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The influence of diet on the gut microbiota and its consequences for health

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Man is an intimate symbiosis between 10 trillion human cells and some 100 trillion bacteria, most of which inhabit the intestine where they constitute an extremely dense and diverse microbiota. This symbiotic balance that has to be established within each newborn is key to the maintenance of health and well being. Its development is markedly influenced by microbial exposure encountered very early in life. Mode of infant feeding, and the post-weaning transition to habitual diet will further shape the microbiota. Recent studies support the concept that diet should be viewed as a means to prevent potentially durable alterations of symbiosis observed in immune-mediated metabolic and inflammatory diseases. Non-digestible dietary fiber will play a major role in this context.

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The human intestinal microbiota in a metagenomic perspective

Considering the well recognized inability to culture a major fraction of the dominant human fecal microbiota, molecular techniques were developed for a culture-independent assessment. This promoted comparative sequencing of 16S rDNA amplicons and more recently sequencing of the combined genomes of all dominant microbes within a given ecosystem, that is, the metagenome [1,2]. The first extensive gene catalog encompassed 3.3 million non-redundant genes from a cohort of 124 European individuals [3]. The cohort explored by metagenomic profiling has since been expanded to 1267 individuals, including American subjects from the Human Microbiome Project as well as Chinese individuals. The catalog of non-redundant human gut microbiome genes was concomitantly expanded to 10 million [4]. Interestingly, the discovery of new genes in the process did not concern genes of the core microbiome (genes shared by >50% of the studied cohort), which remained as a robust entity, but rather consisted of rare genes that are found in a limited fraction of the population.

Aside from the inventory of individual genes, the binning of genes into genomic entities was achieved based on the principle that genes from the same genome would display co-abundance in every microbiome even if their relative abundance could vary between individual metagenomes. This procedure enabled the definition of 741 large metagenomic units (>700 genes), corresponding to bacterial core-genomes of predominantly unknown species (~85%) and 257 near-complete, high quality bacterial genomes. In addition, 6640 smaller metagenomic units were identified representing phages, plasmids, CRISPRs [5•].

Assuming that this data would allow to ultimately highlight the features of the 'average human intestinal microbiota', the bacterial genera distribution of human microbiomes within the landscape of all possible ecological arrangements was explored. Remarkably, instead of an even distribution around an average microbiome, the human population separated into three ecological arrangements of the intestinal microbiota, that were called enterotypes [6]. A single bacterial genus dominated two of them (*Bacteroides* or *Prevotella*) while a fairly limited set of genera (*Ruminococcus*, *Subdoligranulum*, *Methanobrevibacter*) were marker genera for the third. Although the concept of enterotypes has been highly debated among biostatisticians, its main consequences should nonetheless be evaluated from an ecological standpoint, leaving many open questions such as first, when do these ecological arrangements develop in life, second, how stable are they for a given individual, third, do they stratify phenotypes such as disease risk or response/non-response to diet or therapeutics.

Total gut bacterial gene count of the dominant microbiome has emerged as a key stratification parameter of the human population. The range of variation between humans in terms of gene richness of the microbiota is very large, spanning from 200,000 to over 800,000 genes for a given dominant microbiome. Gene richness distribution did not only separate high gene count from low gene count individuals, but also linked with ecological arrangements, *Bacteroides*-dominated ecologies being over-represented among low gene count microbiomes [7••,8••]. One would clearly anticipate a correlation between gene richness and ecosystem metabolite profiles,

for example, low gene counts could associate with higher propionate levels from Bacteroidetes and high gene counts could associate with increased butyrate levels from Firmicutes.

Does diet and life-style impact human intestinal microbiota development?

Sterile *in utero*, the intestine of the newborn is colonized starting immediately during birth. Microbial density establishes very rapidly in the gut of the newborn, reaching adult concentrations within a few days. Subsequent microbiota development is typically characterized by an overall diversification until approximately three years of age [9], including a succession of relays in dominance of various groups of bacteria. It is suspected that colonization-resistance builds up as a function of the normal commensal microbiota, and may rapidly drive stabilization and preclusion of further colonization by exogenous bacteria. This concept supports a unique and essential role of the initial inoculum and microbial exposure encountered very early in life. Microbiota development may thereby be markedly affected by numerous features including mode of delivery (vaginal versus cesarean), maternal microbiomes, hygiene of the neonatal environment, use of antibiotic, infant feeding regimes (breast milk versus formula), and the weaning diet. Cesarean delivery is accompanied by a reduced exposure to maternal microbes, and colonization appears to be durably affected with perturbations visible at six months [10] and up to seven years of age [11]. In terms of epidemiology, C-section birth is associated with increased susceptibility to infectious disorders and enhanced risk of developing allergic disorders [12]. Therefore, it is a serious concern that in some countries the recourse to cesarean section delivery reaches rates that go far beyond strict medical justification.

On the basis of the hygiene hypothesis, a reduced microbiota diversity is one of the major feature of a defective colonization pattern. Comparing microbiota diversity in terms of number of detectable OTUs (operational taxonomic units, defined by 16S rDNA sequence comparisons), through the lifespan in populations of various geographical origin, revealed a higher microbiome diversity in Amerindians and Malawians compared to north-Americans [9]. Important factors could include hygiene during birth and frequent use of antibiotics, but also nutritional transition that may have influenced vertical transfer of microbiota from mother to child in north-American populations already for several generations. The subdominant microbiota may still encompass major functional groups that could be re-established with proper microbiota modulation, although the observed loss of diversity may also represent true disappearance of bacterial species with little perspective for easy restoration. This concept was coined as the 'loss of old friends' hypothesis by Graham Rook [13] and 'missing microbes' by Martin Blaser [14].

Several recent studies have reported on the impact of diet on the microbiota structure. The comparison of children from rural Burkina Faso in Africa and Italy in Europe highlighted extremely marked differences that could be attributed primarily to differences in dietary habits [15]. Associated with a diet rich in plant-derived fiber, African children had a microbiota significantly richer in *Prevotella* and *Xylanibacter* and concomitantly depleted in Firmicutes compared to the European children. Their intestinal ecosystem was also characterized by significantly more Short-Chain Fatty Acids (SCFAs) and less enterobacteriaceae [15].

Studying adult fecal microbiota in a north American cohort, Wu and colleagues reported that enterotypes were associated to long term dietary habits [16]. A diet rich in animal proteins and fat, typical of food intake in western societies that underwent a nutritional transition during the past 60 years or so, will favor the *Bacteroides* enterotype. Conversely, the *Prevotella* enterotype would be most prevalent in people on high fiber diets, rich in fruits and vegetables.

In a study comparing city-dwelling African-Americans and rural native Africans, known to markedly differ in their relative risk of colorectal cancer from which native Africans appear protected, Ou and colleagues brought the link with *Bacteroides*-dominated versus *Prevotella*-dominated ecologies even further [17]. The *Prevotella* ecologies were most prevalent among native Africans and coincided with higher SCFAs, while *Bacteroides* ecologies dominated the intestinal ecology among African-Americans coinciding with higher secondary bile acids.

Schnorr and colleagues explored the microbiota characteristics of a hunter–gatherer community, the Hadza of Tanzania [18]. In terms of dietary habits, this community may be regarded as closely related to our ancestors in the genus *Homo*. Even compared to other rural African cohorts, the microbiota of the Hadza was more diverse, and characterised by enrichment of *Prevotella*, *Treponema* and unclassified Bacteroidetes, as well as a specific set of Clostridiales, and absence of bifidobacteria. Interestingly, as much as 22% of the Hadza microbiota belonged to taxa that remained unassigned at the family or genus level, suggesting the presence of a so far unrecognized diversity. Specific microbiota features were proposed to reflect a tight adaptation of the Hadza intestinal ecosystem to the Hadza's high fiber diet.

Finally, association studies of microbiota, dietary patterns, and health markers in French overweight and obese adults revealed that a healthier dietary pattern was associated with higher microbiota diversity, as well as reduced

levels of cholesterol, inflammation markers, and insulin resistance [19]. These studies clearly illustrate that dietary habits can markedly influence microbiota characteristics, which in turn may drive important modulations of host physiology.

Can diet be used to modulate the human intestinal microbiota?

It is often stated that the microbiome might be modulated. Nutrition and especially non-digestible carbohydrates might in this context be definite assets [20]. Thereby, preventive nutritional measures will provide an attractive option whenever a link is established between microbiota (structure or function) and a reduction of risk for the development of a given disorder, or potentially as a therapy for an established disease condition.

We will herein restrict our discussion to low diversity, that is, reduced species richness of the dominant intestinal microbiota, which has been associated with several immune-disorders and/or metabolic-disorders such as inflammatory bowel diseases, allergies, intestinal cancers and various autoimmune diseases [1,2]. In several of these conditions, low dominant species diversity (reduced microbiome gene richness) has been associated with low grade inflammation. For example, obesity was associated with reduced gene richness and most prominently altered host-phenotypes, including higher inflammatory tone, adiposity, and insulin resistance [7]. In addition, in obese and overweight subjects, microbiome richness was predictive of a reduced response to low-calory diet interventions in terms of weight loss and improvement of metabolism and inflammatory traits [8]. Notably, low gene richness has also been associated with under-representation of *Faecalibacterium prausnitzii*, which exerts anti-inflammatory properties [21–23], and interestingly, the abundance of this species could be promoted by consumption of inulin-type fructans [24].

Comparative microbiota assessments in case–control studies can only reveal associations, and cannot directly underpin a potential causal contribution of the observed microbiota dysbiosis. Nevertheless, reduced species richness marks a true distortion in gut ecology, which in most instances comes with an increased load of Gram-negative bacteria, that often include pro-inflammatory enterobacteria, which have been termed 'pathobionts' [25], and a reduced proportion of oxygen-sensitive, butyrate-producing Gram-positive firmicutes that have recognized anti-inflammatory properties. The end-result is a situation favoring the maintenance of an inflammatory context via an auto-aggravating feed-back loop (vicious circle). Hence, rather than a simple microbiota centered phenomenon, dysbiosis must be viewed as an alteration of symbiosis, which drives a detrimental distortion of microbe–host homeostasis. This concept is supported in a multivariate study of ulcerative colitis patients compared to healthy controls, where lower microbiota diversity associated with dramatically reduced correlations between changes in microbial taxa and mucosal gene expression profiles of intestinal biopsies [26]. Notably, comparable observations were reported for correlated changes in gut microbial taxa and modulation of gene expression in adipose tissue of morbid obese patients that underwent gastric-bypass surgery [23].

Bacteria degrading plant-borne fiber play a unique ecological role by providing the rest of the microbial food chain with a plethora of simple oligomers that serve as energy source for a variety of fermentative microorganisms [27•]. It is hence conceivable that diets with low fiber diversity can induce an impoverishment of the corresponding hydrolytic microorganisms and thereby modulate the overall dominant microbiota. Conversely, diets rich in a diversity of plant fibers could promote the diversification of the overall microbiota by promoting diverse dominant hydrolytic bacteria. This concept is strongly supported by the various diet studies mentioned above [9,15,28].

Counter-intuitively, this would lead to a recommendation for IBD patients or obese individuals to increase their intake of plant-derived complex fibers. A possible mechanistic link between plant fibers and reduced inflammatory tone may be provided by butyrate, which is produced by bacterial bioconversion of dietary fibers [29], although recent observations suggest that this concept may be too simplistic. Cotillard and colleagues showed that a low-calory diet encompassing a diversity of fibers could elicit a 25% increase in microbiome gene richness, only in obese and overweight subjects that were characterized by low gene richness prior to the intervention [8]. Analogously, Salonen and colleagues proposed that diversity is inversely associated with the 'dietary responsiveness' of a given microbiota [30]. Long-term dietary habits and its impact on intestinal ecology may also complicate the predictability of the individual microbiome responses to dietary intervention. Recent observations suggest that metagenome profiles can be used to stratify patients in responder and non-responder populations for various treatments, including dietary interventions. This would indicate that nutrition, and especially plant fibers, may be used to manage the ecology of the intestinal microbiota, but that the intensity and durability of such modulation may depend strongly on the baseline microbial ecology. Consequently, an emerging paradigm exemplifies the strong individuality of responses to nutritional modulation and its dependence on the initial (i.e., baseline) microbiota composition [31••]. This concept has not been considered to date in studies that explored the health benefits of bioactive food constituents, including functional foods such as prebiotics or probiotics.

Prebiotics may be employed as modulators of the diversity of the autochtonous microbiota. However, current

prebiotic approaches are likely limited by the consistent supplementation with relatively low-complexity molecular structures, which are likely to promote only a limited set of specialist microorganisms. In contrast, the potentially more beneficial impact of a broad diversity of soluble and insoluble fiber constituents remains to be determined. Nonetheless, prebiotics have been successfully used in the modulation of low grade inflammation in obesity [24,32••]. Although their application is not aimed at promoting overall microbiota diversity, probiotic supplementation could also be used for microbiota modulation. Nevertheless, a probiotic intervention during the first six months of life using a mixture of a *Bifidobacterium*, a *Propionibacterium*, and two *Lactobacillus* strains, has been reported to significantly reduce the risk for IgE-mediated allergy development, only in cesarean-section delivered children [33]. Again, in this latter example, the duration and intensity of individual responses to probiotic intervention may very well have depended on the initial microbiota composition.

In the case of durably deteriorated ecological settings, moderate dietary interventions may fail to elicit any microbiota modulation. Indeed an aberrant microbiota may reflect an alternative stable state, including an intrinsic resistance to change and resilience. In such cases, an extensive restructuring of the ecological context might be the only option. Fecal microbiota transplantation (FMT) can provide such drastic microbiota restructuring and has been shown to enable the functional reset of the ecosystem. It has been sporadically applied for the past 50 years in the context of *Clostridium difficile* infection with a fair success-rate, but a recent systematic trial established its potency in curing patients suffering from this disease [34,35]. There is little debate on the ability of FMT to allow a functional reset of the microbiota, but the durability of its impacts on both microbiota and host physiology has yet to be thoroughly determined, and may depend strongly on the patient population targeted and the corresponding dysbiosis state [36].

Conclusions

Early life events will be critical for the dynamics of microbiota development towards the adult microbiota, and has substantial potential impacts on risk of infectious and immunity associated disorders. Lifestyle and diet will further influence the structure and function of the human intestinal microbiota, with implications for maintenance of host health and well-being. Low microbiome gene richness (low bacterial diversity) consistently appears as a risk factor associated with detrimental effects on healthy host–microbe symbiosis, and is characteristic for numerous chronic diseases. Importantly, high diversity-fiber diets appear to promote microbiota diversity, favoring over-representation of bacterial taxa equipped to metabolize plant polymers and supporting increased luminal SCFAs production, at the expense of pro-inflammatory Gram-negative bacteria. Functional foods (prebiotics and probiotics) also appear to have potential in the modulation of inflammatory tone and gut barrier function. Importantly, future dietary interventions can benefit from the incorporation of important ecological paradigms such as the promotion of gut microbiota diversity, colonization-resistance, resilience and stability. In this context, it is of great importance to realize that response to dietary modulation may be highly dependent on the baseline microbiota composition, stressing the need for personalization.

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