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Review Article

Gut Microbiota – Our Microbial Self

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Abstract

The gut microbiota (microbial symbionts) and microbiome (their genes, and consequently the corresponding expressed products) are part of us, interfering with our immunity, our capacity to metabolize certain molecules, influencing how we gain body weight and even our mood. The number of microbial cells and metabolites largely exceeds those of human body. Despite individual changes, only two enterotypes prevail worldwide: *Bacteroides* and *Prevotella*. The most relevant microbial groups and their features are herein reviewed. The prevailing gut population, of an individual, is defined early in life and constitute a signature for that individual, although evolving along his life. Factors influencing the type of microbes that successfully colonize the gut include birth mode, host genotype, biogeographical location, diet, drug regimen, and the nutritional and health status of the individual. Gut microbiota reaches an equilibrium in adulthood, resisting to changes to some extent. Despite that steady-state, gut microbiota shows dynamic changes mainly correlated with aging process, alterations in the diet and antibiotics treatment. Obesity, diabetes, and associated disorders are closely linked to gut's health, as happens with certain types of cancer. From the initial strategy on "how to control infection by killing deleterious microbes in our body" we are evolving to a new one on "how to control wellness by favouring beneficial microbes in our body". Questions related to the underlying mechanisms of host-microbe interaction, and to the specific host characteristics that are affected by microbiota, will provide information on to what extent and how far can we intervene.

Keywords: Enterotypes; Diet; Gut; Non-communicable diseases; Host-microbe interactions

A Brief Historical Background

The concept of life entities that cannot be seen by naked human eye dates from the XVII century, thanks to the invention of the microscope by Zaccharias Jansen, and the pioneer work on microscopy by Anton van Leeuwenhoek, which provided accurate descriptions of fungi, bacteria and protozoa, by that time. This microbiologist was the first to describe a gut microbe, which is nowadays thought to be a *Giardia* spp, an intestinal parasite.

Microbiology entered a golden age, during XIX century, with the remarkable works of Louis Pasteur (who buried spontaneous generation theory, and called the attention to the importance of microbes in our daily life) and Koch (who established a set of principles to relate a specific microbe to a disease), among others.

By contacting with the external environment, human body gets very populated by microbes, in particular the gastrointestinal tract (GI). The number of microbial cells in the human body is thought to be about 10 times higher than the number of somatic cells, with GI accounting for about 2 Kg of bacteria, of thousands of different species.

In the early XX century, two microbiologists, Alexander Flemming and Élie Metchnikoff, studied the effect of microbes, and particularly their metabolites, in human health. Flemming, discovered penicillin and performed the first toxicity studies with it, while Metchnikoff became interested on the relations of microbes with our immune system.

During most of the XX century, microbiology was tightly related to medical sciences and microbes were most often related to disease. It is noteworthy that the first intestinal bacteria to be cultivated was *Escherichia coli*, of which some serotypes may cause food poisoning.

Flemming's discovery became famous for their application in the industrial production of antibiotics, after World War II. Thus, the trend of maintaining health by killing pathogens (and many other bacteria) overwhelmed the discoveries of Metchnikoff, of promoting health by means of beneficial bacteria (probiotics).

That paradigm seems to be changing. The central question nowadays is why people, in modern society, who have much less contact with infectious agents, are so prone to inflammatory conditions and allergic diseases. The current view of the GI microbiota composition is quite different than it was prior to the use of molecular biology techniques. Current gut microbiome studies, based on high-volume DNA sequencing and metabolomics, are inherently interdisciplinary, involving biomedical sciences, ecology, and computational biology. However, the inability to

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Table 1: The Evolution of Microbial Gut Microbiota along Life and Main Influencing Factors

	Period of life	Changes/Influencing factors	Relevant genera / species
Newborn (0-9 months)		Mother´s body weight and food habits; birth delivery mode (natural vs caesarean section); feed mode (breastfeeding vs infant formula)	Bacteria from the mother and surroundings are among the first gut colonizers. Breast milk and environment account for enrichment in the genera *Bifidobacterium, Weissella, Lactococcus, Leuconostoc, Enterococcus, Bacteroides, Enterobacter, Ruminococcus, Clostridium*(*)
Toddler (9-18 months)		Environment, food habits	Gut microbial load and variety increase; gen. *Veillonella, Leptotrichia* and *Prevotella* become prevalent
Child (3-16 y)		Food habits are critical, environment is important	Enterotype consolidates; the *Firmicutes* to *Bacteroidetes*' rate increases along child's growth
Adult < 50-60 y		**Prevotella enterotype**: very stable gut microbial population, fine-tuned to adapt to each individual; not easily disturbed nor passible of adjustments trough diet changes **Bacteroides enterotype:**steady gut microbial population, fine-tuned to adapt to each individual; returns to the equilibrium state upon disturbances; passible of transient adjustments through dietary interventions	**Prevotella enterotype**: genera above (*) are present, in addition to the dominance of gen. *Prevotella*, *Bifidobacterium* and members of *Clostridium* clusters IV, XIV, XVIII, including *Faecalibacterium prausnitzii sp.* **Bacteroides enterotype**: genera above (*) are present, in addition to the dominance of *Bacteroides* spp., lactic acid bacteria,*Enterobacteriaceae* and *Faecalibacteriumprausnitzii* sp.
Elderly > 60-70 y		Microbial population changes and gut health may become frail or reach another equilibrium state, as found in centenarians	*Bacteroides* spp. increases as does *Enterobacteriacea*, (particularly *Escherichia coli*); populations of *Bifidobacterium* spp. decrease, as does previous members of clostridia clusters; In centenarians an increase in populations of strict anaerobes is observed, as well as the presence of significant loads of *Eubacterium limosum*

Despite individual variances, gut microbiota globally share common features. The more prevalent microbial groups belong to Phyla *Firmicutes* and *Bacteroidetes*, which ratio evolves from 0.4 in children to 10.9 in adults and goes back again to 0.4 in the elderly. The formation of gut microbiota in the new-born mainly depends on maternal and environmental factors. The consolidation of a healthy gut microbiota is impacted by food habits and environment, during childhood. Gut microbiota attains a stable steady-state in adulthood. Adults (independently of gender, health status, nationality etc.) mostly belong to one of the enterotypes "*Bacteroides*" or "*Prevotella*", according to the dominance of each of these genera. Transient changes in the gut's ecology are more probable in the *Bacteroides*' enterotype and may be positive (when conveyed by the intake of vegetables, complex starches or probiotics) or negative (if caused by the intake of antibiotics, highly processed foods, excess of simple sugars and meat). During ageing, gut microbiota evolves, generally negatively. Conversely, the gut's populations of centenarians seem to share a common pattern.

cultivate every detected microorganism is an obstacle that may impair conclusions.

Results from the first phase Human Microbiome Project [1] and other studies showed that gut's beneficial bacteria are part of a complex microbial ecosystem, which is closely linked to our immune function. International consortia continue to invest vast efforts and money on this topic and new insights on gut's microbiota structure and function have been disclosed and more are still expected. A key goal of such studies is to integrate growing knowledge of human-microbial interactions in the treatment and prevention of chronic and infectious diseases.

Gut Microbiota and Microbiome

The intestinal microbiota is the combination of the microbial communities of symbionts (commensals and mutualists) that colonize the human gastrointestinal tract. Its collective genomes are known as microbiome. Recent discoveries have revealed the importance of the two-way interaction between bacteria and their host. These interactions influence the host's integrity of intestinal epithelium and immune system, host and bacterial gene regulation, and many other functions.

While our knowledge of infectious diseases and the corresponding causative agents is well established, the roles of complex microbiota communities in sustaining health or promoting disease, only recently have been studied in depth.

It is known, that not every bacteria is able to survive in the niche of intestinal mucus' layer. Nevertheless, those possessing that ability may be either deleterious to the intestinal barrier (as some enteropathogens), or cope with the host, as do microbiota. GI microbiota is adapted to such habitat through the production of specific signaling molecules (mainly short-chain fatty acids, SCFA), enzymes that degrade the mucus, along with the capacity to stimulate mucin's synthesis.

Mucus contributes with nutrients that sustain the microbiota, and the microbiota favors the host by breaking down some nutrients (as resistant starch and polyphenols), by synthetizing certain vitamins and aminoacids, many health-beneficial compounds, and not forgetting its role in antagonizing or competing with enteropathogens [2]. It is hypothesized that the vast majority of those activities is mediated by diet, particularly at early ages, and that changes in microbiota impacts host's metabolism, immunity, and even mood. When this host-microbial partnership is compromised, the risk to develop a disease drastically increases.

Given its relevance, gut microbiota has been recently recognized as an additional human organ, composed of several trillions of symbiotic bacteria, carrying a genome that is 100 to 400 times larger than the human genome. As a result, more than four million bacterial gene products may interact with our organism, thus impacting our health condition [3].

The distribution of the microbiota along the GI tract is not uniform: inhabitants of stomach are scarce (due to the pH barrier of hydrochloric acid), and the number of microbes increases gradually in the small intestine reaching very high concentrations in the colon [2].

Until the late sixties of the 20th century, *Bifidobacterium* spp. and *Bacteroides* spp. were considered the dominant groups in the human gastrointestinal tract (GI) of healthy adults. Aerobes, referred to as coliforms, streptococci and lactobacilli, were considered minor groups. Clostridia, staphylococci and aerobic spore-formers were reported as rare [4]. This has recently been found to be not true, since clostridia and Archaea appear to be more representative than previously thought, although the role of these strictly anaerobic bacteria in human GI is still poorly known [5].

It is now recognized that gut microbiota is diverse, containing more than a 1000 identified species belonging to *Bacteria* (957), *Eucarya* (92) and *Archaea* (8) co-existing in a homeostatic state. The more common phyla are *Firmicutes* and *Bacteroidetes* [5]. The prevalent species of gut microbiota may be influenced by many factors including environment and geography [6], food habits [7,8], medication regimens, probiotics [2,9], and host-related factors such as genome [2,9,11].

The formation of human GI microbiota starts in the lactation period. Milk, the secretion of the mammary gland, is the primary food source for mammals before they are able to digest other types of food. Early-lactation milk (colostrum) contains mother's antibodies that contribute to decrease the risk of diseases and helps the new-born build up his/her gut microbiota, besides its short-term positive impact on child's immunity [3,10]. Rubio et al. [10] found that maternal factors can influence the composition of breast milk and consequently the child's microbiota. According to those authors, bacteria found in breast milk are not environmental contaminants, besides changing along the lactation and in response to maternal factors. The same authors observed that milk from obese mothers tends to contain a different and less diverse bacterial community when compared with milk from normal weight mothers. Moreover, the type of birth delivery seems to influence milk composition in bacteria, beyond the environmental contamination [10,11].

Generally, the composition of human´s breast milk is dominated by bacilli (>75%), although evolving along lactation, as referred above. Breast milk contains oligosaccharides that support the growth of both, members of *Bacteroidetes* and *Bifidobacterium* spp [3,10] thus strongly contributing to the building of an healthy microbial gut community.

The species that colonize the gut, right after infant delivery (originated from various sources), belong to the gen. *Bifidobacterium*, *Clostridium*, *Ruminococcus*, *Enterococcus*, *Enterobacter* and *Bacteroides* [3,7]. On the other hand, the most common genera found in colostrum are *Weisella* and *Leuconostoc* (both lactic acid bacteria) followed by *Staphylococcus*, *Streptococcus*, and *Lactococcus* [2]. *Bifidobacterium* is more abundant with lean mothers and is highly prevalent during life [3,5,11]. Later in

lactation, the proportion of other bacteria increases.

The adult's GI microbiota is a diversified, complex and quite steady community, including many non-cultivable microbes which functions are yet to be discovered [5,9]. Although GI microbiota is host-specific, there are broad similarities allowing grouping microbiota mainly in two enterotypes: *Prevotella* and *Bacteroides*, the second one more common in western societies, and more susceptible to changes (either positive or negative) as explained bellow. Normally the adult's microbiota reaches a relatively stable equilibrium state, and resists to changes to a certain extent. However, if the perturbations overwhelm its capacity to resist, shifts in microbial populations will occur and may result in a range of diseases [9]. In this regard, *Prevotella* enterotype seems more enduring but also generally associated with good health [1,3,8].

Aging is characterized by a deterioration of energy homeostasis with a loss of muscle mass, among other changes. The human gut microbiota also undergoes substantial alterations, as does the functionality of the host's immune system, resulting in a greater susceptibility to infections. The core microbiota of elderly subjects is distinct from that previously established for young adults. With elderly subjects, a greater proportion of *Bacteroides* spp and a distinct abundance pattern of other groups is observed. Thus, an increase in the proportion of *Escherichia coli* and other *Enterobacteriaceae* [3,5] is generally registered, as well as a decrease of anti-inflammatory symbionts, namely *Bifidobacterium* spp. and *Faecalibacterium prauznitzii* as as well as other members of clostridia clusters [4,8]. Gastrointestinal microbiota of the elderly is generally characterized by decreased butyrate production capacity (see below), reflecting an increased risk of degenerative diseases [5,8].

As detailed below, clostridia clusters contain major degraders of resistant starch contributing to the wellbeing of the host. Since this beneficial bacterial group is significantly depleted in elderly

Increase in milk, particularly those from gen. *Veillonella*, *Leptotrichia*, and *Prevotella* [10], diversifying the gastro-intestinal (GI) microbial populations. Despite some fluctuations, particularly in the two first years, the load and diversity of gut microbiota increases until adult age [8].There is an interaction between the host genetics and the specific profile of symbiont microbiota that colonizes his gut [8,9,11], namely contributed by host's innate immunity and obesity-related genes. Genetic factors interplay with the above-mentioned external factors (as the lactation mode and the use of antibiotics early in life) in selecting a customized GI community. Infancy is a critical period for intestinal colonization. An inadequate gut microbiota composition early in life seems to account for the deviant programming of later immunity and overall health status [3,11-13].

Gut microbiota changes along life. In infancy, the rate of *Firmicutes* to *Bacteroidetes* is around 0.4, evolving to 10.9 during adulthood and decreasing to 0.3-0.4 in the elderly [8].

Gastrointestinal microbiota of the elderly is generally characterized by decreased butyrate production capacity (see below), reflecting an increased risk of degenerative diseases [5,8].

As detailed below, clostridia clusters contain major degraders of resistant starch contributing to the wellbeing of the host. Since this beneficial bacterial group is significantly depleted in elderly subjects, it seems to be counterbalanced by an increased proportion of facultative anaerobes, including many non-cultivable bacteria, which probably perform some of the tasks normally carried out by the depleted groups. Much is still to be disclosed, since the microbiota of centenarians is apparently distinct for those of young adults and from ages in between, maybe constituting a signature of long life. One of those representatives appears to be *Eubacterium limosum* (and related species) which numbers are more than 10 fold increased in centenarians [8,9]. *Eubacterium* spp. have been reported to transform dietary phytoestrogens into forms that might have a positive impact on health [5]. Moreover, little is known about the role of gut anaerobes, beyond their detoxifying properties, as some are able to convert end-products of other microbial groups contributing to the elimination of gases.

Most Relevant Gut Microbial Groups and their Main Features

Despite the enterotype, the two most prevalent and relevant phyla of GI microbiota are *Bacteroidetes* and *Firmicutes* [3,5,6,9,11,12].

The Gram-negative bacteria that belong to the phylum *Bacteroidetes constitute* a diverse microbial group within the human gastrointestinal tract [5,12].Of particular relevance and highly prevalent are some *Bacteroides* spp. and *Prevotella* spp. These bacteria (particularly *Prevotella* spp.) are able to degrade complex polysaccharides from plants, including non-digestible starch, cellulose and pectins. Moreover, some *Bacteroides* spp. may use urea as nitrogen source [5,10].

Members of *Firmicutes* may account for 50-80% of GI microbiota in healthy adults, and belong to four classes: *Clostridia*, *Erypsipelotrichi* and *Negativicutes*. This group includes the low GC content, gram-positive bacteria of the genus *Lactobacillus*, *Enterococcus* and *Streptococcus*, as well as spore-formers as *Clostridium* spp., *Bacillus* spp. and related species. This later property confers special survival skills in and out GI [5]. While the class *Bacilli* includes many health-promoting and probiotic strains, the second cluster (of spore-formers) is normally associated to disease and includes pathogens as *Clostridium difficile*. However, members of the *Clostridium* clusters, namely IV, XIVa and XVIII, have been found to be remarkably important to gut's health by promoting the integrity of the intestinal barrier and by keeping a balanced immune system [5]. These populations are thought to ensure a healthy flow of mucus by stimulating the secretion of certain compounds that, in its turn favor certain bacterial groups and thus shaping the greater gut ecosystem. Conversely, defects in the mucous layer are associated to the depletion of these bacterial groups (from clostridia clusters)

and the rise of aberrant communities of microbes that generally cause disease [9,12,13].

Lactobacillus spp. are important members of *Firmicutes* and the regular intake of probiotic strains of *Lactobacillus* spp. have a beneficial effect on human health causing specific induction of gene expression, besides the direct action of their metabolites, mostly in individuals of *Bacteroides* enterotype [2,5,11,14]. Recent studies show that members of the related genera *Leuconostoc* and *Weissella* are widely distributed in colonic mucosa and may represent up to 24% of total microbial community [5]. It is noteworthy that some previously misclassified *Lactobacillus* spp. integrate now other genera as *Weissella* and *Atopobium*. Other relevant GI bacteria from Lactocabillales order are *Streptococcus* spp. and *Enterococcus* spp. [5,15,16]. Both genera are among the first established species in the infant GI tract. Data on the role of *Streptococcus* spp. and *Enterococcus* spp. on human health are conflicting because both genera encompass opportunistic pathogens and probiotic strains (as detailed below). Members of the Bacillales order, typically *Staphylococcus* spp. may also be found among early GI colonizers (particularly in babies delivered by caesarean section and/or bottle-fed). However, they are invariably associated to several health risks, as the development of asthma and rhinitis. Furthermore, the presence of *Staphylococcus* ssp. in the GI tract of premature infants may result in fatal sepsis [4].

Still within *Firmicutes* is the class *Negativicutes* of asaccharolytic bacteria, capable of using end-products of sugar metabolism of other GI bacteria. Among the bacterial metabolites of *Negativicutes* is propionate, which is included in the group of microbiota's short chain fatty acids (SCFA), which are beneficial metabolites with key roles in microbial-host interactions. Propionate is used by adipose tissue and by the liver, playing an important role in the satiety sensation, influencing energy homeostasis and showing anti-inflammatory potential [5].

Besides members of *Firmicutes* and *Bacteroidetes*, other GI colonizers although not dominant may perform keys functions in the gut. As referred before, *Bifidobacterium* spp. is a prevalent fraction of the human gastrointestinal microbiota, particularly in infants [5,10,17]. These bacteria are associated to host wellness and many strains are commercialized as probiotics. Some strains of *Bifidobacterium* spp. are able to ferment complex carbohydrates such as starch, arabinogalactan, arabic gum, and gastric mucin [5,9]. Their survival is stimulated by the presence of non-digestible oligosaccharides, also known as prebiotics [2]. Diets containing meat and dairy are claimed to support the growth of *Bifidobacterium* spp. [9,18].

The recently introduced phylum *Tenericutes*, and phylum Fusobacteria include many bacteria that are associated to inflammatory bowel disease (IBD). These groups seem to be implicated, not only in intestinal inflammation but also in ulcerative colitis and colorectal cancer (e.g. *Fusobacterium* spp.) [5].

On the other hand, *Enterobacteriaceae* constitute the most abundant and prevalent group within the phylum *Proteobacteria*. Strains of *Escherichia coli*, the first intestinal isolated bacterium, vary from commensal or probiotic strains to pathogens often associated with food poisoning and diarrhoea. The abundance of *E. coli* increases with age but remains subdominant in elderly healthy subjects. Still within the phylum *Proteobacteria*, *Oxalobacter formigenes* and *Ancylobacter polymorphus* are unique intestinal bacteria that only use oxaloacetate, as carbon source, regulating oxaloacetate concentrations in faeces and urine, and indirectly preventing the formation of kidney stones [5]. Another relevant species is *Akkermansia muciniphila* from the candidate phylum TM7, which abundance is inversely correlated with obesity [5,19,20].

Coriobacteriales species are frequently detected in gastrointestinal microbiota. Some species are able to deconjugate bile acids, a feature positively correlated with low plasma cholesterol levels, while others convert dietary isoflavones to other equally beneficial products. Plant-origin isoflavones have been proposed to prevent hormone-dependent diseases, their conversion impacting their biological effectiveness. Yet, one of the conversion products, s-equol is referred to have anti-carcinogenic properties. s-equol is a non-steroidal phytoestrogen flavonoid produced by the microbial metabolism of the *isoflavonoid daidzein* contained in certain vegetable foods as chickpea and pistachio. s-equol is referred to have potential chemoprotective and estrogen receptor (ER) modulating activities [21].Among the bacterial products, s-equol appears to be the most relevant to human physiology [5].

This compound may increase bone mineral density, affect vasomotor symptoms, and is thought to decrease the proliferation rate of susceptible cancer cells [2,5].

Members of the order *Actinomycetales* include *Propionibacterium* spp., Corynebacterium spp. and Rothia spp. These species contribute to the degradation of gluten, their abundance and activity might be relevant for celiac disease, and other conditions related to gluten digestion [5]. Others, as *Micrococcus* spp. may cause infection, particularly in immuno-suppressed patients [5].

Methanogenic *Archae* have been extensively studied, as the process of methane synthesis (from CO_2 and H_2) results in significant gas removal from GI tract. A significant reduction of these populations has been registered in patients with IBD [5].

In what concerns to eukaryotes, the most prevalent *Eukarya* members in human GI tract are yeast, followed by filamentous fungi and intestinal parasites [5]. Probiotic, commensal and opportunistic pathogens are found among yeasts, similar to what happens with bacteria, while filamentous fungi do not seem to be relevant to the host, to our present knowledge.

Microbial Ecology and Host-Microbial Symbiosis

When complex animal life appeared on earth, microbes had already existed for billions of years. A major innovation in animal evolution was the gut—a tube that takes nutrients in one end and expels waste from the other. It also takes microbes, which achieved mobility this way. In the host's side, perhaps one evolutionary innovation was to scoop up the microbial communities necessary for survival in

a world of scarcity of food. Intestinal bacteria can use nutrients consumed by the host helping breaking down resistant starch, and some non-digestible polymers. Gut microbiome seem to prefer non-digestible polysaccharides from which produces intermediate (digestible) products and organic acids such as acetate, propionate, and butyrate (also known as SCFA), which have been found to intervene in the regulation of some important features of host-microbe symbiosis.

Another key factor, in the establishment of symbiosis, is the intestinal mucus, which selects the colonizing microbes according to their ability to metabolize the complex sugars it contains. These colonizers (the microbiota) ferment compounds that the human host cannot digest (mostly from vegetables) and help control opportunistic pathogens. The immune system receives signals from microbiota, conveyed partly in microbial metabolites as SCFA, indicating that the right populations are in place. In short, microbiota-host interactions include breaking down dietary components, building up and modulating the immune system, modulate hormone secretion and degrading toxins [12,13]. Gut microbiome also regulates insulin sensitivity, phytochemicals metabolism and end-products release, as gases [7-9,13].

Our hunter-gatherers ancestors consumed up to 10 times as much soluble fiber as modern populations, and hence generating far more fermentation by-products interacting with the immune system. Our fiber-poor modern diet may have weakened that signal, causing immune system to hyper-react and be easily prone to inflammation. It has been verified that diets high in certain fats and sugars deplete anti-inflammatory bacteria, thin the mucous layer, and foster systemic inflammation [13]. These different trends can still be inferred from nowadays observations. Filippo et al. (2010) [22] compared the intestinal microbiota of children from rural Africa, who consumed a plant-rich diet, to that of children from Europe, who consumed a low-fiber diet. Opposite trends between the two groups were found. The African children had a lower rate of *Firmicutes* to *Bacteroidetes* than western children did. Among *Bacteroidetes*, the dominant genera in the microbiota of African children were *Prevotella* and *Xylanibacter*, whereas those of the European children were the *Bacteroides* spp. and *Alistipes* spp. It is noteworthy that *Prevotella* spp. and *Xylanibacter* spp. can ferment both xylan and cellulose, abundant in the rural enriched-plant diet, and to liberate energy from it. Conversely, the European children carried higher levels of *Enterobacteriaceae* (particularly *Shigella* spp. and Escherichia spp.), which are often related to inflammatory bowel conditions.

The microbiota of an individual represents his unique signature, encompassing a great diversity of microbial species. Multiple data are in support that environment plays an important role in dictating bacterial colonization. Healthy twins, living in different environments, have similar microbiota at the genus level but dissimilarities at the finer levels of resolution are observed (that is, at the species and strains' level) [6,11].

Despite individual variations, human GI microbiota can be grouped in only three majors groups, or enterotypes, according to the relative abundances of three bacterial genera, *Bacteroides*, *Prevotella* (both of the phylum *Bacteroidetes*) and *Ruminococcus* (of the phylum *Firmicutes*) [12]. "*Ruminococcus*" enterotype is quite rare and most individuals, including those with chronic intestinal disease, can be classified into the broad enterotypes "*Bacteroides*" and "*Prevotella*". Enterotypes seem to be quite stable and quite independent of phenotypic factors [11,12,23]. Nevertheless, there is a long-term microbiota regulation by food habits, as well as short-term regulation by specific food ingredients, nutrients and probiotics. In this concern, it was found that the *Bacteroides* enterotype (associated to the intake of protein and animal fat) responds to short-term changes in the diet, while the *Prevotella* enterotype (associated to the intake of complex carbohydrates) seems to have no response [12,23,24]. Thus, in the *Bacteroides* enterotype, shifting the dietary pattern from high-fat/low-fiber (e.g. western-type diet) to low-fat/high-fiber (e.g. vegetarian regimen or similar) results in gut's microbial population adjustments, with perceived effects in about 24h. Thus, *Prevotella* spp. and related genera, as well as *Bifidobacterium* spp. seem to (at least transitorily) increase in proportion to the ingested amounts of resistant starch, other polysaccharides and oligosaccharides, although the microbial fermentation of dietary substrates in the colon, and the extent of population changes, is host-dependent [8]. According to Burcelin (2012) [3] the grouping of individuals, responding differently to diet and drug intake, relies on a number of well-balanced host-microbial molecular relationships. One of the best evidences is that the GI microbiota differs between obese and lean individuals [3,10,12,25-27] and between vegetarians and omnivores [8]. The type and proportion of the bacteria from the *Clostridium* clusters was found to change according to diet: The gut microbiota of vegetarians is dominated by some clostridia clusters' members as *Clostridium coccoides* and *Clostridium ramosum* but notably *Faecalibacterium prausnitzii*, a well-recognized key symbiont (see below) [28] is absent from the gut of vegetarians. Apparently, *F. prausnitzii* and related bacteria are found, at high levels, in populations that consume fish and meat [8,28].

The influence of microbiota in our health status is far more deep than thought a few years ago, influencing innumerable human metabolic routes. Multiple pathways are used by microbiota to influence brain development, stress, physiology, mood, cognition, and behaviour. These include, but are not limited to, direct communication with the brain via the vagus nerve, immune-mediated pathways (e.g., cytokine production), limitation of oxidative stress, enhancement of nutrient bioavailability and neurotransmitter precursors (for example, tryptophan), and proper maintenance of the gastrointestinal barrier [29,30].

One important but understudied mechanism of host-microbiota interaction appears to involve hormones. The microbiota produces and secretes hormones, responds to host hormones and regulates their expression levels, thus affecting immunity, mood, sexual attraction, appetite and metabolism of the host. On the other side, hormones impact microbial growth, attachment to surfaces, virulence and metabolism [30,31]. The communication between the gut microbiota and the brain is thought to be mediated mainly

by the long branching vagus nerve by several (mostly unrevealed) mechanisms mediated by hormones. [30]. Consequently, a new field of study, nutritional psychiatry, recently emerged aiming at linking the ultimate effects of nutrients and non-essential dietary compounds (e.g. bioactive peptides and phytochemicals) on brain's structure and function and hence on psychological health. The mechanisms by which some nutrients (as minerals and vitamins) influence mood can be explained in part by their role in the production of neurotransmitters. However, the connection between mood and non-essential dietary components (for example, phytochemicals) is thought to be related to their role in the antioxidant defence system as well as their ability to provide anti-inflammatory support, involving gut microbiota [30].

Two major groups of hormones are most likely involved in bacterial effects on host behaviour: neuro-hormones (as serotonin, dopamine, epinephrine and norepinephrine), and stress hormones (as cortisol, corticosterone, adrenocorticosterone and corticotropin). It is noteworthy that serotonin (5-hydroxytryptamine), one of the main neurotransmitters in the brain, is mainly found in the intestine (over 90%). Intestinal serotonin secretion is affected by diet, and regulates intestinal movement, mood, appetite, sleep and cognitive functions. This dual role suggests that serotonin may link the intestine (including its microbiota) to host behaviour. A revision on the established links between hormones, the human host and its microbiota is presented by Neuman et al. (2015) [31].

How Microbiota Influences Human's Health

To protect the gut from excessive bacterial exposure, the intestinal epithelium is coated with a thick and continuous mucin layer that limits and restricts the exposure of gut surfaces to luminal microbes. The epithelium's N-linked and O-linked glycosylation patterns, as well as its mucin content, depend on early feeding methods and further development, particularly during childhood. The carbohydrate structures of mucin provide important binding sites for gut bacteria and also represent rich sources of nutrients. Moreover, the mucosal immune system distinguishes between harmful pathogens and beneficial commensal bacteria, delivering completely opposing downstream responses to each bacterial group [11,13].Our microbiota has immunomodulatory properties, and *Clostridium* clusters IV, XIV and XVIII were found as playing a key role in keeping the gut barrier tight and healthy, for which Sokol et al. presented the first evidence in 2008 [28]. Conversely, inflammatory bowel disease (IBD) has been attributed to certain pathogens but the current accepted hypothesis is that Crohn's disease and ulcerative colitis, both forms of IBD, are caused by dysregulated immune responses directed towards the commensal microbiota [23,24,31].

A decrease in the abundance and biodiversity of *Firmicutes* has been observed repeatedly in Crohn disease, and Sokol et al. [28] found *Faecalibacterium prausnitzii*, a member of IVth *Clostridium* cluster, in the phylum *Firmicutes*, to play a key role. This bacterium exhibits anti-inflammatory effects, partly due to secreted metabolites, which interact with the immune system. These findings seem to apply worldwide and not only in European populations, suggesting that the role of commensal and mutualistic bacteria in inflammation overrides genetic determinants and other individual and environmental factors. *F. prausnitzii* can be a sort of keystone species in the gut ecosystem, or one of the many clostridia-related bacteria that perform the same protective functions, inducing T cells and preventing immune overreaction [13].The loss of certain bacteria in human IBD and the evidence of general dysbiosis, which creates an imbalance between protective and "pro-inflammatory" commensals, led to a significant interest in the use of probiotics to redress microbial imbalances in the gut of IBD patients [11,28].

Obesity has been associated to an increased proportion of *Firmicutes* (e.g. gen. *Bacillus*, *Staphylococcus* and *Clostridium*) to *Bacteroidetes* (e.g. gen. *Bacteroides* and *Prevotella*) [6,14] and a decrease in *Methanobrevibacter smithii* [8]. Additionally, it has been shown that the gut microbiota of lean individuals is more diverse than that of obese individuals [8]. High fat diets trigger alterations in microbiota promoting the development of gram-negatives, which often produce toxic lipopolysaccharides (LPS). Excessive levels of LPS (defined as metabolicendotoxemia) are related to gut, hepatic, and adipose tissue inflammation as well as diabetes, through mostly undisclosed mechanisms [3,8]. Alkanani et al. (2014) [20] showed that the development of diabetes in animal models involves the intestinal microbiota. Moreover, *Acinetobacter* spp., and *Enterobacteriaceae*, were found to be more abundant in infants that develop allergies [5].

Within the *Bacteroides* enterotype, the dominance of *Bacteroides* spp. in contrast to *Prevotella* spp. seems to be implicated in obesity, insulin resistance and dyslipidaemia [5]. The triggering of the inflammatory process can occur in response to a disruption of the interaction between bacteria and the immune system. The most probable causes being changes in the diet or the use of antibiotics [3,13]. A correlation between the early-life use of antibiotics and the later development of inflammatory disorders, including asthma, IBD, colorectal cancer and childhood obesity, has been reported [13].

Many consider probiotics an effective strategy to maintain gut's health. Probiotic strains are found among several bacterial and yeast groups, and are commonly associated to dairy products. Until 1900, yogurt was a staple food in diets of Western Asia, Caucasus, India and border regions, as is the case of Turkey and Greece. By this time, Elie Metchnikoff (a Nobel laureate) was the director of "Institut Pasteur". He promoted important studies on the identification and characterization of yogurt's bacteria, and introduced the term "probiotic" [14] hypothesizing that "the dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes" cit. by [14]. Molecular and genetic studies have helped to uncover the mechanistic basis for the beneficial, yet discussable, bioactivities of probiotics [20].

Besides dairy products, some pharmaceutical preparations contain probiotic strains (e.g., *Sacaharomyces boulardii* and *Lactobacillus plantarum*) commonly used in the treatment of a variety of gastrointestinal conditions, such as infectious diarrhoea, diarrhoea

associated with antibiotics use, irritable bowel syndrome, and IBD (e.g., ulcerative colitis and Crohn's disease). Probiotics are being used for preventing tooth decay and/or treating other oral health problems such as gingivitis and periodontitis. The development of effective probiotic formulations in various populations, requires a better understanding of GI's microbiota dynamics [16].

To present date, neither FDA nor EFSA (respectively, American and European food regulatory agencies) have approved any health claim for food probiotics. Nevertheless, based on scientific evidences and a safe history of use, Anukam and Reid (2007) [16] present a list of the lactic acid probiotic bacterial strains, most of them included in commercial dairy products:

-Gen. *Lactobacillus* (*L. rhamnosus GG, L. rhamnosus* GR-1, *L. rhamnosus* HN001, *L. reuteri* RC-14, L. *reuteri SD2112, L. casei DN114001, L. casei Shirota, L. acidophilus LA-1, L. acidophilus LB, L. acidophilus NCFM, L. plantarum* 299v, *L. salivarius* UCC118, *L. fermentum* VRI003, *L. johnsonii* Lj-1, *L. paracasei* F19)

-Gen. *Bifidobacterium* (*B. lactis* Bb 12, B. lactis HN019, *B. infantis* 35624, *B. breve strain Yakult, B. animalis* DN 117-001, B. *longum* BB536)

-Gen. *Lactococcus* (*Lactococcuslactis* L1A)

Yogurt is the most classical example of a probiotic food. Even if no other cultures are added, the starter cultures *Streptococcus salivarius* var. *thermophilus* and *Lactobacillus delbrueckiis* spp. *bulgaricus*, (independently of the strain) are recognized to enhance lactose digestion in lactose intolerant individuals [26]. Although probiotics may have innumerable beneficial effects, some strains of *Lactobacillus* sp. and *Bifidobacterium* sp. may potentiate weight gain [8].

The above list of probiotics does not include enterococci, although evidences are being built in this direction. *Enterococcus* is a complex genus that includes opportunistic pathogens as well as commensal bacteria and potential probiotics [17]. They are members of the order Lactobacillales(also including gen. *Lactobacillus*) and are commonly found in numerous cheeses, without presenting any health risk.

In a recent study, piglets were fed with a supplement of the probiotic *Enterococcus faecium* NCIMB 10415 showing a reduction in diarrhoea caused by *E. coli* and a greater increase in body mass. These findings were attributed to a sterical interference between the *E. faecium* probiotic and the pathogen to binding sites in the intestinal mucosa (although other mechanisms may also be involved) causing a reduction in the adhesive properties of the pathogen and thus to its decreased virulence [16].

Probiotic usage should be controlled and complemented by the ingestion of prebiotics, generally oligosaccharides (as inulin and oligofructose [1]) that improve probiotic viability, and also stimulate other gut microbes, namely *F. prausnitzii*. Thus, the ingestion of probiotics and prebiotics combined is expected to improve the efficacy of the changes.

Another example of a bacterial group that sustains gut's health is the sulphate-reducing bacteria of the phylum *Proteobacteria*. They are able to metabolize intermediate and end-products of Suphur-containing compounds (diet-derived or released from mucins) thus avoiding the accumulation of H_2S, which is highly toxic and inhibits butyrate oxidation, besides its possible involvement in colorectal cancer aetiology [5].

As referred before, the members of the *Clostridium* clusters (e.g. *Lachnospiraceae* family) are gut's permanent residents to which key tasks are attributed. These groups contain major degraders of resistant starch from which they produce butyrate and other SCFA. Butyrate can be used as an energy source by the gut epithelial cells. Moreover, butyrate has anti-carcinogenic and anti-inflammatory properties, as well as beneficial effects on glucose metabolism and energy homeostasis [5].

A case of control of a deleterious species by a symbiont can be illustrated with *Lachnospiraceae* family, which includes *Dorea* spp., *Blautia spp.,* and *Ruminococcus* spp. The former are major gas producers and are most probably implicated in irritable bowel syndrome [5], while Blautia spp. and *Ruminococcus* spp. (belonging to the same family and encompassing between 2.5 and 16% of total GI microbiota) may use H_2 and CO_2, produced by *Dorea* spp. and other deleterious bacteria [13], thus helping the elimination of gases and preventing inflammation.

Several GI pathogens, as *Clostridium difficile*, *Salmonella* spp., *Campylobacter* spp. and *Helicobacter pylori* may remain asymptomatic, mainly depending on GI microbial ecology, as well as on environmental and immunological factors [11].

Food interacts intimately with the microbiota with a variable impact. Today's high-processed foods have been referred to alter the balance of microbial groups, causing decreasing immunity, increasing virulence of otherwise asymptomatic opportunist pathogens, and triggering inflammatory responses [5,11,30]. Some commonly used food additives, as emulsifiers and sweeteners can alter microbial population dynamics, independently of host's enterotype [32,33].

Evidences are being build showing that artificial sweeteners, in general, are responsible for alterations in microbial metabolic pathways, impacting host susceptibility to metabolic disease, causing dysbiosis and glucose intolerance [34]. Aspartame, in particular, was reported to increase the abundance of *Enterobacteriaceae* and *Clostridium leptum* and possibly also interfering in the *Firmicutes* to *Bacteroidetes* ratio [34]. Regarding emulsifiers, Chassaing et al.(2015) [32] reported that polysorbate 80 and carboxymethylcellulose, even when consumed at moderate doses, changed the gut microbiota stimulating pro-inflammatory bacteria, which translocation across epithelial cells became facilitated. Changes also resulted in increased expression of flagellin and eventually toxic LPS.

[1] *inulin is a term applied to a heterogeneous blend of fructose polymers widely distributed in nature, as plant storage carbohydrates, while oligofructose is a subgroup of inulin, consisting of polymers with a degree of polymerization ≤10*

Conversely, fermented foods (e.g. cheese and wine) provide an array of microbial metabolites and other compounds (e.g. bioactive peptides and flavonoids), which may positively act upon microbiota profile, the effect being more pronounced in the *Bacteroides* enterotype. Reported effects on health are many and include a positive contribution to mood and mental health. Selhub et al (2014) [30] argue that fermented foods, carrying microbial metabolites (including many still unidentified compounds) are players of a gut-brain-microbiota intersection with favorable outcomes to the host's mental status.

Concluding Remarks

Human GI microbiota has been object of many studies for more than a century but only recently its importance was recognized, as foreseen by Metchnikoff.

In nowadays wealth societies, the contact with microbial loads has been minimized, although not entirely for our benefit. It has been found that the contact with pets and livestock during the childhood decreases in 50% the risk of Crohn's disease, by promoting a healthier gut microbiota [13]. In addition, as referred above, the children delivered by vaginal birth-mode and those that are breastfed for several months have higher chances of having more favorable microbiota than children delivered by caesarean section and/or bottle-fed with infant formula [3,10].

Gut microbiota plays a critical role in health and disease, the interactions between microbes and its host constituting a critical factor but they should be viewed as a result of core-functions performed by a microbial community rather than by a single species. This ecosystem has shown to be a forgotten organ of the human body deserving more attention and being the object of a growing number of studies.

The factors that enable a commensal bacterium to colonize a host's gut are not yet fully elucidated but there is a general acceptance that the mutual benefits provide the key to this successful partnership. It is noteworthy that despite the recent advancements, most of data acquired to date have been obtained from faecal samples, while ignoring the microbial metabolism occurring in small intestine, which can bias the conclusions. Despite that fact, the works herein reviewed should not be minimized, as they greatly contribute to this fast-growing research field.

Humans broadly belong to two enterotypes, which seem to be determined by long-term diet [12,23]:

- The *Bacteroides* enterotype, is most frequently associated with a diet rich in animal protein, saturated fats, and poor in fiber; this enterotype has been the object of more studies because is common in western societies; individuals are generally more prone to obesity and an array of metabolic diseases; Nevertheless, shifts in the diet cause fine adjustments in the microbiota with short-term positive outcomes.

- The *Prevotella* enterotype, is associated with a predominantly plant-based nutrition (high in complex carbohydrates) and low consumption of meat and dairy (low-fat/high-fiber diet); this enterotype is generally associated to less susceptibility to inflammation and obesity and better gut's health. This type of gut microbiota is a very stable population, resilient to changes.

The ingestion of large amounts of fiber, since early in life promotes the accumulation of SCFA, and other metabolites resultant from fiber fermentation. These metabolites indirectly promote the integrity of the intestinal mucus layer and the correct functioning of the immune system [13,35]. A fiber enriched-diet from childhood onwards is expected to have long-term effects, by shaping the microbiota and by calibrating the immune system. In these cases, the *Prevotella* enterotype is generally observed.

Nevertheless, although not changing the enterotype, transitory changes in microbiota can be induced in adults, particularly those of the *Bacteroides* enterotype that aim improving their health and wellness. These changes may consist in a transition from a western-type diet to a mostly vegetarian diet and/or seeding the gut's microbiota regularly with probiotics and prebiotics. Non-digestible carbohydrates (or prebiotics) help control obesity and related metabolic diseases by several mechanisms. A modulation of gut signaling peptides has consequences for a decrease in appetite and amelioration of gut barrier functions. During obesity and diabetes, fibers, resistant starch and oligosaccharides indirectly improve glucose tolerance, target entero-endocrine cell activity, and leptin sensitivity. At a broader level, these carbohydrates promote gut fermentation, help modulating gene expression, interfering with the development of adipose tissue and regulating inflammatory responses [8].

During weight-loss diets it is a normal practice to reduce total carbohydrate intake, a change that is necessarily accompanied by some reduction in dietary fiber and resistant starch. These diets had been shown to negatively impact the gut microbiota by decreasing the proportion and total numbers of bifidobacteria and butyrate-producing bacteria. Thus decreased concentrations of microbially produced SCFA were registered, with the above-described negative consequences [35].

Although diet-mediated mechanisms are mostly unknown, diet definitely mediates host-microbe symbiosis. Important in this process are bacterial fermentation products (obtained from selected nutrients) and their impact on the regulation of the intestinal barrier function. Also relevant is the indirect regulation, by the diet, of the expression of several genes associated to the metabolism of both, microbes and their human hosts. Further insights into diet/microbiota relationships and body immune system will eventually have an impact on nutritional guidelines for both healthy individuals and patients with chronic intestinal diseases and metabolic diseases, such as obesity and diabetes. It is important, therefore, to establish how far can the intestinal microbiota be thought of as static, within an adult individual, or at to what extent can it be subjected to dietary control. The ability to manipulate the microbiota through diet should provide a route for delivering health benefits.

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