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Review

Rethinking Diet to Aid Human–Microbe Symbiosis

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The spread of the Western lifestyle has been accompanied by microbial changes thought to underlie the emergence of chronic, nontransmissible, immune-related diseases. The past decade has seen the unprecedented development of therapies for 'replenishing' the microbiota of sick individuals. However, functional and ecological solutions helping the host and the gut microbiota to cope with the ecological stressors of modern life are still lacking. In this review, we discuss how recent advances in gut microbiome science are leading to the identification of microbe-derived and health-relevant metabolites. These molecules will guide the selection of the next-generation of probiotics and dietary recommendations, which should also take the resident gut microbiota into account, to optimise efficacy. These solutions for maintaining a well-functioning gut ecosystem and promoting good health should be customised, palatable, and as widely accessible as possible.

Trends

Diet is a key lever for microbiota-targeting strategies.

The gut microbiota is a source of numerous bioactive molecules.

Opportunities exist for the development of preventive strategies for host–microbe dysbiosis.

The knowledge of a subject's microbiota can help to optimise dietary intervention.

Diet customisation is a prerequisite for maximal beneficial effects.

Next-generation probiotics should be selected for their ability to complement gut microbiome deficiencies.

Microbiota in 3D: Dysbiosis, Disease, and Diet

Humans have co-evolved with their gut microbiota for millions of years, but this symbiosis is now jeopardised by unprecedented changes in human lifestyle and environment. Antibiotic use, diets poor in microbiota-accessible carbohydrates, excessive sanitation and birth by Caesarean section are known to have profound effects on the gut microbiota [1]. Even unanticipated factors, such as environmental temperatures or circadian rhythms, are now thought to contribute to contemporary changes in the *Homo sapiens* gut microbiota [2,3]. The concomitant emergence in Western countries of chronic, noncommunicable diseases, such as inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), cancer, diabetes and asthma [1], led the suggestions that the disruption of human–microbe symbiosis might be contributing to the emergence of these diseases. Evidence supporting this hypothesis is now emerging and is fuelling the combined efforts of the academic and private sectors to target the microbiota with the aim of preventing or curing diseases.

In this review, we discuss the importance of diet as a factor contributing to host–microbe symbiosis, by driving the production of gut microbe-derived bioactive metabolites. We also discuss how the microbiota can be used to predict the response to dietary intervention and the need to select a new generation of probiotics able to complement the functional deficiencies of the gut microbiota and to customize dietary recommendations according to the gut microbiota of the individual.

Dietary Changes during the Course of Human Evolution

Human evolution has been accompanied by periodic fundamental changes in lifestyle reflected in dietary habits. Humans were nomadic hunter-gatherers during the Palaeolithic period or Old Stone Age, which began 2 million years ago. A profound shift in human lifestyle occurred with the Agricultural Revolution of the Neolithic period, also known as the New Stone Age (10 000 years BC). During this period, humans began to lead a sedentary life, domesticating various animals

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and plants, which formed the basis of a new lifestyle based on farming and foraging. New foods, such as cereals and dairy products, appeared, and population density increased [4]. The last marked shift in human dietary habits began with the Industrial Revolution, less than 200 years ago, which marked the start of a radical shift away from local and seasonal foods. The modern diet is characterised by a high intake of animal products and sugars, the use of preservatives, and a low intake of plant-based foods, such as fruits, vegetables, and wholegrain cereals [4].

Many recent studies have focused on the co-evolution of microbial species with their hosts and have examined the impact of westernisation on the gut microbiota, by profiling the gut microbiota in traditional human populations that have not yet adopted a Western lifestyle. The traditional practices of these populations, from Africa, South America, and Asia, probably resemble our own ancient lifestyles. Studies of these populations can help us to determine the effects of lifestyle (hunting and gathering as in the Palaeolithic Period, or agriculture as in the Neolithic Period) on the co-evolution of humans and their gut microbiota. By characterising features of microbial adaptation to profound changes in human diet, we may be able to identify factors underlying modern diseases and increase our understanding of the evolution and adaptation of microbiota throughout human history [5].

The traditional populations studied have consisted of individuals from single tribes, such as hunter-gatherers from Hazda [6,7], adults and children from Malawi [8], children from Burkina Faso [9], Papua New Guineans [10], and Amerindians [11]. Alternatively, some studies have focused on two tribes with contrasting lifestyles (hunter-gatherer versus agricultural), in Peru [12] and Central Africa [13], for example. Modern diets contain much less fibre and much more fat than ancient diets [14]. Daily fibre intakes in ancient diets could reach 100 g [15], mostly in the form of soluble fibre [16], whereas adults in industrialised countries typically eat only 15 g of fibre, falling short of the recommended daily intake of 20–30 g, mostly in the form of insoluble fibre [16]. People in rural Africa may consume from 60 to 120 g fibre per day [16]. Fat accounts for more than 30% of total calories in the Western diet, but less than 20% in rural African diets [14]. One of the consequence of fibre depletion is a decrease in short-chain fatty acid production, potentially favouring the establishment of Enterobacteriaceae [9].

Several key consensus findings have emerged from these studies. The microbiota is more diverse structurally and functionally (with enhanced polysaccharide breakdown capacities, in particular) in rural and remote populations from developing countries than in urban industrialised populations. Some bacterial taxa or functions may have disappeared from the gut during westernisation [17]. The taxa probably lost include *Treponema*, a genus of anaerobic bacteria from the phylum Spirochaetae highly specialised in the degradation of recalcitrant fibre [18]. A loss of taxa and diversity through poor diet has been experimentally demonstrated in mice. Mice with a human gut microbiota fed a low-fibre diet display a loss of gut microbial diversity over several generations [19].

Towards the Replenishment of the Gut Microbiota with Missing Functions

The past decade has seen the unprecedented emergence of new tools (DNA and RNA sequencing, metabolomics, gnotobiology, and *in vitro* gut models) for exploring the molecular events linking gut microbes to host health. Concerted efforts are currently being made to identify molecules produced by the gut microbiota that ultimately affect host metabolic, immune, or neuronal pathways (Figure 1). Identification of the metabolic pathways responsible for producing these molecules would make it possible to develop strategies for complementing missing functions in the microbiota or inhibiting pathways overproducing deleterious molecules. We will review the metabolites demonstrated or strongly suspected to have a relevant impact on the host.

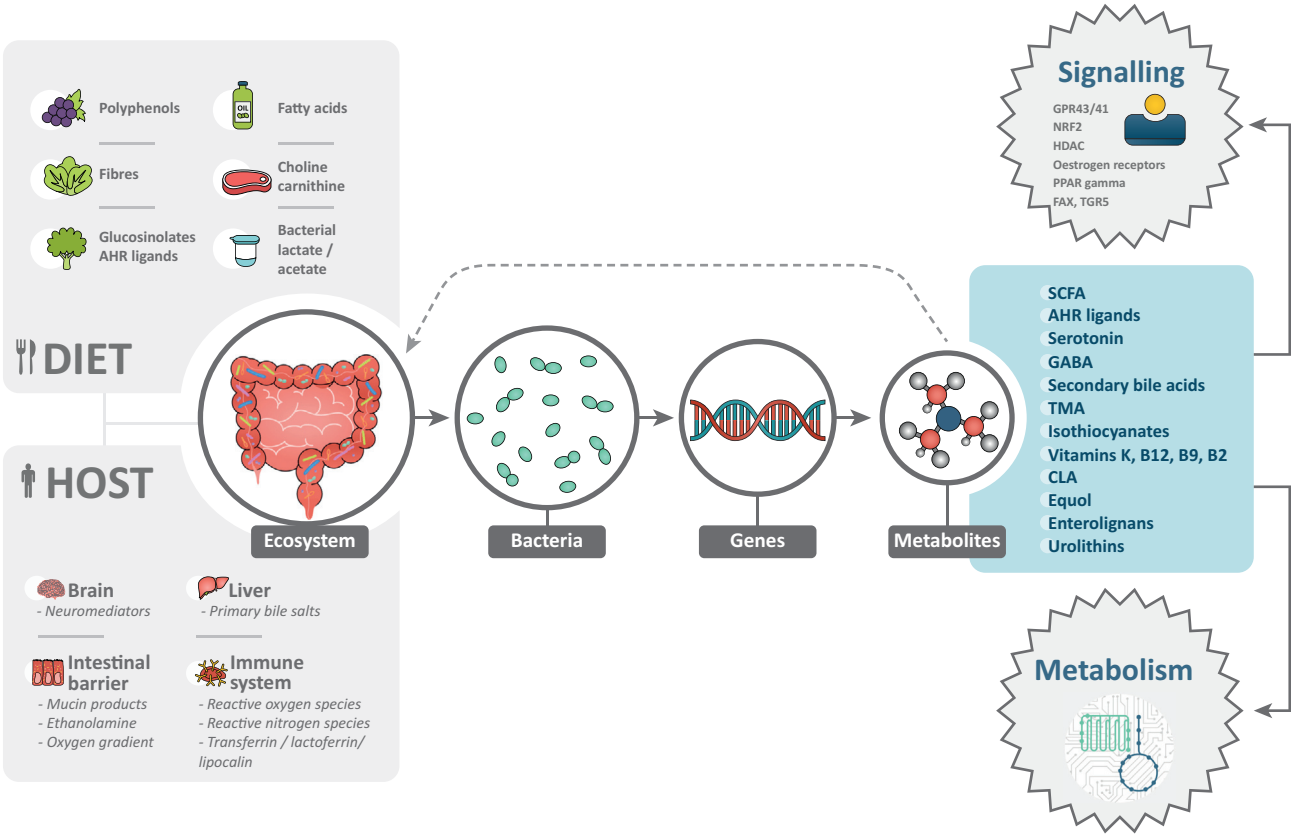

Figure 1. Targets for Microbiota-Based Solutions to Aid Human–Microbe Symbiosis. The gut microbiota is a source of a wide range of bioactive molecules, converted from the diet and host substrates, that participate in host signalling and metabolism. Dietary and host-derived factors set luminal conditions (redox, pH, carbohydrate and electron acceptor availability) that are important in shaping the gut microbiota. Abbreviations: AHR, aryl-hydrocarbon receptor; GABA, gamma-aminobutyric acid; TMA, trimethylamine; CLA, conjugated linoleic acids.

Metabolites Produced by Microbes

Short-Chain Fatty Acids

Undigested dietary components (principally fibres) reach the colon, where they are fermented by the gut microbiota and converted into short-chain fatty acids (SCFAs), mostly acetate, propionate, and butyrate. The host cells use these SCFAs as signalling molecules or substrates [20]. Butyrate has been shown to play a key role in gut physiology, as a major carbon source for colonocytes, regulating critical functions of the intestine, such as intestinal motility, mucus production, visceral sensitivity, the epithelial barrier, immune homeostasis and the mucosal oxygen gradient [21]. The effects of SCFAs on host cells are well documented and involve G protein-coupled protein receptors–GPR43, GPR41, and GPR109A (also known as: FFAR2, FFAR3, and NIACR1, respectively)–and histone deacetylases (HDAC), which regulate the transcription of genes potentially involved in immune and metabolic diseases [20,22,23].

Beyond their role in host health, SCFAs affect gut microbiota functioning. For example, a low luminal pH favours butyrate production and inhibits gram-negative pathogens [24,25], and foods that decrease luminal pH (fibres, lactic acid bacteria or *Bifidobacterium*) have been shown to stimulate butyrate production [25,26]. Luminal pH should, therefore, be considered a relevant target for treatments or dietary recommendations aiming to modulate gut microbiota functioning.

Vitamins

Menaquinone, folate, cobalamin, and riboflavin are produced by gut microbes to fulfil their own energetic and metabolic requirements. From the host perspective, these molecules act as vitamins (vitamins K, B9, B12, and B2, respectively). Vitamin K plays a key role in blood coagulation, bone metabolism, and, possibly, insulin sensitivity [27]. Broad-range antibiotic treatments decrease hepatic vitamin K2 concentrations, suggesting that the gut microbiota is a significant source of vitamin K [28]. Vitamin B9 is an essential vitamin involved in cell division, and a deficiency of this vitamin is associated with higher risks of cancer, anaemia, and neural tube defects during embryogenesis [29]. Vitamin B12 is a metabolic cofactor, deficiencies of which led to an increase in the risks of dementia in the elderly and cardiovascular disease [30,31]. Vitamin B2 is a precursor for the cofactors flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). Its deficiency is associated with neuromuscular and neurological disorders, cancer and predisposition to *Listeria* infection [32,33].

The bacterial genes required for vitamin production are now well documented [34]. It should therefore be possible to explore the role of the gut microbiota and probiotics as vitamin suppliers in more detail.

Dietary Metabolites Transformed by Microbes

Phytoestrogens

Isoflavones, lignans, and ellagitannins are plant polyphenols that can be 'bioactivated' by gut microbes to form equol, enterolignans (enterolactone or enterodiol), and urolithins, respectively [35]. These bioactivated products are collectively called phytoestrogens as they can bind to oestrogen receptors (ER-alpha and/or ER beta) [36,37]. This binding may underlie their protective effects against breast and prostate cancers [35]. Polyphenol consumption is also associated with protection against metabolic syndrome [38], the decline of cognitive function associated with neurological diseases [39], and cardiovascular disease [40]. The capacity of the gut microbiota to bioactivate dietary polyphenols varies considerably between individuals, and may be correlated with the protective effects of these compounds [35].

Isothiocyanates

Plants of the Brassicaceae family (also known as crucifers) are the main dietary source of glucosinolates, the precursors of isothiocyanates. Glucosinolates are converted into isothiocyanates by bacterial or plant myrosinases, which are inactivated by cooking. The glucosinolates present in cooked crucifers must, therefore, be converted into isothiocyanates by gut microbial myrosinases, and the efficiency of this conversion varies between individuals [41]. Isothiocyanates induce cytoprotective proteins by activating the Keap1–Nrf2–ARE pathway [42], which regulates the expression of genes encoding antioxidant proteins, drug-metabolising enzymes, drug efflux pumps, heat shock proteins, and proteasome subunits [43]. The products of these Nrf2-regulated genes attenuate the deleterious effects of toxic xenobiotics by limiting oxidative stress and repairing damaged proteins. These and other mechanisms [42] are thought to underlie the observed protective effects of crucifer consumption against cancer [44–46].

Aryl-Hydrocarbon Receptor Ligands

Crucifers are also very rich in indole-3-carbinol (I3C), which is oxidised to 3,3′-diindolylmethane (DIM) in the acidic conditions of the stomach. DIM is a potent activator of Nrf2 and the aryl-hydrocarbon receptor (AhR) [47]. AhR is a transcription factor initially shown to bind xenobiotics, such as dioxin, but now known to bind diverse synthetic and natural ligands [48]. AhR plays an important role in immune homeostasis, by interfering with regulatory T cells, Th17, and innate lymphoid cells, and regulating the production of IL-22, a cytokine important for epithelial repair [49]. The protective effects of crucifers described above may also be at least partly mediated by AhR. AhR ligands are obtained from the diet, or from gut microbes, which can produce them

(i.e. indole, tryptamine, indole acid acetic, indole-3-acetaldehyde) from tryptophan, through the action of tryptophanases or tryptophan hydroxylases and decarboxylases [50–52]. A recent study showed that the microbiota of caspase recruitment domain family member 9-deficient ($CARD9^{-/-}$) mice produced fewer AhR-ligands, resulting in a higher susceptibility to experimentally induced colitis [53]. Thus, gut microbiota-derived AhR-ligands are biologically relevant and play a significant role in gut homeostasis.

Conjugated Linoleic Acids

The human colon receives about 6 to 8 g of lipids per day, mostly in the form of ω-6 fatty acids. The gut microbiota can conjugate ω-6 to produce conjugated linoleic acids (CLAs) [54]. CLAs increase insulin sensitivity, have anti-inflammatory properties, and reduce carcinogenesis, atherosclerosis, and adiposity [55]. These health benefits may result from their action on peroxisome proliferator-activated receptors (PPAR) gamma and alpha, cyclooxygenases, and lipoxygenases [55]. *Propionibacterium*, *Bifidobacterium, Lactobacillus, and Roseburia* species produce CLA, with considerable variability between strains and between species [54]. Genes encoding proteins involved in CLA production have recently been identified in lactic acid bacteria [56], opening up new possibilities for (i) selecting strains with high levels of CLA production and (ii) mining metagenomics data to explore links between microbial CLA production and health or disease.

The 'Fish Odour' Molecule

Trimethylamine (TMA) is the molecule responsible for unpleasant fishy odours. In humans, dietary choline and L-carnitine are converted into TMA by the gut microbiota [57]. TMA is then absorbed and oxidised by the liver enzyme FMO3, to generate trimethylamine-N-oxide (TMAO). TMAO is pro-atherogenic in mice and was found to be associated with a high risk of cardiovascular disease in a human population in the United States [57]. Red meat, poultry, and eggs are rich in choline and carnitine, and TMA and TMAO are together thought to constitute the missing link between animal product consumption and atherosclerosis. Based on this hypothesis, the development of a drug capable of inhibiting the bacterial synthesis of TMA, 3,3-dimethyl-1-butanol (DMB), has already been described [58]. The targeting of the gut microbiota TMA pathway thus appears to be a promising way of preventing cardiovascular diseases in the US population, but the extrapolation of these findings to other dietary and geographic contexts might require additional investigations [59].

Host Metabolites Influenced by Diet and Transformed by Microbes

Bile Salts

Primary bile acids are produced from cholesterol in the liver and are conjugated with taurine or glycine to form bile salts. They are secreted into the gastrointestinal (GI) tract to solubilise lipids, to facilitate their absorption. Bile salts are deconjugated by bile salt hydrolases (BSH), which are produced by many gut microbes [60]. These microbial metabolites are further used by host cells as signalling molecules activating the farnesoid X, pregnane X, and vitamin D receptors, the G protein-coupled receptor TGR5 (TGR5), and cell signalling pathways (c-*jun* N-terminal kinase 1/2, AKT, and ERK 1/2) [61], to regulate bile acid and glucose levels, and fatty acid and lipoprotein synthesis [61].

In addition to their effects on the host, bile salts are also known to play a role in shaping the gut microbiota [62]. Indeed, bile salts have differential bactericidal effects: Firmicutes and Proteobacteria are generally more resistant to bile salts than Bacteroides [63]. Thus, as bile salt production increases with the consumption of a high-fat diet, Yokota *et al*. have suggested that the Firmicutes/Bacteroides ratio, previously reported to be positively associated with obesity, reflects high levels of food and fat intake [62]. *Bilophila wadsworthia* is another potential bacterial marker of the type of fat consumed, as this pro-inflammatory pathobiont flourishes when fats of

Box 1. The Renaissance of Probiotics

Probiotics have long been selected on the basis of their capacity to survive the harsh conditions of the upper digestive tract, to adhere to epithelial cells, to inhibit pathogens, and/or their effects on epithelial, immune or neuronal cells [26,97]. Today, our increasingly extensive knowledge of new microbiota-related pathways relevant ecologically and to health, is making it possible to re-select probiotics on the basis of the function of the gut microbiota they should complement. Commensal organisms have considerable potential for use as new probiotics, but technological limitations (such as the need for strict anaerobic conditions), and antibiotic resistance may restrict their use to therapeutic applications. By contrast, lactic acid bacteria and *Bifidobacterium* are known to resist industrial process, and many studies have already shown that they can produce bioactive compounds, such as CLAs [98], neuromediators [99], Ahr-ligands [100], polyphenols [101], iron scavengers [102,103], vitamins [104,105], TMA [106], SCFA [107], and antioxidants [108]. Future studies will almost certainly identify additional functions that these bacteria can deliver. Consequently, lactic acid bacteria and *Bifidobacterium* libraries are a source of promising candidates for next-generation probiotics.

animal origin are consumed [64]. Overall, these results suggest that attention should be paid to the quantity and quality of lipids consumed, as these molecules may have potent deleterious effects on the structure of the gut microbiota.

These advances in our understanding of gut microbiota function can serve as the basis of novel strategies for the complementation of gut microbiota dysfunction (Box 1).

The Microbiota Challenge: It's Not a Level Playing Ground

One Diet, Many Microbial Possibilities

Microbiota responses to dietary intervention are known to vary considerably between subjects [65,66]. Studies of individuals with a microbiota response to a particular intervention have provided information about the ecology of the responding microbiota. Table 1 provides a summary of clinical studies in which the subjects were stratified for the baseline composition, metabolite content and richness of the microbiota or the response to a given dietary intervention. The interventions tested included the consumption of a fermented milk product (FMP) [67]. The identification of two distinct patterns of response to FMP ingestion (i.e. 'permissive' and 'resistant' microbiota) indicated that the live bacteria present in fermented products might have different impacts on the host and/or microbiota according to the nature of the microbiota present [68]. Microbiota richness has been identified as a factor controlling the extent of microbial modulation after the consumption of specific diets for weight loss, or rich in non-starch polysaccharides or fibre [69–72]. The presence of a 'rich' microbiota is associated with higher caproate and valerate concentrations and a higher *Prevotella*:*Bacteroides* ratio. The richness of the baseline microbiota was found to be correlated with greater microbiota stability during dietary intervention in several studies. More diverse microbial ecosystems have already been shown to be more stable, particularly for the gut microbiota in elderly subjects [73]. This topic has been the subject of several recent reviews [74,75]. The positive correlation between baseline microbiota richness and stability following dietary intervention probably reflects a higher level of functional redundancy in rich microbiota [74]. As shown above, subjects with low and high microbiota richness often respond differently to dietary intervention. Differences between individuals with high and low microbiota richnesses have been characterized in a cohort of obese and lean individuals [76]. From an ecological perspective, low microbiota richness is generally associated with higher abundance of members of Proteobacteria–including oxygen tolerant species–and Bacteroidetes, whereas high microbiota richness is associated with a high abundance of members of Firmicutes, Actinobacteria and Verrucomicrobia.

Approaches based on the stratification of subjects, based on the response of the microbiota, and according to the initial state of their microbiota, have been described principally in terms of richness, metabolites, and the abundance of particular microbial taxa, with specifically *Bifidobacterium* [77–79] and recently the more global community. Based on this concept, clinical trials

Table 1. Example Clinical Studies Using the Baseline Microbiota to Assess Microbiota or Host Responses Following Dietary Intervention

Cohort	Intervention (type and duration)	Stratification based on	Microbiota response following intervention	Refs
Microbiota responses				
Overweight-obese (*N* = 49)	Calorie restriction 6 weeks	Microbiota richness	Large increase in microbiota richness in the low-microbiota richness group No change in microbiota richness in the high-microbiota richness group	[81]
Healthy subjects (*N* = 33)	*Lactobacillus paracasei* DG (*N* = 14) and control (*N* = 16) 4 weeks	Faecal butyrate (<25 mmol/kg of wet faeces)	Increase in butyrate, and an increase in *Ruminococcus* species and a Bacteroidales genus in the group with low faecal butyrate concentration	[95]
Overweight-obese individuals (*N* = 78)	Different diets: High fibre: high-fibre rye bread and whole-grain pasta (*N* = 28) Low fibre (*N* = 24) Inulin and oligofructose (*N* = 13) Four types of diet as reported below (*N* = 13) 10–12 weeks	Microbiota stability	Lower stability of microbiota in subjects with a lower abundance of *Eubacterium ruminantium* and *Clostridium felsineum*	[70]
		Change in *Bifidobacterium* during intervention	Higher *Bifidobacterium* levels in subjects with lower baseline *Bifidobacterium* levels	[70]
Obese individuals *N* = 14	Four types of diet: Maintenance diet (1 week) Resistant starch (3 weeks) Non-starch polysaccharides (3 weeks) Weight-loss diet (3 weeks)	Microbiota modulation	Microbiota responsiveness was negatively associated with baseline diversity	[71] [96]
Healthy adults (*N* = 19)	Two diets with 2 doses of dietary fibre (10 or 40 g) 5 days each	Microbiota stability	Greater stability of microbiota in subjects with high baseline microbiota richness	[72]
Healthy women (*N* = 14)	Fermented milk product (FMP) 7 weeks	Detection of *Lactococcus lactis* after the cessation of FMP	Subjects with lower *L. lactis* clearance displayed greater modulation of the gut microbiota and have a higher relative abundance of Barnesiellaceae Odoribacteraceae and Clostridiaceae	[67]
Healthy subjects (*N* = 31)	Biscuits with partially hydrolysed guar gum (PHGG) and fructooligosaccharides 21 days	Change in bacterial groups	Subjects with low baseline *Bifidobacterium* levels displayed larger increases in *Bifidobacterium* levels following consumption of biscuits	[79]

Table 1. (continued)

Cohort	Intervention (type and duration)	Stratification based on	Microbiota response following intervention	Refs
Clinical responses				
Rome III IBS children (*N* = 12)	Low fermentable substrate 1 week	GI symptoms: abdominal pain frequency	Responders had a higher abundance of *Sporobacter, Subdoligranulum*, and a lower abundance of *Bacteroides*	[97]
Rome III IBS children (*N* = 33)	Low FODMAP 2 days	GI symptoms: abdominal pain frequency	Responders had higher levels of *Bacteroides*, Ruminococcaceae, *Faecalibacterium prausnitzii* and KEGG orthologues related to FODMAP carbohydrate metabolism	[85]
Overweight-obese (*N* = 49)	Calorie restriction 6 weeks	Inflammation variables	Subjects with higher gene richness at baseline displayed a greater improvement in adipose tissue and systemic inflammation variables	[81]
Overweight-obese (*N* = 49)	Calorie restriction 6 weeks	Metabolic variables	Subjects with a higher baseline level of *A. muciniphila* displayed a greater improvement in insulin sensitivity markers and other clinical parameters	[82]
Overweight - obese *N* = 45	Calorie restriction 6 weeks	Weight reduction	Individuals who lost less weight and rapidly regained weight during the stabilisation period had a higher abundance of *Lactobacillus/Leuconostoc/ Pediococcus* at baseline	[83]
Obese individuals from three independent cohorts (*N* = 78)	Diverse dietary interventions	Cholesterol levels	Subjects with lower cholesterol levels had a higher abundance of *C. sphenoides*	[70]
		Homeostasis model assessment of insulin resistance (HOMA) response	HOMA response predicted by baseline abundance of *Clostridium* clusters XVI, XVIa, bacilli and Proteobacteria	
		C-reactive protein	C-reactive protein response predicted by baseline abundance of *Clostridium*. Clusters VI, XI, XVIa,XVIII	
Healthy subjects (*N* = 20)	High-barley diet 3 days	Glucose metabolism	Subjects with a weaker glycaemic response had higher baseline *Prevotella* abundance	[84]
Healthy subjects (*N* = 7)	Low-calorie artificial sweeteners 1 week	Glycaemic response	Subjects with a stronger glycaemic response had a microbiota different from that of other subjects	[98]
Nondiabetic adults (*N* = 800)	Standardised and real-life meals 1 week	Glycaemic response	Algorithm based on clinical and microbiota data	[65]

have recently been set up to determine whether baseline gut microbiota composition and function differ between individuals with low and high dietary fibre intakes [80].

Microbiota, the X-factor in Dietary Interventions

The magnitude of the response of the gut microbiota to a dietary intervention (as discussed above) may reflect differences in impact on the clinical parameters of the host. Indeed, recent studies have also stratified subjects on the basis of clinical outcome (Table 1). Cotillard *et al.* showed that the response of inflammation parameters to a 6-week low-calorie diet was stronger in overweight/obese individuals with a high microbiota richness (60% of subjects) than in those with a lower microbiota richness [81]. In the same cohort, Dao *et al.* observed that subjects with a higher baseline level of *Akkermansia muciniphila* displayed a greater improvement in insulin sensitivity markers and other clinical parameters after a low-calorie diet [82]. Subjects from the same cohort who lost less weight during the calorie reduction phase and regained weight during the 6-week stabilisation period had higher baseline levels of *Lactobacillus/Leuconostoc/Pediococcus* in faecal samples, as shown by quantitative PCR [83]. Similarly, Kovatcheva *et al.* reported that healthy individuals with a higher abundance of *Prevotella coprii* in the gut responded better to 3 days of a diet enriched in barley than those with lower levels of this microbe, as demonstrated by metabolic findings, such as improvements in glucose metabolism [84]. In one study, children with IBS were fed a diet low in fermentable oligo-, di-, monosaccharides and polyols (FODMAPs) for 2 days. Those with gut microbiota populations containing larger numbers of taxa known to break down sugar efficiently (*Bacteroides*, Ruminococcaceae, and *Faecalibacterium prausnitzii*) before the intervention experienced greater pain relief [85].

Although using the gut microbiota as an enrolment and stratification factor seem to hold promises, challenges remain, particularly as concerns the representativeness of a single stool sample collected at one time point, given the between-day or even within-day variability of the faecal microbiota [2]. This issue is of particular importance in subjects displaying larger microbiota fluctuations, such as those with a lower microbiota richness, diseases such as IBD [86], infections, travel, or on antibiotics [87,88]. An understanding of natural between- and within-day variability and the collection of clinical data will be crucial in future clinical studies.

From Apple® to Apples: From Big Data to Tailored Nutrition

As discussed above, the same diet can have different impacts in different hosts and on different microbiota. Thus, one of the future challenges in the field of nutrition will be to personalise nutrition, taking into account the gut microbiota, host genetics, and environmental factors (Figure 2), to make individual-relevant dietary recommendations. In a recent study, Zeevi *et al.* demonstrated the validity of this concept, by showing that personalised dietary recommendations, computed from a set of host, environmental and microbial variables, lowered postprandial glycaemic response in humans more effectively than the recommendations of experts [65]. The plethora of smartphone applications (apps) now available makes it possible for the general public to obtain access to tailored nutritional recommendations that seem to be indeed effective [89].

In the future, dietary recommendations will probably also be tailored to stimulate, inhibit or complement gut microbial functions shown to be relevant to health. In the absence of recommendations, diets in which specific nutrients are restricted have recently emerged as a means of relieving GI symptoms (Box 2). However their long-term consequences for the gut microbiota remain unknown. The development of dietary recommendations in the future will be made possible by (i) the increasing efforts of the scientific community to understand the effects of gut microbial metabolites on host health, (ii) the exponential amounts of microbiota data and metadata accumulating, fueled by pioneer self-trackers [90] and large microbiota cohorts, (iii) falling costs of genome sequencing, which will make the generalisation of microbiota self-tracking

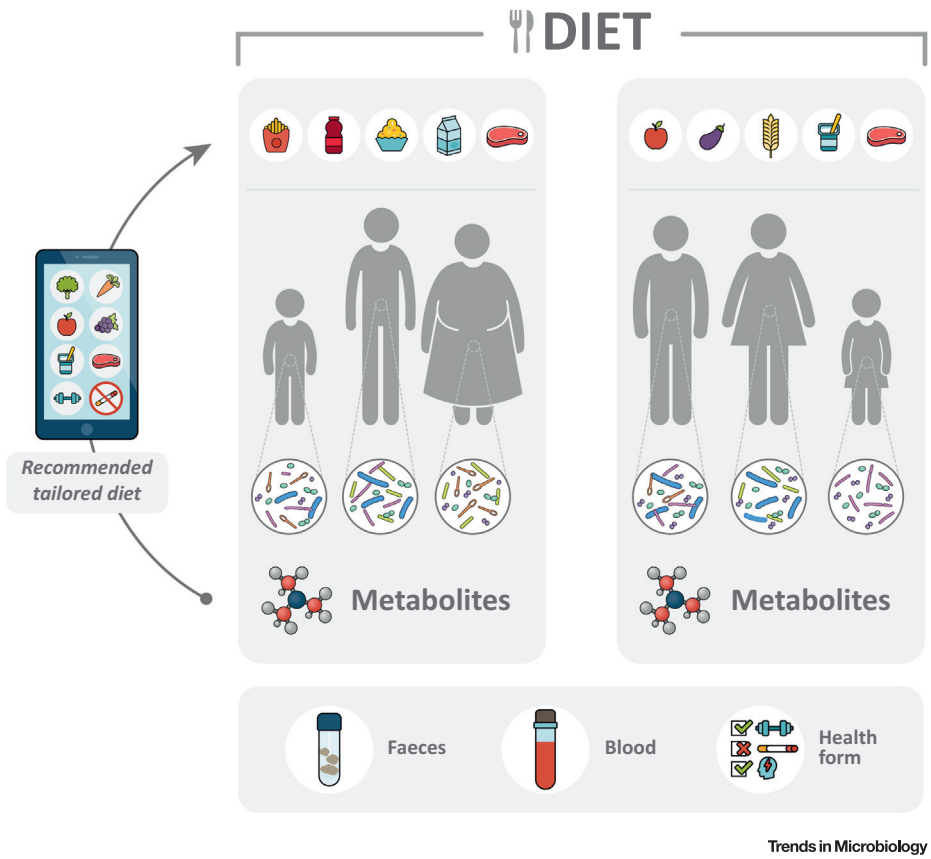

Figure 2. Dietary Recommendations Based on the Microbiota, Diet Preference, and the Metabolic and Immune State of Individuals. In the near future, it should be possible to improve the selection of appropriate subjects for inclusion in clinical studies, based on diet, for example, and to improve and predict clinical outcomes by taking the initial state of the microbiota into account and identifying microbiota-based markers correlated with outcome.

Outstanding Questions

What level of personalised nutrition will be achievable in the future?

How feasible is the reintegration of traditional habits, specifically those of a dietary nature, into modern life?

Will more widespread microbiota assessment in the general population help to integrate diet into strategies for preventing dysbiosis?

Will integrative approaches based on metabolic interactions between the microbiota and the host be adaptable to real-life situations?

Box 2. Recent Emergence of Restrictive Diets

Diets to reduce GI symptoms are becoming increasingly popular. A diet low in poorly absorbed and fermentable carbohydrates, the so-called "low FODMAPs" (fermentable oligo-, di-, monosaccharides and polyols) diet, reduces gastrointestinal symptoms in patients with IBS. It remains unclear whether the microbiota changes related to this diet have a long-term impact on host health, and only a few studies have addressed this issue. The exclusion of gluten may also modify the composition of the gut microbiota, although this aspect has yet to be studied in detail. The long-term safety, efficacy and impact on the gut microbiota of these exclusive diets require further evaluation in longitudinal cohorts.

possible and, finally, (iv) the development of mathematical methods for mining big data for the gut microbiota [91].

Concluding Remarks

Westernisation has had unexpected consequences for human health. For example, adequate vitamin D levels in the Scottish population relied for more than 14 000 years on a tenuous equilibrium between biological traits (i.e. maximally depigmented skin optimising vitamin D production), sunlight exposure (i.e. outdoor activities) and dietary habits (i.e. consumption of vitamin-D rich foods, such as cod or herring). However, the recent urbanisation of Scotland

(starting ~200 years ago) was accompanied by a decrease in vitamin D-rich fish consumption and a decrease in outdoor activities, with these two changes contributing to the disruption of the fragile vitamin D equilibrium and leading to unprecedented levels of vitamin D deficiency at the population scale [92]. This deficiency is thought to be a risk factor for emerging immune-related diseases. Public health agencies therefore recommend supplementing the diet with vitamin D and increasing exposure to daylight [92]. This example highlights how relatively recent changes on the scale of human history can disrupt long-established equilibria controlled by genetics, behaviour, diet, and environment. It also illustrates how an understanding of the molecular factors at work in such equilibria (vitamin D in this example) can facilitate the design of dietary and behavioral strategies to limit the consequences of urbanisation.

In the future, similar developments will probably emerge in the gut microbiota field. For example, it is now widely accepted that the exposure of human babies to their mothers' vaginal microbiota during delivery optimises early intestinal colonisation, with potential long-term benefits. Clinicians have, thus, started to swab babies delivered by Caesarean section with vaginal secretions from the mother [93]. The real benefits of this practice have yet to be assessed, but it shows that scientists are already trying to find ways to attenuate the effects of Western stressors on the gut microbiota.

Dietary interventions are the most robust and attainable approach for modulating the gut microbiota at the population scale. Public health agencies are already promoting microbiota-sound practices, such as increasing fibre consumption, decreasing meat intake and diversifying the diet. In the future, dietary recommendations will almost certainly promote other types of food providing factors essential for the correct functioning of the gut microbiota. As dietary recommendations are known to be poorly followed by populations [94], dietary supplementation with next-generation probiotics (Box 1) selected for their ability to deliver functions missing from the dysbiotic gut microbiota would be very useful. The recent discovery of key gut microbiota-derived metabolic end products will facilitate the design of this new generation of functional foods. The more widespread use of gut microbiota profiling will also make it easier to identify the individuals most likely to benefit from such functional foods and dietary guidance.

In conclusion, public and private research is currently focusing on 'resetting' the microbiota of individuals with disease, but we also need to find solutions to prevent the disruption of human–microbe symbiosis. Personalised diets, supplemented with the next-generation of probiotics, will undoubtedly be a component of the preventive solutions on offer in the future (see Outstanding Questions).

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