Feeding the microbiota: transducer of nutrient signals for the host

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ABSTRACT

Advances in microbiome science cast light on traditional concepts on nutritional science, and are poised for clinical translation. Epidemiologic observations which linked lifestyle factors to risk of disease are being re-interpreted with mechanistic insight based on improved understanding of the microbiota. Examples include the role of dietary fibre in disease prevention, the deleterious effects of highly restricted diets, and the contribution of the microbiota to over- and undernutrition. While the microbiota transduces nutrient signals for the host, food and habitual diet shape the composition of the gut microbiota at every stage of life. The composition and diversity of food intake determines which microbes will colonise, flourish, persist, or become extinct. Disruption of the developing microbiota in infancy contributes to the risk of immune and metabolic disease in later life, whereas loss of microbes in the elderly due to monotonous diets has been linked with unhealthy ageing and frailty. This should influence modern dietary advice regarding prevention and management of chronic non-communicable inflammatory and metabolic disorders, and will inform the design of infant and future food formula. The microbiota profile is also emerging as a biomarker to predict responsiveness to dietary interventions and promises to make personalised nutrition a reality.

Significance of this study

- The microbiota transduces nutrient signals from the diet to the host.
- Diet regulates the composition of the microbiota.
- Many diet-derived microbial metabolites are beneficial but specific metabolites may be associated with the risk of disease and represent a source of biomarkers of metabolic responses in the host to dietary intake.
- Monotonous diets lead to a reduction in biodiversity of the microbiota.
- Loss of diversity of the microbiota is linked with risk of infections and inflammation.
- The microbiota is a plausible target for modifying or preventing the adverse effects of undernutrition and overnutrition.
- The microbiota can be used as a biomarker to predict responsiveness to specific dietary constituents, for example, fibre.

INTRODUCTION

Microbiome science is challenging traditional concepts of nutrition, creating new paradigms for dietary assessment and revealing new avenues of research for future foods. The most important lessons from microbial science are simple yet elegant; when we eat, we feed not only ourselves but also our microbes. Maintenance of a healthy microbiota requires a healthy diet, the requirements for which vary with the age of the host and with disease, and vertical transmission of the microbiota implies that expectant mothers are, in essence, eating for a new generation! These simple concepts have obvious implications for modern approaches to nutrition.

Advances in understanding the composition and function of the indigenous microbiota continue apace, particularly since the introduction of molecular techniques to study microbial communities which were previously either uncharacterised or dismissed as being 'unculturable'. The role of the microbiota in health and disease has undergone an upgrade in status from that of a 'neglected organ' to one of an ecosystem which transduces nutrient and other environmental signals to the host metabolism and homoeostasis.[1–3] It is increasingly apparent that many aspects of traditional dietetics and nutritional science are becoming more nuanced, with deeper understanding derived from emerging microbiome science. Opportunities for translating microbiome science to clinical medicine and to new concepts of future foods are a realistic prospect. Comprehensive descriptions of the relationship between diet and the microbiota may be found in earlier reviews.[2–8] Here, we present an overview of recent information of particular relevance to clinical practice and likely to have a transformative impact on modern approaches to nutritional assessment and on the design of future foods.

A NETWORK OF CONNECTIVITY

The host response to environmental challenge involves activation of a signalling internet composed of immune, metabolic and neuroendocrine systems, shaped by the microbiota, each component of which is influenced by diet and nutritional signals.[9 10] Since immune and metabolic cascades converge at several cross points, it is not surprising that chronic inflammatory and metabolic disorders share common pathogenic processes and commonly co-occur. Indeed, the increasing frequency of such disorders in socioeconomically developed countries has been linked, in part, to the modifying influence of human lifestyle factors, such as antibiotic exposure and

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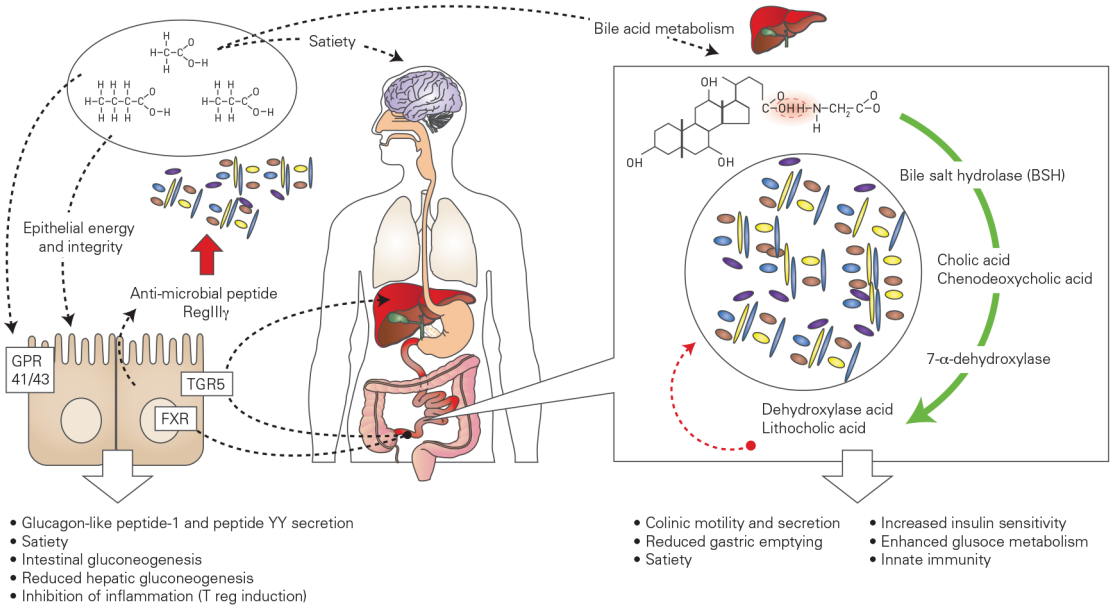

Figure 1 Complexity and interconnectivity among diet-microbe-host interactions. Dietary fat stimulates release of bile acids into the upper GI tract from which they undergo enterohepatic circulation following progressive deconjugation and conversion of primary to secondary bile acids, which have direct and indirect modifying effects on the composition of the microbiota by modifying the expression and production of host-derived antimicrobial factors, such as regenerating islet-derived protein 3 gamma (RegIIIγ). Bile acids signal through surface receptors (TGR5) and the nuclear receptor (FXR) have several downstream effects on GI motility and secretion, central signalling (satiety), metabolism and immunity. While bile salt hydrolase upregulates RegIIIγ, a high-fat diet may associate with reduced RegIIIγ, whereas some components of the microbiota, such as Akkermansia, upregulate RegIIIγ. These physiological events occur in the context of other diet-derived bacterial metabolites including short chain fatty acids (SCFA), which not only contribute to energy harvest for the host but also have pleiotropic effects on the brain–gut axis, neuroendocrine system and hepatic and peripheral tissue metabolism reviewed by Koh *et al*.[19] SCFA signal via G-protein-coupled receptors; the activities shown are representative, not comprehensive. Red arrows: antimicrobial. FXR, farnesoid X receptor; TGR5, takeda G-protein-coupled receptor 5.

habitual diet, and their influence on the developing microbiota.[11 12] The microbiota is assembled during the first few years of life, a time when its influence on immune, metabolic and other host systemsis maximal and its vulnerability to antibiotics greatest. Dietary intake, on the other hand, determines which microbes colonise, flourish, are retained or disappear and may be a source of foodborne microbes.[13]

The complexity of diet-microbiota-host interactions is exemplified by the relationship between bile acids and the microbiota. Bile acids, once considered in a limited role in micelle formation and lipid absorption, are now recognised as signalling molecules, akin to hormones, that modify host metabolism, immunity and the microbiota.[14–17] The antimicrobial effect of bile in the lumen of the upper GI tract has long been known, as has the role of the microbiota in deconjugation and conversion of primary to secondary bile acids. However, the antimicrobial effect of secondary bile acids, for example, against *Clostridium difficile* has recently emerged.[16] Furthermore, bile acids have an indirect conditioning influence on the composition of the microbiota by regulating the expression of host-derived antimicrobial factors such as regenerating islet-derived protein 3 gamma (figure 1) and by influencing barrier function and inflammasome activity.[17 18]

In addition to microbial modification of host-derived signalling molecules, the microbiota is a source of nutritional signals, many of which have pleiotropic effects on the host and which extend beyond energy harvest. This is well illustrated by the diversity of effects of short chain fatty acids (SCFA), the most abundant of which in the human gut are acetate (C2), propionate (C3) and butyrate (C4), the main products of microbial fermentation of dietary fibre and resistant starch. These are a source of energy for the colonic epithelium but also interact with host metabolites including bile salts and local hormones such as glucagon-like peptide-1 and peptide YY. SCFA are regulators of host immunity, metabolic homoeostasis and gut-brain signalling (figure 1). Unravelling the range of SCFA signalling with the host has prompted a reinterpretation of the health benefits of dietary fibre, and while the health benefits of SCFA under physiological conditions are accepted, the role of excess acetate, in particular, in obesity and metabolic disease in the host is controversial and may be dose dependent and context dependent.[19–21]

LINKING SPECIFIC MICROBIAL METABOLITES WITH HEALTH AND DISEASE

The repertoire of diet-derived, microbially produced bioactive metabolites in the gut is incompletely documented. Gut microbes are a source of vitamins including K, folate, thiamine and other B vitamins in addition to tryptophan.[22] Tryptophan is an essential, diet-derived amino acid that undergoes microbial metabolism to indoles which are ligands for the aryl hydrocarbon receptor (AHR) and promotes immune cell production of interleukin-22, the latter protecting against intestinal inflammation. Genetic susceptibility to inflammatory bowel disease due to deletion of the *Card 9* gene (caspase recruitment domain family member 9) is associated with an altered or colitogenic microbiota with an impaired capacity to metabolise tryptophan to AHR ligands.[23] This is another example of the complexity of diet-microbe-host metabolic interactions, which require a personalised therapeutic

approach in genetically susceptible hosts. Another curious interplay between nutrients, microbes and host immunity arises in the case of riboflavin (vitamin B_2) production by the microbiota. Thus, mucosal associated invariant T cells which protect the host from pathogens may also respond to transitory microbial-derived metabolites or neoantigens such as those generated during microbial production of riboflavin.[24]

Several dietary-derived metabolites which have been linked with disease risk are subject to microbial modification and are potentially tractable. For example, oxalate, which is associated with risk of renal stones, may be degraded by *Oxalobacter formigenes* and many *Lactobacillus* species. However, trials of oxalate-degrading putative probiotics have been disappointing to date.[25]

In contrast, microbial metabolism of choline, a dietary phospholipid, glycine betaine (in certain legumes) or the amino acid, L-carnitine, which is abundant in red meat and other foods, may contribute to the risk of atherosclerosis by supporting increased microbial production of trimethylamine (TMA). After absorption, TMA undergoes hepatic oxidation to TMA N-oxide which is associated with accelerated atherosclerosis by various mechanisms including altered sterol and bile acid metabolism and macrophage activation.[26] In addition to the bacterial role in producing TMA, other members of the microbiota (archeal methanogens) can dissimilate TMA,[27] indicating a complex overall role for the microbiota in modulating this atherogenic metabolite.

Several other bacterial constituents or metabolites have been linked with metabolic disease in the host but their relationship with dietary intake is less clear and their role in humans is uncertain. For example, lipopolysaccharide (LPS), a cell wall constituent of Gram-negative bacteria has been associated with a high-fat diet and linked with risk of inflammatory and obesity-related metabolic disorders including diabetes (metabolic endotoxemia).[28 29] Increased plasma levels of LPS are associated with a high-fat diet, but whether this is a physiological response to fat with chylomicron-mediated absorption, or whether it is a proxy marker of mucosal barrier function and bacterial translocation, is unclear.

FEEDING THE NEONATAL MICROBIOTA

The microbiome influences the development and maturation of host immunity, metabolism, brain–gut axis and other systems. Consequently, attention on dietary and other lifestyle factors shaping the assembly of the microbiota has been reinvigorated. Constituents of human milk include essential nutrients, immunoprotective molecules such as secretory IgA, lactoferrin, defensin 1, lysozyme, complex lipids and conjugated glycans. Human milk oligosaccharides (HMOs) are a group of free glycans which contribute directly and indirectly to the maturation of the neonatal gut and its microbiota.[30–32]

The concentration of HMO in human milk (5–20 g/L) and colostrum (20–25 g/L) greatly exceeds that of similar molecules in bovine milk or traditional formula milk.[33] HMOs contain lactose at their reducing end, but are highly varied in structure (>100 different HMO structures are known) due to their varying degree of polymerisation and different configurations of glycosidic linkages between the five building blocks: galactose, glucose, N-acetylglucosamine, fucose and N-acetylneuraminic acid. Lactose may be extended by lacto-N-biose or N-acetyllactosamine, allowing a classification into type 1 or type 2 chain HMOs, while lactose and the type 1 and type 2 chains are also frequently fucosylated and sialylated at various positions.[33] Furthermore, HMO content and composition vary considerably during lactation[34 35] and whether delivery was preterm or full term.[36] Additional heterogeneity arises with fucosylation status due to the (in)activity of the *Se* and *Le* genes, encoding fucosyltransferases that also determine blood group type, and result in four milk types.[37 38]

HMOs are resistant to hydrolysis by gastric pH and digestive enzymes, undergo minimal absorption, and become substrates for the developing infant gut microbiota. They also protect against various pathogens by acting as biological decoys (antiadhesins) to offset invasiveness.[33] HMOs are responsible, in part, for the timely presence and dominance of specific members of the genus *Bifidobacterium* in the gut microbiota of breast-fed infants.[39–41] Consistent with this apparent HMO–*Bifidobacterium* link, it has been observed that reduced fucosylation of HMOs from mothers with inactive *Se* and/or *Le* genes impacts on the composition of bifidobacterial communities in the infant gut.[42 43] Furthermore, it has become apparent that the genomes of these anaerobic microbes encode a broad spectrum of glycan-degrading enzymes, some of which represent species-specific glycosyl hydrolases that metabolise particular HMOs, such as fucosyl-lactose, sialyl-lactose and lacto-N-tetraose.[44–47] Molecular analyses show that *Bifidobacterium longum* subsp *infantis* and *Bifidobacterium bifidum* are endowed with the widest range of HMO-degrading abilities, whereas other infant-associated bifidobacteria such as *Bifidobacterium breve* and *B. longum* subsp *longum* are much more limited in this regard.[48] However, it has been shown for *B. breve* that this species cross feeds on the HMO-derived carbohydrates released by the extracellular enzymes of *B. bifidum* indicating that certain bifidobacterial species support each other, whereas others are more 'egocentric' in nature as they internalise the HMOs prior to hydrolysis.[49] Intrinsic metabolic interactions among the various infant-associated bifidobacteria are incompletely understood, as are the exchanges between bifidobacteria and other gut microbiota components, and how these influence the developing host.

In addition to supplying the newborn with a personalised functional food, breast milk may also act as a vehicle for vertical transmission of microbes, including bifidobacteria, to the developing gut microbiota.[50 51] Such vertical transfer has been linked to the optimal development of early innate immunity.[52] The neonatal and infant microbiota exert its maximal influence on the maturation of acquired and innate immunity during a critical window in the first few years of life, reviewed in the studies by Charbonneau *et al*, Kau *et al*, Hand *et al* and Shanahan and Sheehan.[2 5 7 9]

The disparity in content of HMO or HMO-like content of human and bovine milk[33] is one of the reasons for recommending exclusive breastfeeding in the first 6 months of neonatal life.[53] Commercial milk formulae, traditionally based on bovine milk, are now supplemented with specific carbohydrates, such as galacto-oligosaccharides to replicate some of the HMO-associated functionalities.[54 55] Large-scale production of relatively simple HMOs, such as sialyl-lactose, fucosyllactose and Lacto-N-(neo)tetraose, will facilitate the development of next generation, 'humanised' milk with added or enhanced functionality.[56 57] As alluded in the next section below, the benefit of dietary supplementation with such an oligosaccharide has been demonstrated in models of infant undernutrition.

THE UNDERNOURISHED MICROBIOTA

It is long known that consequences of early life under-nutrition include persistent growth stunting, impaired cognitive

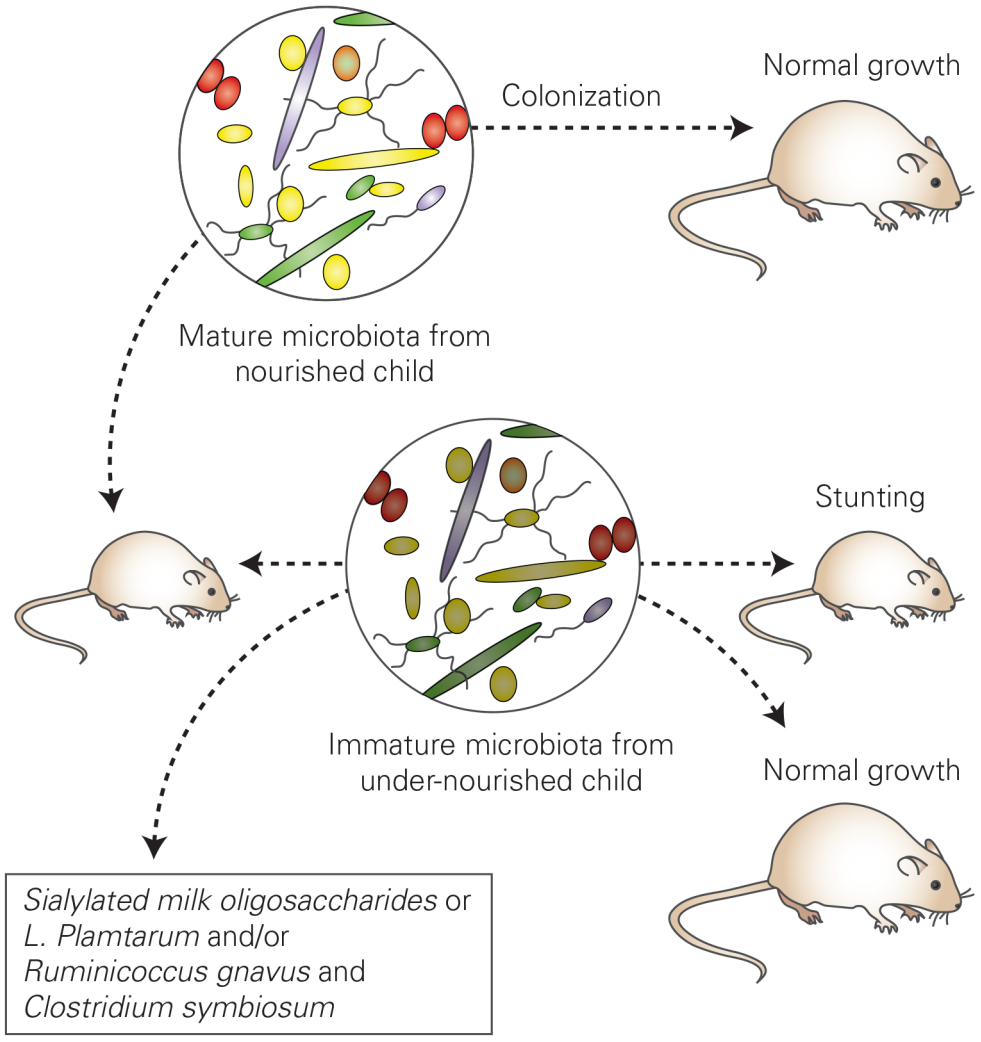

Figure 2 The undernourished microbiota. Colonisation of young mice with microbiota from healthy children leads to normal growth even if fed a nutrient deficient diet, whereas mice colonised by microbiota from a malnourished child exhibits stunting of growth. However, normal growth can be achieved by supplementation of the microbiota with specific microbial species at the time of initial colonisation or by dietary supplementation with sialylated milk oligosaccharides.

development and increased risk of infectious and other diseases. Now, it appears that the gut microbiota of malnourished children is also immature.[58] Moreover, experimental models of gnotobiotic mice colonised with human microbiota and fed human diets suggest a causal relationship between microbiota immaturity and impaired brain, immune and metabolic development in the host.[59–62]

Bacterial taxa which might promote weight gain or limit the activity of the undernutrition-related microbiota have been identified prompting speculation that microbial manipulation might help shift metabolism away from energy extraction by amino acid breakdown and towards growth and building lean body mass.[60] In the absence of a microbiota, chronic undernutrition is associated with resistance to growth hormone, whereas the microbiota permits postnatal growth by conferring sensitivity to growth hormone with increased insulin-like growth factor activity in peripheral tissues. *Lactobacillus plantarum* mimics these effects of the microbiota in a strain-dependent manner. This has obvious preventive and therapeutic implications but the results cannot be extrapolated to all lactobacilli.[61] However, microbiota-dependent growth can also been stimulated by HMOs from breast milk or by artificial supplementation with human sialylated milk oligosaccharides.[62] (Figure 2).

THE MICROBIOME AND OVERNUTRITION

Energy intake that is surplus to energy expenditure is stored as fat and, if prolonged, is a risk factor for obesity. However, this fact is only a half-truth, because the ratio of energy intake to expenditure is conditioned by an underlying network of immune, metabolic and microbial signalling, influenced by host genetics, environmental and lifestyle factors. Several lines of evidence have linked the microbiota with the risk of developing obesity and related metabolic disorders.[3 7 63 64] First, there is biological plausibility; the microbiota is a net contributor to host nutrition. Germ-free animals must consume additional calories to maintain a body weight equivalent to that of colonised animals, and the microbiota contributes to energy harvest from the diet and has a regulatory influence on fat storage. Second, diet-induced obesity in experimental animals has been linked with changes in the microbiota and suggests that the dietary impact exceeds that of genetics and immunity. Third, transplants of human donor

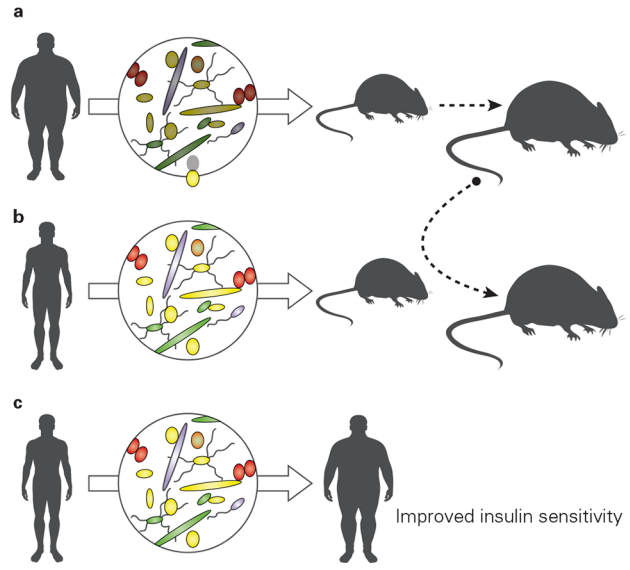

Figure 3 Microbiota in overnutrition. Schematic representation of the use of experimental 'humanised' mice (germ-free animals colonised with human microbiota from donors of various phenotypes, obese (A) and lean (B)), to demonstrate the potential impact of the microbiota on weight and metabolism of the host. Murine-to-murine transfers demonstrate the same effect and permit dietary manipulation. Human-to-human faecal microbial transplantation has also demonstrated the beneficial influence of a microbiota from a lean donor with improved insulin sensitivity in obese recipients (C). FMT, faecal microbial transplantation.

microbiota to 'humanised' mice (germ-free animals colonised with human microbiota) and fed different diets provide compelling evidence for the functional impact of the microbiota on energy balance (figure 3). Particularly noteworthy are human-to-mouse transplants from twin pairs discordant for obesity which demonstrate transmissible, diet-dependent obesity.[65] Finally, evidence in humans for a pathogenic role for the microbiota in obesity is more limited and indirect. Reported alterations in the microbiota in lean and obese humans have been conflicting and challenged,[66] but the number of gut microbial genes (bacterial richness) has been positively correlated with metabolic markers with low microbial gene counts associated with adiposity and insulin resistance.[67] In addition, *Prevotella copri* and *Bacteroides vulgatus* have been identified as driving an association between biosynthesis of branched chain amino acids and insulin resistance.[68] More compellingly, microbial transplantation from lean to overweight individuals has been associated with short-term improvements in metabolic health including glucose tolerance.[69] Conversely, there is an anecdotal report of weight gain in an individual following faecal microbial transplantation from an overweight donor.[70] In addition, epidemiological studies have linked disturbances of neonatal microbiota due to antibiotic exposure with an increased risk of metabolic disease in later life.[11] Furthermore, changes in the microbiota have been mechanistically linked with the action of bariatric surgery which is the single most effective therapeutic strategy for morbid obesity.[71]

The scale of the contribution of the microbiota to weight gain is unclear and whether it translates to humans to a degree similar to that seen in experimental animals is uncertain. Moreover, targeting the microbiota in the prevention of obesity will require more precise understanding of the molecular mechanisms involved. These may include not only increased caloric bioavailability but also diverse effects on metabolism, satiety, insulin resistance and inflammatory tone.[9 10] Meanwhile, specific components of the microbiota, such as *Akkermansia muciniphila*, have been inversely linked with obesity and insulin resistance in rodents and in humans.[72–74] The potential impact of dietary supplementation with this organism and/or with prebiotic polyphenols and inulin-type fructans which enhance the abundance of *Akkermansia* in the gut is being investigated in metabolic and cardiovascular disorders.[74–77]

DIETARY DIVERSITY—NOT JUST THE SPICE OF LIFE BUT ALSO STAPLE

Clinical dietary assessments have traditionally focused on quantity and quality of nutrient intake with little attention to dietary diversity. However, the microbiota varies with age, and the impact of diet is likely to be most significant at the extremes of life. In a large study of the elderly in different residential settings ranging from community dwelling to long stay institutional care, collapse of microbial diversity was associated with a shift toward a monotonous diet. More importantly, the loss of microbial diversity was linked with increased markers of inflammation and frailty. Although correlation should not be transmuted to causation, the directionality of the changes suggested causation with dietary change preceding the loss of microbial diversity and the severity of the latter increasing with duration of exposure to the monotonous diet.[78] (Figure 4).

To model the impact of reduced dietary diversity on the microbiota, humanised mice were deployed in which human faecal microbiota was introduced into germ-free mice which were then fed a low-fibre diet. This resulted in a progressive loss of microbial diversity which could be at least partially restored with reintroduction of dietary fibre. However, once the reduced microbial diversity with missing taxa were transmitted to subsequent generations, the reintroduction of fibre was insufficient to reverse the loss.[79] These data imply that not only does dietary diversity maintain microbial diversity but an individual's diet today influences the microbiota of future generations—a concept that needs to be addressed during antenatal education and maternal nutrition.

THE PERSONALISED MICROBIOME

Although dietary intake has consistently been shown to shape the composition and function of the human gut microbiota, the magnitude of impact of a dietary intervention varies widely among individuals. Factors which determine an individual's responsiveness to dietary intervention are incompletely understood but appear to include prior dietary practices and prior GI microbial composition.[80 81] This has been demonstrated using gnotobiotic mice colonised with faecal microbiota from humans consuming a typical American diet in comparison with those consuming a calorie-restricted but nutritionally adequate diet. The American diet was associated with reduced microbial diversity and richness and was less responsive and incompletely rescued by a healthy diet, requiring supplementation with microbiota from micefed with the healthy diet for full microbial replenishment. In contrast, the microbiota in mice transplanted with faeces from humans on the healthier diet was more responsive to either form of dietary intervention.[81] Additional evidence for the influence of prior dietary practice on the composition of the microbiota and response to subsequent dietary intervention has been derived from modelling so-called yo-yo dieting with alternating cycles of calorie restriction and excess. Thus, obesity-induced alterations to the microbiome tend to persist after

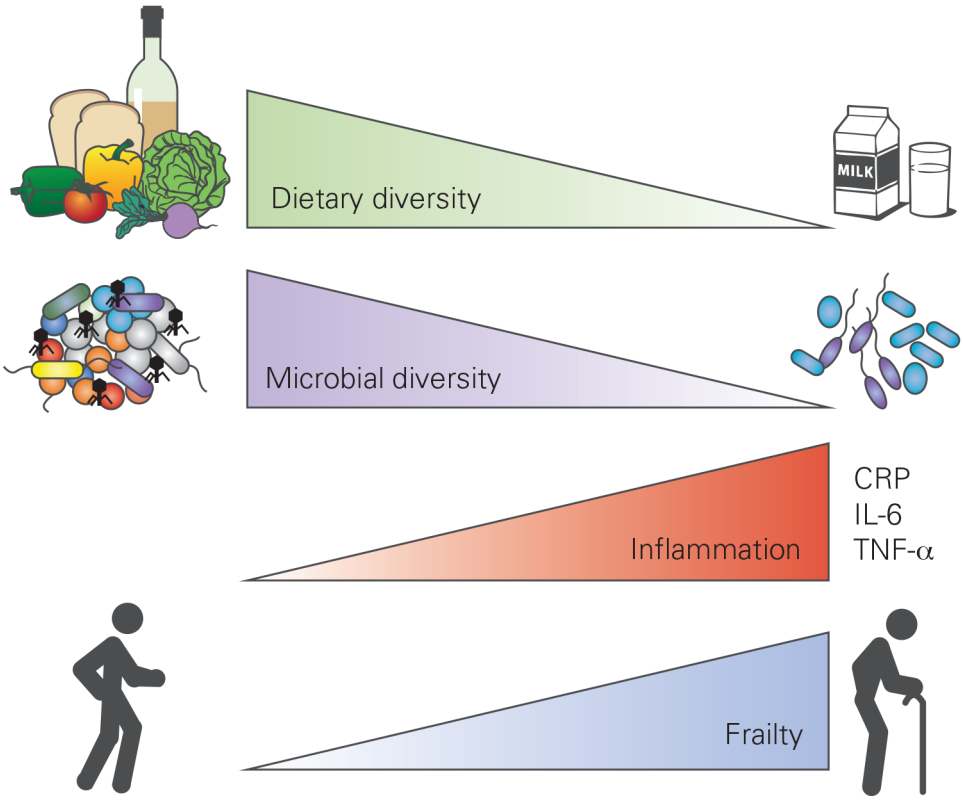

Figure 4 Diversity as staple, not simply spice of life. Diversity of dietary intake correlates with microbial diversity in the gut which is linked with inflammatory tone and risk of frailty in the elderly. Thus, a monotonous or restricted diet (although with adequate calories and essential nutrients) which is often liquidised and convenient in the case of the elderly is linked with loss of microbial diversity, and perhaps more importantly, with loss of key microbial functions and a risk of a gain in pathobionts, including susceptibility to overgrowth of *Clostridium difficile*. CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α.

calorie restriction and lead to more rapid and enhanced weight regain when calories are reintroduced.[82]

The relationship between the microbiota and interindividual variation in response to dietary interventions emphasises the potential importance of personalised therapeutic approaches to host metabolism. When healthy human subjects were fed a 3 day diet supplemented with barley fibre, those who responded with improved glucose tolerance were shown to have a higher *Prevotella*/*Bacteroides* ratio than the non-responders. Increased capacity to ferment complex polysaccharides was attributed to enrichment of *P. copri* in the responders. The results were supported by comparative studies in germ-free mice transplanted with the microbiotas from the responder and non-responders.[83]

Interindividual variability in dietary responses also applies to consumption of food-grade bacteria including probiotics. When *B. longum* AH1206 was fed to humans, it persisted in one-third of recipients for at least 6 months. Engraftment was linked with low abundance of resident *B. longum*, and engraftment appeared to be prevented by competitive exclusion in the presence of phylogenetically related organisms. Thus, it seems that precision reconstitution of the human microbiome may be possible and should be predictable based on analysis of the pretreatment microbiome.[84]

Profiling the composition of the human microbiota is still limited by the resolving power of many molecular strategies which seldom accurately go beyond the genus level for many microbiota members. Nevertheless, the potential to identify personal microbiomes using metagenomic codes has been successfully validated.[85] The demonstration that dietary advice can be personalised using the microbiome as a biomarker promises new diagnostic approaches to the nutritional assessment of humans.

THE PREDICTIVE MICROBIOME

Profiling the microbiota as a biomarker of responsiveness to diet has been applied to personalised nutrition in an elegant study of interpersonal variability of postprandial glucose responses to identical meals.[86] High interindividual variability to the same diet undermines the value of universal dietary recommendations. Therefore, a machine-learning algorithm incorporating microbiota profiling with relevant physical, lifestyle, metabolic and nutritional parameters was devised to accurately predict individual human responses to meals. This predictive strategy was then used to personalise dietary intervention and modify postprandial glucose responses. The same investigators have also deployed a machine-learning algorithm using microbiota composition alone to predict risk of diet-induced obesity and weight regain after dieting in mice.[86] The potential to adapt such strategies to other disorders including chronic inflammatory and cardiovascular disorders is provocative.

Metabolic biomarkers including blood lipids have long been used to assess risk of cardiovascular disease but recently the gut microbiome has been shown to contribute to interindividual variation in blood lipids.[87] In a robust study of almost 900 human volunteers, the microbiota accounted, in part, for much of variability in body mass index and blood lipids, independent of host gender, age and genetics. The microbiota influence was observed

at the level of triglycerides and high-density lipoproteins, but not low-density lipoproteins or total cholesterol. Incorporating microbiota compositional data into a novel risk model outperformed the risk model without microbiome. Furthermore, broad microbiotal diversity appeared to favour cardiovascular and metabolic health, and associations with changes in specific bacterial taxa were identified.

DIETARY ADDITIVES AND THE MICROBIOTA

Most of the chemical additives to processed foods are considered safe when ingested in normal amounts, although they lack formal toxicity testing, but in several instances, dietary components are now known to undergo metabolism by the microbiota. In some cases, microbial transformation of dietary bioactives may have undesirable consequences. Two recently identified examples are particularly noteworthy—artificial sweeteners and emulsifiers. The widespread use of artificial sweeteners is intended to combat obesity by providing flavour without calories. However, there is provocative evidence suggesting that commonly used artificial sweeteners may induce functional changes in the gut microbiota and drive glucose intolerance.[88] This metabolic effect was transferrable to gnotobiotic mice by faecal transplantation. Replication of these results, quantification of clinical impact and whether it applies uniformly or to a subset of individuals is required, because epidemiological studies have not indicated adverse metabolic outcomes with artificial sweeteners.[89]

Emulsifying agents are detergent-like compounds added to processed foods such as ice cream to keep particles in suspension particularly during storage. Experimental studies in mice have demonstrated that these supplements may disrupt GI mucus with enhanced penetration by microbes in addition to alterations in the composition of the microbiota (reductions in Bacteroidales and increased numbers of *Ruminococcus gnavus* and other mucolytic bacteria).[90 91] The impact of these changes was low-grade inflammation, weight gain and development of metabolic syndrome. The altered microbiota composition was necessary and sufficient to drive these pathophysiological changes because emulsifiers had no deleterious impact on germ-free animals, whereas microbiota from animals fed emulsifiers transferred the disorder to germ-free recipients regardless of further emulsifier consumption. Whether the results relate to human disease susceptibility is uncertain, but it is noteworthy that mice with genetic susceptibility to intestinal inflammation and metabolic syndrome were found to be particularly prone to disease exacerbation when fed the emulsifiers. Furthermore, dietary emulsifiers were shown to exacerbate colon carcinogenesis in a preclinical model of colitis-associated cancer.[92]

SPECIALISED DIETS

While an assessment of the variable influence of different diets is beyond the scope of this overview, it is likely that the microbiota will have to be taken into account when dieticians of the future review an individual's habitual diet and the long-term consequences of any prolonged restriction. Dietary advice regarding added fibre can now be informed by microbiome science.[83] Likewise, the health benefits of adherence to a Mediterranean diet,[93] and the relationship between the microbiota and its associated metabolome in people consuming varied diets from vegan to omnivore is now evidence based.[94]

CONCLUDING COMMENTS

Health maintenance and fitness are no longer solely about human physiology. Maintenance of a healthy microbiome is inseparable from host health. Strategies for therapeutic manipulation of the microbiome in different metabolic, inflammatory or neoplastic disorders may require specific design and tailored to individual susceptibility. However, for most individuals, general principles by which one may mind one's microbes have emerged. Birth by vaginal delivery, breast-fed by a well-nourished mother and avoidance of antibiotics in infancy are a good start. Healthy lifestyle factors under one's control and within the scope of common sense include: a diversified diet, limited use of processed foods, avoidance of prolonged restricted diets, consumption of adequate dietary fibre, exercise[95] and moderation in all respects are all supported by modern microbiome science.

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Contributors All authors contributed to the content of the manuscript.

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