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The impact of nutrition on intestinal bacterial communities

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What we eat influences the species composition of our gut microbiota. This is not only because diet composition determines the supply of substrates for microbial growth (in the form of dietary residue, mainly fibre, that reaches the large intestine) but also because of impacts on gut transit and the gut environment. In turn the metabolic activities of the gut microbiota, which have important health consequences, are influenced by diet and diet-driven changes in microbiota composition. Better understanding of the metabolic capabilities and host-interactions of dominant members of the gut microbiota will aid our ability to improve human health through diet.

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Introduction

Most surveys of gut microbiota composition are based on high throughput analysis of nucleic acid sequences from faecal samples. Within human populations these reveal compositional differences with age and development, including between pre-weaned infants, adults and the frail elderly [1,2]. While host factors, especially immune function and the gut environment, can be important, diet is increasingly offered as the explanation for many of these differences. Thus the supply of human milk oligosaccharides drives the *Bifidobacterium*-dominated microbiota of breast-fed infants [3], while limited dietary intake that is low in fibre may explain changes seen in the frail elderly [1]. Marked differences are also reported between communities separated by geography and lifestyle, for example between industrialised European or North American cohorts and rural Africans or South Americans [2,4,5]. A multiplicity of factors may be relevant, including genotypes, antibiotic use and inocula from the environment [6] but differences in dietary intake are frequently offered as an explanation for such variation in gut microbiota composition. This makes it important therefore to consider what direct evidence exists for dietary modulation of microbiota composition.

Impact of diet on microbiota composition

While observational studies can provide correlations, provided that accurate data on nutritional intake are available, it should be recognized that they cannot provide proof that diet is the cause of shifts in microbiota composition. For this we need to consider studies involving gut microbiota profiling in which the human diet has been deliberately altered. Such studies vary in the degree of dietary control, with some relying only on dietary recommendation and some providing defined supplements to volunteers following their habitual diets. Supplementation studies have been used in particular to obtain evidence for the impact of prebiotics upon the gut microbiota and have often studied selected groups of 'target' bacteria, notably bifidobacteria [7] although more comprehensive surveys have revealed changes in multiple groups [8–10]. Only a few studies have controlled complete dietary intake over a period of time in human volunteers, thus minimizing the influence of background variations in dietary intake [11–13,14••]. Walker *et al.* [11] used a cross-over design in which volunteers switched between diets with the same protein, fat and carbohydrate proportions, but with either resistant starch (RS) or wheat-bran as the main dietary source of non-digestible (ND) carbohydrate. This study identified different species that became strongly enriched within the community either by the RS or by the wheat bran diet [11,15]. These responses occurred rapidly (within 2–3 days) and were found to be reversed following a subsequent dietary switch. Interestingly, it was also noted that overall microbiota composition was more strongly influenced by the individual volunteer than by the diet. One likely explanation for this is that only a minority of species are responsive to the specific dietary manipulation (change in ND carbohydrate) employed [11,15]. In another controlled dietary intervention study, David *et al.* [13] provided volunteers with 'animal-based' or 'plant-based' diets that differed widely in protein, fat, fibre and carbohydrate content. This also resulted in rapid shifts in microbial community composition but these changes were more wide ranging than those seen following controlled changes only in ND carbohydrates.

Diet is also reported to influence overall gut microbiota diversity. In adults, low alpha diversity within the microbial community has been linked with poor health outcomes. In particular, Le Chatelier *et al.* [16] showed that microbiota diversity within human populations followed a bimodal distribution with higher (HGC) and lower (LGC) diversity peaks. The LGC individuals on average showed a higher incidence of metabolic syndrome. The microbiota diversity of obese LGC (but not HGC) individuals could however be increased through dietary management, suggesting that the habitual diet may have been responsible for the LGC state [17]. Interestingly, in the study of Walker *et al.* [11] diversity was significantly lower on the RS-enriched diet than on the NSP (wheat bran-enriched) diet, indicating that the complexity and variety of non-digestible carbohydrate substrates may have a real impact on community diversity. The LGC microbiota tended to be dominated by *Bacteroides*, and may correspond to one of the three 'enterotypes' previously proposed by the same researchers [18]. Interestingly, Wu *et al.* [19] reported that they could subdivide US volunteers into two 'enterotypes': those with *Prevotella*-dominant microbial communities had higher habitual plant fibre intake and those with *Bacteroides*-dominant communities had higher protein and fat intake, indicating that alternative states of the intestinal microbiota may be driven by long-term dietary habits.

Microbial ecology

Changes in microbial community composition can occur in response to changes in growth requirements (sources of energy, nitrogen, micronutrients) or growth-inhibitory factors (*e.g.*, pH, toxic metabolites, bacteriophage-mediated lysis). Iron availability has been shown to modulate butyrate-producing bacteria [20] as well as pathogenic proteobacteria [21] while there also is likely to be competition for and exchange of vitamins between different groups of gut bacteria [22]. Two classes of molecule that are likely to play roles in selective inhibition of bacterial groups are phytochemicals [23,24] and dietary fats. The 'animal based' diet of David *et al.* [13] which consisted of almost 70% of calories from fat and 30% from protein resulted in enrichment of *Bacteroides*, *Alistipes* and *Bilophila* spp. in the faecal microbiota of human volunteers, with selective inhibition of other groups by increased bile acid [25] proposed as a possible mechanism. On the other hand the absence of fibre in this diet was assumed to contribute to the decrease in many Firmicutes by comparison with the 'plant-based' diet [13]. The availability of carbohydrates as the main energy sources for microbial growth offers opportunities for beneficial manipulation of the microbiota and is considered further below.

Bacterial utilization of ND carbohydrates

The spectacular increase in genome sequence information for cultured representatives of the gut microbiota should be of great help in predicting the responses of gut bacteria to dietary factors, especially changes in the intake of different non-digestible carbohydrates. While this information is proving helpful, there are also limitations to what can be inferred. Detailed knowledge of microbial CAZyme (carbohydrate active enzyme) families allows for profiling of representative bacteria and prediction of their likely substrate-degrading abilities [26–28] and understanding has been advanced by the identification of polysaccharide utilization loci in the Bacteroidetes [29] and in the Lachnospiraceae family of Firmicutes [30]. Nevertheless, the wide functional diversity within CAZyme families means that function still cannot be predicted with any great confidence from sequence data alone, while degradation of a given polymer may not be accompanied by the ability to take up and utilize the products [30]. This makes it essential to confirm substrate utilization patterns for individual strains experimentally, but data on isolated strains still cannot predict the competitive ability of a given species within the complex community. Competition within the community has been addressed recently using a continuous flow fermentor community derived from a faecal inoculum that is supplied with single ND carbohydrates. Chung *et al.* [31•] found that among the Bacteroidetes in three different microbial communities, inulin selected for the species *B. uniformis* or *B. caccae*, depending on the faecal donor, whereas apple pectin selected for six different *Bacteroides* species. While broadly consistent with the CAZyme profiles of each species, this outcome would have been difficult to predict *a priori*. Another significant point to emerge is that environmental conditions can alter competition for the same substrate. Thus, controlling the pH at 5.5 tended to limit *Bacteroides* growth, allowing Gram-positive bacteria to compete more successfully [31•,32]. Dietary fibre intake increases fermentation and short chain fatty acid production and also influences gut transit, with consequences for absorption and gut pH [33,34] (Figure 1). Interestingly, a recent survey reported that stool consistency, which is likely to be related to gut transit, was the variable most reliably correlated with inter-individual differences in faecal microbiota composition [35•].

Much non-digestible dietary fibre arrives in the large intestine in the form of insoluble complex particles (plant fragments, starch particles) rather than as soluble carbohydrate. Degradation of such material is likely to involve specialist groups of bacteria that have the ability to adhere to the substrate [36] and that are equipped with sophisticated enzyme systems that can attack such recalcitrant material. Examples are *Ruminococcus bromii*, a bacterium able to degrade raw starch particles [37,38•], and *R. champanellensis*, the only human gut bacterium so far show to degrade crystalline cellulose [39], which produce extracellular amylosome and cellulosome complexes