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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