, the current treatment and management options available for CD and UC are plagued by side effects, lack of efficacy, and frequent symptom relapse (78-80).

In an attempt to avoid or minimize IBD treatment side effects, and improve overall patient quality of life, remediating dysbiosis of the gut microbiota is being considered as an alternative treatment approach. Rationale for targeting the microbiota of the gut arises from the observed higher rates of IBD in developed western countries, where microbiota influencing factors such as diet, hygiene, and environment differ. The microbiota influencing effects of environment are exemplified in a 2011 study which observed that individuals immigrating from developing countries to westernized countries in Europe experienced an increased chance of developing IBD, especially UC, compared to those immigrating to other developing countries (81). A westernized diet high in fats and refined carbohydrates is strongly associated with IBD compared to diets consisting primarily of complex carbohydrates and poly-unsaturated fats (82). Furthermore, it has been shown that a distinct enterotype of gut microbiota indicative of a western diet can occur irrespective of geographic location, suggesting that diet alone may play the primary role in determining the pre-clinical makeup of gut flora [83]. Given the effect of environment and diet on gut microbiota and IBD rates, it is conceivable that shifts in gut flora are a probable factor in the establishment of a pro-IBD state and the onset and progression of IBD. Additionally, IBD patients are more likely to have taken antibiotics in the 2-5 years preceding the development of IBD symptoms compared to healthy populations, further supporting the notion that perturbation of the gut microbiota is central to IBD development (84).

Investigation into the gut microbiota of IBD patients reveals several significant changes in bacterial populations. A study investigating the gut microbiota of CD and UC patients detected a marked increase in the number of *Actinobacteria* and *Proteobacteria*, along with a significant decrease in the number of *Bacteroidetes* and *Lachnospiraceae* for both types of IBD when compared to healthy controls (85). Also, in general, IBD patients are marked by a decrease in diversity of gut microbiota and increase in fungi such as Candida, Penicillium and Saccharomyces (86). A study examining CD patients demonstrated that there was a significant increase in *Ruminococcus gnavus* and a decrease of *Dialister invisus*, *Faecalibacterium prausnitzii* and *Bifidobacterium adolescentis* compared to their unaffected relatives and matched healthy controls (87). In UC patients, reduced numbers of *firmicutes* and *bacteroidetes* have been observed (88, 89), along with reduced numbers of *Clostridium coccoides*, *Clostridium leptum*, *Roseburia*, *Ruminococcus*, *Enterococcus*, *Lactobacillis*, and *Faecalibacterium prausnitzii* (90). Strains positively associated with UC development include *Escherichia sp*, *Helicobacter sp*, *Campylobacter sp*, and *Pseudomonas aeruginosa* (90).

Clostridium difficile infection

Clostridium difficile infection (CDI) is a gastrointestinal disease that often develops in patients treated with microbiota-disrupting antibiotic or immunosuppressant medications who come in contact with *C. difficile* spores, and is the most common cause of hospital acquired diarrhoea (91). Compared with those from control subjects and patients with an initial episode, the fecal communities in patients with recurrent *Clostridium difficile* associated diarrhoea were highly variable in bacterial composition and were characterized by markedly decreased diversity (92). Preservation and restoration of the microbial diversity could represent novel strategies for prevention and treatment of recurrent CDI. Fecal microbial transplantation administered to CDI patients, sourced from healthy individuals, is an effective way of treating. Apart from this, probiotics have also emerged as another promising treatment for CDI that works by restoring gut microbiota to a healthy state.

GUT MICROBIAL REMEDIATION

Prebiotics

The notion of prebiotics was put forth by Marcel Roberfroid in 1995, and defined as "non-digestible food ingredients that benefit the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon" (93). Prebiotics include, but are not limited to, dietary carbohydrates such as resistant starches, non-starch polysaccharides, and oligosaccharides; these agents act as substrates for the growth of bacteria in the large intestine, having avoided digestion by host enzymes (94). Studies concerning prebiotics have not been as extensive as research concerning probiotics or FMT, however, the studies that do exist point to prebiotics as being effective to some extent in remediating gut dysbiosis (95). It is possible that prebiotics may be useful as an adjunct

in the administration of probiotics, acting to initiate and support probiotic growth.

Probiotics

Probiotics are "live microorganisms which provide a health benefit on the host when administered in adequate amounts'', as defined by the Food and Agriculture Organization of the United Nations and the WHO (96). Conditions improved by administration of probiotics range from liver injury (97), to several neurological disorders (98). Examples of highly studied and prescribed probiotics are *Lactobacillus* and *Bifidobacterium* (99). *Lactobacillus gasseri BNR17* inhibits overall weight gain and fat storage in Sprague-Dawley rats fed high-sucrose diets, and induces a reduction of glucose levels and improves diabetic symptoms in type 2 diabetes mice (100, 101). Metabolic changes following treatment with *L. gasseri* are thought to occur through stimulated expression of glucose transporter 4 (GLUT4) and fatty oxidation-related genes (ACO, CPT1, PPARα, PPARδ), down-regulation of fatty acid synthesis-related genes (SREBP-1c and ACC), and the lowering of leptin and insulin serum levels (102). Besides the role of Lactobacillus in alleviating the diseases primarily discussed in this review, certain *Lactobacillus* strains have been demonstrated to ameliorate neurological conditions (103). In particular, *L. rhammosus* and *L. casei Shirota* were individually shown to alleviate anxiety and depression-like behaviour in both mice and humans respectively (104, 105, also see 105a). Additionally, *L. reuteri* was shown capable of modulating the enteric nervous system, although with no clear mode of action (106).

Numerous other strains are being investigated and show promise, such as *Akkermansia muciniphilia*, a mucindegrading bacterium which has been shown to be reduced in individuals suffering from IBD (107) and obesity (108). Administration of antibiotics causes major collateral damage to the healthy commensal bacteria of an individual, with a resulting decrease in the diversity and species richness of the gut microbiota (109). Probiotics are being looked to as a potential agent in the alleviation of post-antibiotic disturbance to the gut microbiota. A recent large scale clinical trial involving children up to the age of 18 years evaluated the potential of several probiotics as a treatment method to alleviate antibiotic-associated diarrhea (AAD). Among the several probiotics tested, *Lactobacillus rhamnosus* and *Saccharomyces boulardii* were found to be significantly efficacious and safe in alleviating AAD when administered between dosages of 5-40 billion colony forming units/day (110). Several probiotics are being studied as potential microbiome stabilizers in human and have been proven to be effective. The list of probiotics and their gut microbial modulatory effect in patients is noted in Table 2.

Table 2. *Probiotics and their efficiency in restoring gut microbiota*

Probiotics	Pre-existing disrupting factor	Claims stated in the paper	Evidence based claim	References
Escherichia coli Nissle	Liver cirrhosis	Restores	More Bifidobacteria and Lactobacillus	(111)
Saccharomyces boulardii lyo	Active diarrhoea	Improves	More 'habitual microbiota'	(112)
Lactobacillus plantarum 8PA3 + Bifidobacterium bifidum	Colon cancer	Restores	More E. coli and enterococci	(113)
L. brevis CD2+Lactobacillus salivaris FV2+L. plantarum FV9 L. paracasei Lpc37+L. acidophilus 74-2+Bifido animalis DGCC420	IBS	Restores	More clostridia and Ruminococcus	(114, 115)
L. rhamnosus GG+L. rhamnosus Lc705+Propionibacterium freudenreichii shermanii JS+B. breve Bb99	IBS	Restores	More clostridia	(116-118)
L. acidophilus 4356+L. plantarum 14917+L. rhamnosus 7469	Liver disease	Improves	Less firmicutes, more bacteriodetes	(118)
L. acidophilus+L. paracasei +Lactobacillus delbrueckii spp Bulgaricus+L. plantarum+B. longum+B. infantis+B. breve	Pouchitis	Altered	More anaerobes	(119)
L. acidophilus+L. paracasei +Lactobacillus delbrueckii spp Bulgaricus+L. plantarum+B. longum+B. infantis+B. breve	IBS	Altered	Less bacteroides	(120)

Fecal microbial transplantation

Fecal microbial (microbiota) transplantation (FMT) is the process of transferring the gut microbiota from a healthy donor to the gut of a patient suffering from dysbiosis of the gut flora, usually through liquefied fecal enema. The aim of FMT is to establish and maintain a microbiota profile matching the healthy donor within the patient, alleviating symptoms originating from microbial dysbiosis. Fecal microbial transplantation can be traced as far back as to its use in 4th century China (121). The first modern employment of fecal transplantation was conducted in 1958 as a treatment method for pseudomembranous enterocolitis (122). Donor FMT bacteria have been shown to persist and replace or coexist with recipient populations for at least 3 months (123). Currently, FMT is being considered for medical applications including the treatment of obesity, diabetes, IBD and CDI. A small number of FMT trials have been conducted in rats to alleviate obesity and insulin resistance with some success (30, 124). To our knowledge there exists only one report of human FMT use to alleviate metabolic disorders. A study of FMT from lean healthy donors to patients recently diagnosed with type 2 diabetes resulted in heightened insulin sensitivity, however, non-significant weight loss was recorded after 6 weeks (125).

In the last decade, FMT therapy has shown the greatest success in the treatment of CDI at a clinical level. *Clostridium difficile* infections may reoccur due to instability of the gut microbiota, as often seen in immune-compromised patients following organ transplant or HIV infection (126). Fecal transplants are emerging as a safe and effective treatment method to prevent CDI recurrence, having shown success at a clinical level. A small cohort study found that 85.7% of patients receiving FMT did not have CDI recurrence following CDI brought on by immunosuppression during hematopoietic stem cell transplants (127). A large scale study observing FMT administered to a mixed group of immune-compromised patients (HIV/AIDS, organ transplant, cancer, immune-suppression for IBD) found similar results, with an overall cure rate of 89% for CDI recurrence following FMT (128). 16S rRNA gene sequencing of patient feces post FMT treatment has revealed that patient microbiota profile does indeed shift to match the donor FMT bacterial composition, which alleviates the improper metabolism of primary bile salts thought to be responsible for CDI symptoms (129). A myriad of similar studies have demonstrated the effectiveness of FMT for treating CDI, making FMT a promising treatment for widespread clinical use in the future and opening the door to other possible medical applications for FMT (128, 130-134).

The high efficacy and reproducibility of CDI abrogation through FMT treatment has sparked excitement in potentially transferring over this success to the treatment of IBD, with FMT as an alternative to drug regimens which are plagued by heavy side effects. However, to date, data concerning FMT treatment and IBD still remains limited compared to its application for CDI (90). Of the recent studies that have evaluated FMT in IBD patients at a clinical level, the results look promising, however, remission rates do not match the success of treating CDI through FMT therapy (135). A meta-analysis of IBD treatment over 2 decades indicates that CD has to date responded better from FMT, with an remission rate of 61%, whereas UC remission rates have been estimated to average 22% (136). However, another meta-analysis has reported remission rates upward of 63% for IBD patients in general, in which 76% of those patients ceased taking medication for their disorder (137). Furthermore, a case study evaluating the efficacy of FMT to treat a CD patient non-responsive to immune-suppressants found that after treatment the patient underwent and maintained dramatic remission of disease symptoms (138). This finding is significant as FMT may also prove to serve as a method of treatment for patients non-responding to conventional treatment (Fig. 1).

Despite encouraging initial clinical outcomes, there still exist some obstacles to FMT treatment and the development of administrative techniques. Currently, FMT is usually administered through a nasogastric or nasojejunal tube and to a lesser extent, through enema or colonoscopy (139). A small cohort study observed that IBD patient's expressed displeasure concerning discomfort during colonoscopy, and thus refused repeated treatment over short periods of time (84). However, it should be noted that the same study concluded that IBD patient's generally had a positive attitude towards FMT, as they viewed it as a "natural" alternative medicine. Improvement in treatment delivery could potentially occur in some cases through the use of percutaneous endoscopy cecostomy (PEC), a semi-permanent abdominal port that connects a tube to the intestinal lumen. A recent case study followed a 24 year old male UC patient with recurrent steroid-dependent UC that underwent FMT *via* PEC once per day for a month, and observed a subsequent 12 month drug-free remission (140). Eventually, the development of an effective colorless, odourless, oral FMT pill would be ideal as it could potentially provide a standardized and non-invasive treatment method.

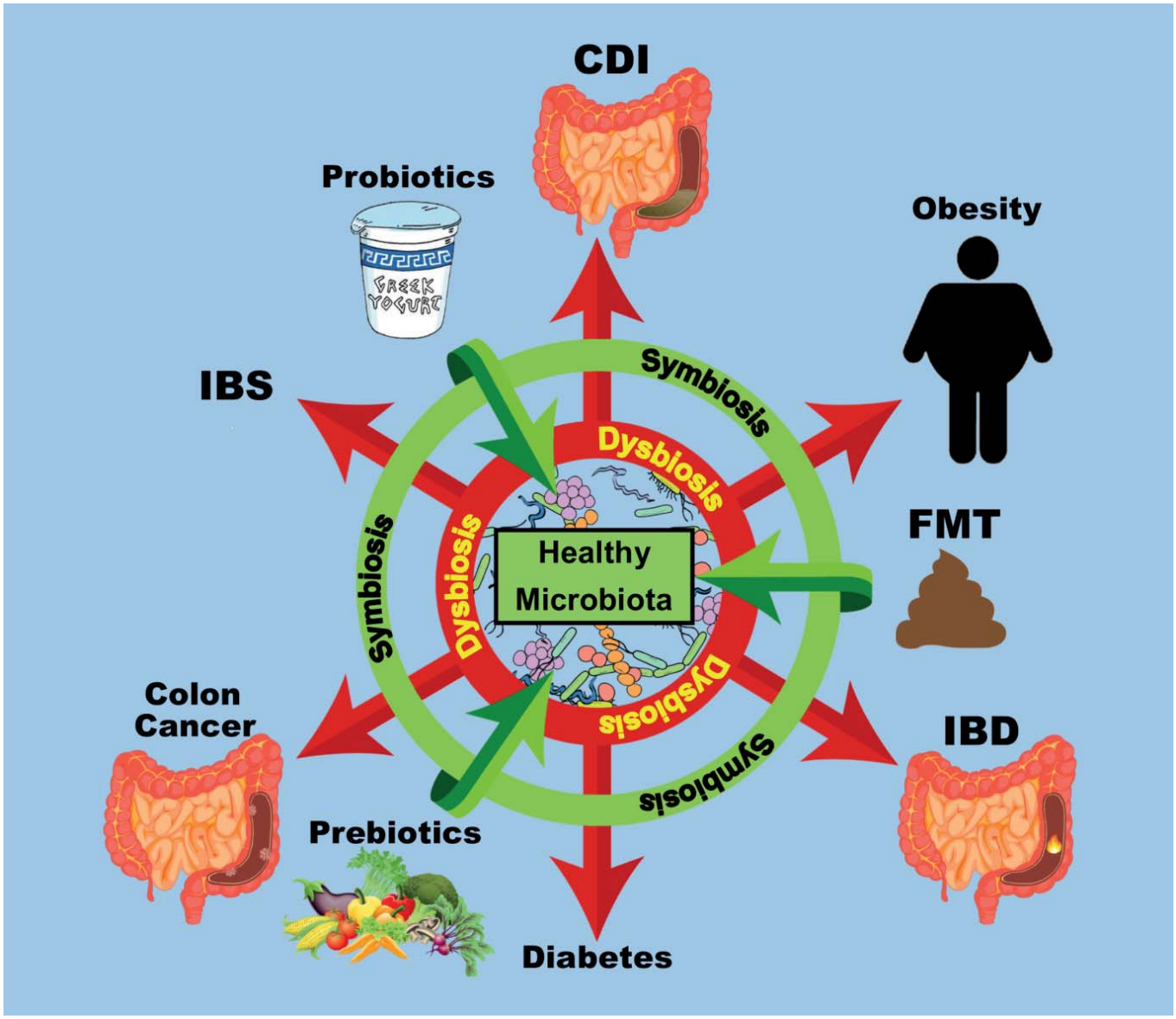

Figure 1. *Change in healthy microbial composition leads to dysbiosis (red arrows) and is associated with obesity, diabetes, colorectal cancer, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) and Clostridium difficile infections (CDI). Prebiotics, probiotics and fecal microbial transplantation (FMT) remediate microbial symbiosis (green arrows) and return the microbial composition to a healthy state.*

CONCLUSION

Health is a multifactorial concept, and the microbiome is emerging as a novel reservoir of information that is helpful in defining the parameters of both good health and illness. Interest in the human microbiome has increased considerably after completion of the human microbiome project in 2012. Scientists and clinicians have realized that the commensal microorganisms that comprise the human gut microbiota are not simply passengers in the host, but actually drive metabolic, immunological and some neurological functions in the host as well, such as behaviour. Dysbiosis of microbiota is associated with obesity, diabetes, CRC, IBS, IBD and CDI. Although not covered in detail, dysbiosis negatively affects several organs, such as observed in nervous system disorders (multiple sclerosis and Parkinson's disease), cardiometabolic diseases (141), and in gout and related diseases associated

with fungal dysbiosis (142, 143), underscoring the belief that the microbiota should be considered as a vital endocrine organ. Prebiotics, probiotics and FMT are capable of remediating and returning the gut microbiota to a healthy state, for which they have the potential to be used as a cure for these diseases (Fig. 1). We have highlighted some key disease areas in which the microbiota and its microbiome are thought to have not just an association, but also participate in tight crosstalk to modulate key physiological processes in the host. By better understanding the mechanisms and contributions that microbiota make to these diseases, we hope to not only to elucidate the molecular meaning of health, but to also aid in the development of novel therapeutics and strategies to modulate the microbiota to treat or prevent disease. In some instances it may be possible to track changes in the microbiome to detect gut-related diseases. In the future, information regarding gut microbial composition can be used efficiently to stratify patients in order to accurately assign personalised treatments. Evidence also points to the gut microbiota being an environmental factor in drug metabolism, for example, lack of therapeutic effect from intravenous metformin in comparison to oral administration, and inactivation of the cardiac drug digoxin by *Eggerthella lenta* in the gut. Thus, a future vision of personalised healthcare must consider the microbiome and host genome together. The sound of microbiome in human health and disease (also see 144) is increasingly emerging indeed.

Conflicts of interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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