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Interaction between the Microbiome and Diet: The Hologenome Concept

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Abstract

All plants and animals, including humans, are holobionts consisting of a host and diverse microorganisms, referred to as the microbiome or microbiota. The hologenome concept posits that the holobiont with its hologenome (sum of host and microbiome genes) can function as a single entity, acting in consortium, and therefore also as a unit of selection in evolution. Diet affects the microbiome by increasing or decreasing the population of some bacteria relative to others and by introducing new bacteria into the microbiome. Such phenomena can result in physiological changes within the host as well as within the holobiont as a whole. Novel microbes can be introduced into the microbiome by uncooked food; Changes in the relative number of bacteria can occur in the colon where food remnants, such as dietary fiber, that escape digestion in the upper digestive tract, are broken down into short chain fatty acids and many other compounds-beneficial, neutral or harmful. Diet-induced changes in the microbiome contribute to the health of humans by providing nutrients, priming the immune system, regulating development and eating behavior, and contributing to energy homeostasis, obesity and occasionally to disease.

Keywords: Holobiont; Hologenome; Microbiome; Obesity; Prebiotic; Probiotic

Introduction: The Hologenome Concept

Until recently, studies on symbioses have concentrated on a single primary symbiont and its host. However, with the advent of molecular (culture-independent) techniques in microbiology during the last 20 years, it is now clear that all plants and animals, including humans, live in close association with hundreds or thousands of different microbial species. Symbiosis-once thought to be a peripheral phenomenon-is the hallmark of life on earth [1]. In many cases, the number of symbiotic microorganisms and their combined genetic information exceed that of their host. In humans, for example, there are about the same number of bacterial cells in the colon as the total number of human cells [2,3]. Because the microbial community in and on the human body is composed of several thousand different species of bacteria, the genetic information encoded in the microbial genomes (about eight million unique genes) is more than 400 times greater than the 19,000 genes in the human genome [4].

Since certain specialized terms are used throughout this review, we would like to define these terms before discussing the data and concepts. Symbiosis (from Greek σύν "together" and βίωσις "living") is the close and often long-term interaction between two or more different biological species. The term “host” is used here to denote the larger, mostly multicellular organism in or on which the microbial symbionts reside. The term holobiont, introduced by Margulis [5], describes a host animal or plant and all of its symbiotic microorganisms, including Bacteria, Archaea, fungi, algae and viruses. The aggregate of all microorganisms of a holobiont is known as the microbiome, a term coined by Lederberg and McCray [6] or microbiota. Zilber-Rosenberg and Rosenberg [7] introduced the term hologenome to describe the sum of the genetic information of the host and its microbiome.

The hologenome concept of evolution posits that the holobiont (host + symbionts) with its hologenome (host genome + all symbiont genomes) functions as a distinct interactive biological entity and thus can be an important unit of selection in evolution [8,9]. The microbial symbionts play a role in the anatomy, physiology, development, innate and adaptive immunity, behavior, genetic variation and evolution of holobionts [1,10,11]. One of the consequences of considering the holobiont as a unit of selection is that genetic variation can be brought about by changes in either the host genome or the microbiome. Genetic variation in the host genome results from genetic rearrangements and mutations. Genetic variation in the microbiome can occur much more rapidly and predictably in response to changes in the environment, especially, changes in diet [9]. For example, when a particular bacterial species in the human gut increases relative to other species as a result of a component in the diet, this leads to genetic variation in the hologenome, i.e., gene amplification. Such a genetic variation can affect the adaptation of the holobiont to the new condition. This review will discuss animal and with greater detail human findings, demonstrating that diet leads to genetic variation in the microbiome and also will examine how these genetic variations can affect adaptation and physiology of the holobiont.

Diet Affects the Microbiome of Animals

Ruminants: Because they are important sources of human food and global greenhouse gas emissions, the effect of diet on rumen microbial community structure has been investigated widely using culture-based and DNA-based molecular methods [12-21]. The overall data indicate that dietary factors dominate over host species genetic traits in determining microbial community composition. In a large study involving 742 samples from 32 rumen species and 35 countries [21], diet was the major factor determining relative abundance: Bacterial communities from forage-fed animals were similar to each other, those from concentrate-fed animals were similar to each other, but distinct

from those in forage-fed animals, and those from animals fed mixed diets were intermediate between these. When the effect of fish oil, a highly unsaturated source of fatty acids, in the diet of dairy cattle was tested a significant increase in the proportion of propionic acid producing bacteria and a decrease in the proportion of butyric acid producing bacteria were observed in the rumen [22]. Yáñez-Ruiz et al. [23] have reviewed methods for manipulating the cow rumen microbiome by diet during early life.

Mice: Mice are often used as model systems for investigating human physiology and health. One important area that is studied in mice is obesity, the incidence of which continues to be high worldwide. It was shown in many strains of mice that compositional changes in the fecal microbiota associated with obesity were primarily a result of a high fat diet [24-26]. A high-calorie, high-fat/simple carbohydrate, obesity-inducing 'Western' diet fed to wild-type mice brought about an overall decrease in the diversity of the gut microbiota, in addition to a decrease in Bacteroidetes, a large increase in the relative abundance of *Rikenellaceae* and an increase in a single class of Firmicutes-the Mollicutes. The gut microbiota exhibited a linear dose response to dietary perturbations, taking an average of 3.5 days for each diet-responsive bacterial group to reach a new steady state. Consumption of a high-fat, high-sugar diet reproducibly altered the gut microbiota despite differences in host genotype [27]. Interestingly, prebiotic fructans can partially reverse the effect of a high-fat diet in obese mice by modulating gut microbiota and holobiont physiological responses [28].

Another important dietary nutrient that affects human health and has been shown to affect the gut microbiome of mice is dietary salt [29]. Whereas gut microbiome in a normal diet is composed mostly of species from the Bacteroidetes phylum, high-salt diet causes a shift in relative abundance to other phyla. The genus *Allobaculum* significantly spikes after high-salt feeding. These data suggest a new perspective on how salt can impact the body.

Regarding food additives, it has been shown recently in mice that relatively low concentrations of two commonly used emulsifiers in the food industry, carboxymethylcellulose and polysorbate-80, induce altered bacterial species composition in addition to increased pro-inflammatory potential and obesity/metabolic syndrome in wild-type hosts [30]. These results suggest that the broad industrial use of emulsifying agents in ready-made foods might be contributing to an increased societal incidence of obesity/metabolic syndrome and other chronic inflammatory diseases.

Fish: One of the first experiments to show the effect of diet on microbiota of fish was performed on rainbow trout in 1989 [31]. The fish were fed two different diets, one containing low lipid and the other high lipid. Using conventional culture methods, not molecular DNA techniques, qualitative differences in fecal bacterial composition were observed; the fecal microbiota of fish fed low lipid diet consisted primarily of *Acinetobacter* and enterobacteria, whereas fish fed the high lipid diet contained also abundant *Aeromonas, Flavobacterium*, *Pseudomonas* and *coryneforms*. Recently, Ringø et al. [32] have reviewed the extensive literature on fish diets and microbiomes.

Miscellaneous: Changes in the gut microbiota as a function of diet have also been shown in many other animals, including dogs [33], cats [34], chickens [35], pigs [36], seals [37], howler monkeys [38] and frogs [39]. In those animals that have been examined, compositional changes in the gut microbiome have also been correlated with overall changes in physiology.

Diet Affects the Microbiome of Humans

Numerous studies have shown that diet alters the microbiome in the human gut, from infancy to old age, and these changes have considerable physiological effects, which will be discussed later. The changes in microbiome by diet, as discussed above, can be considered as genetic variation of the holobiont.

Most of the microbiota a baby acquires comes from the mother during passage through the birth canal and subsequently by breast feeding. Human milk has traditionally been considered to be sterile; however, recent studies have shown that it contains diverse bacteria which include microbial groups such as staphylococci, streptococci, lactic acid bacteria, and genera such as *Serratia*, *Pseudomonas*, *Corynebacterium*, *Ralstonia*, *Propionibacterium*, *Sphingomonas, Bradyrhizobiaceae* and *Bifidobacterium* [40]. Remarkably, human milk is not only, as accepted today, the best source of nutrition for a new-born baby and a source of microbes, but it also contains specific prebiotic oligosaccharides, indigestible by the baby`s alimentary tract enzymes, that serve as carbon and energy sources for the beneficial bacteria in the baby's gut [41].

The cessation of breast-feeding and the introduction of solid foods beginning at about 6 months of age results in large changes in the microbiome. The gut microbiota of children no longer breast-fed becomes enriched in genera that are prevalent in adults, such as *Lachnospiraceae*, *Roseburia, Clostrium*, and *Anaerostipes*, rather than *Bifidobacterium* and *Lactobacillus* which dominated the gut microbiota of breast-fed infants [42]. It was observed that consuming solid foods with high fiber content selects for bacteria that have the capacity to degrade these polysaccharides [43].

Comparison of the gut microbiota of European children and that of children from a rural African village, where the diet is high in fiber showed significant differences between the two groups [44]. The rural African children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes phyla, with a unique abundance of bacteria from the genera *Prevotella* and *Xylanibacter*, known to contain a set of bacterial genes for cellulose and xylan hydrolysis. Furthermore, Enterobacteriaceae (*Shigella* and *Escherichia*) were significantly underrepresented in the African children compared to the European children. It was suggested that in this case gut microbiota coevolved with the polysaccharide-rich diet, enabling individuals to maximize energy intake from fibers.

Not only long-term dietary intake influences the composition of the gut microbiome, but also short-term changes in diet alter microbial community structure in a rapid and predictable manner. In a clinical study, David et al. [45] were able to induce, in just five days, differences in microbiotas, that would be metabolically more fit to the type of diet administered, entirely animal or entirely plant products. An animal-based diet increases the abundance of bile-tolerant microorganisms, such as *Alistipes*, *Bilophila* and Bacteroides, and decreases the levels of Firmicutes that metabolize dietary plant polysaccharides, such as *Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii*. These differences in microbiota as a function of diet are similar to those observed between herbivorous and carnivorous mammals [46], reflecting trade-offs between carbohydrate and protein fermentation. Furthermore, volunteers placed on a three-day high or low-calorie diet, showed that in the case of the energy increase, even this short-term was associated with an increased Firmicutes/Bacterioidetes ratio [47]. In summary, the human gut microbiome can rapidly respond to altered diets, facilitating the diversity of human dietary lifestyles.

The data also show that diet plays a dominant role in shaping inter-individual variations in host-associated microbial communities. For example, dietary non-digestible carbohydrates can produce marked changes in the gut microbiome community, but these changes depend on the initial composition of an individual's gut microbiome [48].

A dietary prebiotic is classically defined as a selectively fermented carbohydrate ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health [49]. The implication of this definition is that prebiotics in the form of functional carbohydrates change the gut microbiota and its metabolic activity similarly to natural fiber present in the normal human diet, except that prebiotics are targeted at specific bacteria and are degraded in a specific form and therefore can be more controlled. The most extensively studied prebiotics are inulins (fructans), fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS), all of which are indigestible by human digestive enzymes and are anaerobically fermented by bacteria, mainly in the colon [50,51].

The classical definition of prebiotics, relating to carbohydrates alone, seems today to be inadequate since any material reaching the human gastrointestinal tract can change the microbiota. An interesting example is flavanols, which are part of the wide group of compounds known as polyphenols (see also later). The flavonols are found in cocoa and chocolate and a wide variety of foods and beverages, including cranberries, apples, peanuts, onions, tea and red wine, and are known to change the microbiome and also to be broken down by it, and therefore can be considered prebiotics. In a randomized, controlled, double-blind, crossover intervention study with healthy humans, it was shown that cocoa-derived flavanols significantly increased the populations of beneficial bacteria (*Bifidobacteria* and *Lactobacillus*), while decreasing the number of pathogenic *Clostridium* [52].

Diet-driven Acquisition of Microbiota

Diet can not only bring about genetic variation in the hologenome by altering the relative abundance of pre-existing microbiota, but can also change the hologenome by introducing novel microorganisms. One of the major evolutionary events in animals was the ability to digest complex plant polysaccharides. In the case of cellulose degradation by cockroaches and termites, it has been suggested that the evolution of a sophisticated community of hindgut microorganisms may be viewed as a gradual process of internalizing consortia of external anaerobic microbes that digest plant litter in the soil [53]. Instead of plant debris decaying to varying degrees in the external environment prior to ingestion, it is digested in the hindgut by microbes after ingestion. Similar arguments have been put forth for the origin of herbivorous dinosaurs [54] and the first plant-eating mammals [55]. Also in humans, plant fiber is broken down to varying degrees by gut bacteria.

Foods that are not cooked contain numerous and diverse live microorganisms that can become a source of novel microbes. Some of them may become established in the gut and provide health benefits. In 1907, the Nobel laurate Metchnikoff hypothesized that ingestion of lactic-acid bacteria in the form of yogurt enhances longevity [56]. Evidence is now available that yogurt consumption is beneficial for intestinal health by restoring normal gut microbiota and suppressing inflammation [57]. In addition to yogurt, foods that contain large numbers of beneficial bacteria include miso soup, sauerkraut, kombucha tea, dark chocolate, pickles, kimchi and kefir.

Japanese cuisine contains the complex polysaccharide agar found in seaweed. Examples of foods containing agar include wagashi, a dessert made of small cubes of agar jelly, mizu yōkan, another popular Japanese food, and sushi. Interestingly, the Japanese have acquired and retained in their microbiome the ability to digest agar. They have a bacterium in their gut that contains a gene that codes for the enzyme agarase. Westerners lack this bacterium and cannot break down agar in their colon. The question then arises how the agarase gene was acquired by Japanese gut bacteria. The source of the gene was traced to a marine bacterium that was present on a dietary seaweed. However, this marine bacterium cannot survive in the human gut. DNA analysis showed that the gene was horizontally transferred from the marine bacterium to a resident gut bacterium and became part of the hologenome of the Japanese [58].

Probiotics, in some cases, can be considered an applied example of this principle. Probiotics has been defined as "Live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" [59]. Unlike variation of holobionts by acquisition of microbes from the environment, probiotic technology involves the nonrandom introduction of specific bacteria to improve the health of the host. One example demonstrating the possibilities harbored in probiotics is the experiment carried out on mice fed a high-fat diet that contained in its water *Escherichia coli* that were genetically-engineered to produce N-acylphosphatidylethanolamines (NAPEs) [60]. The control mice, fed non-engineered *E. coli*, gained weight while the mice receiving the genetically-engineered *E. coli* did not. NAPEs are precursors of the lipid compounds N-acylethanolamides that are synthesized in the intestine and are known to reduce food intake and obesity.

Diet-induced Changes in the Microbiome Affect Holobiont Physiology

Considering the holobiont as a distinct biological entity and a unit of selection in evolution, interaction between the normal microbiota and the host generally leads to improved fitness. Although the idea that resident microbial communities are important contributors to fitness of their hosts is not new, we are now developing a broader and deeper appreciation of the wide range of interactions occurring within the holobiont between the host and the microbiota. In humans, symbiotic microbes protect against pathogens [61-63], provide nutrients, including vitamins and amino acids [64], prime the adaptive or antigen-specific immune system during development and into adulthood [65,66], regulate postnatal angiogenesis [67], play a key role in energy homeostasis and obesity [68-77], affect human behavior [78-81] and sometimes contribute to inflammation [82], and diseases such as diabetes [83].

In most animals, including humans, the gut harbors the largest bulk of the microbiome, which naturally interacts in a complex manner with the diet. Each component of the diet can, in principle, cause a change in the microbiome and different microbiomes can have different effects on a certain diet. The changes resulting from these interactions may lead to specific and sometimes novel physiological effects on the holobiont. In this section we will discuss briefly the interaction of some components of the human diet with the microbiome and their resulting metabolic effects.

A major part of the interaction between diet and microbiota in humans involves the conversion of plant-based dietary fiber and other non-digestible food ingredients into short chain fatty acids (SCFAs) by

microbial fermentation in the colon. The principal SCFAs produced via bacterial fermentation are acetate, propionate, and butyrate, present in the human colon in the approximate molar ratio of 60:20:20 [84]. SCFAs show important and pleiotropic functional effects via their influence on key regulatory proteins. SCFAs affect cell proliferation and function and microbe-to-host relationship, have anti-inflammatory, anti-tumorigenic properties and are major players in energy metabolism and maintenance and function of the immune system. Given the many effects of SCFAs, they also play a role in affecting various modern-day diseases including obesity, diabetes, inflammatory bowel diseases, and colorectal cancer [85].

SCFAs contribute up to 5-10% of the total energy in a healthy body [86]. Acetate, the main SCFA in the blood, plays a key metabolic role for peripheral tissues being a substrate for energy production, lipogenesis and cholesterol synthesis [87]. Recent research suggests that propionate reduces energy intake by attenuating reward-based eating behavior in the striatum, the subcortical part of the forebrain that is a critical component of the reward system [88]. Butyrate production by gut microbiota acts as an important energy and carbon source for colonocytes, it is protective against colon cancer and acts also as an anti-inflammatory, antioxidative agent and plays a role in intestinal barrier functions [89]. Butyrate, via its effect on regulatory proteins which influences gene expression, has also multiple effects on brain function and behavior [90]. In light of the new findings regarding mechanisms of action of SCFAs in general and butyrate in particular, a hypothesis was put forth: A high fiber diet may improve brain health [91].

One of the most intriguing multi-factorial problems to be solved, as already mentioned, is world-wide obesity. The first indication of the role of the microbiota in the pathogenesis of obesity was published 12 years ago [68]. With the same diet intake, conventionally raised mice gained more body weight and body fat than germ free mice. Furthermore, transplantation of microbiota harvested from conventionally raised mice into germ free mice resulted in an increase in body weight and a decrease in insulin sensitivity [68]. Not only were germ-free mice leaner than conventionally raised mice, but they were also resistant to western-type high-fat diet induced obesity [69]. Transplantation of microbiota harvested from either genetically-obese mice [70] or high-fat diet induced obese mice [71] into germ free mice mimicked the obese insulin resistant phenotype. Supporting the animal data, a small human study in male patients with metabolic syndrome, which received intestinal microbiota from a lean donor via duodenal tube, showed improvement in insulin sensitivity [72].

An elegant experiment by the Gordon group [73] demonstrated that both microbiota and diet influence obesity. Separate groups of germ-free mice were infected with microbiota from obese or lean human discordant twins. Bacteria from the feces of the obese twin caused significantly greater increase in body mass and adiposity than bacteria from the lean twin. Differences in body composition were correlated with differences in fermentation of short-chain fatty acids (increased in lean) and metabolism of branched chain amino acids (increased in obese). Placing the obese and lean mice in the same cage (mice are coprophagic-feces eaters) prevented development of increased body mass in the obese mice- only when they were fed a diet low in saturated fatty acids and high in fruit and vegetables. These data show that diet and microbiota interact to influence the biology of the host.

It has been shown in mice [68] and humans [74] that obesity is correlated with different bacterial communities and that a gradual transition occurs in humans from the obese microbiota to the lean microbiota during a course of a restrictive energy intake. People whose colon contains a relatively low diversity of bacteria and bacterial genes were found to contain higher levels of body fat and inflammation than those with high gut-microbial richness [75,76]. The data suggesting a relationship between obesity and the diversity of intestinal microbiota open the future possibility of treating obesity by gut microbiota manipulation. Regarding "obese bacteria", it should be noted, they are also associated with normal weight gain during the third trimester of pregnancy [77], where they may be highly beneficial, as they promote energy storage in fat tissue and provide for the growth and development of the fetus and subsequently for the production of mother`s milk for the infant after birth, all of which are central to the fitness of mammals. The origins of host-microbial interactions that underlie much of the present-day obesity epidemic may lie in reproductive biology and survival mechanisms correlated with food shortage in the past.

Amongst the different foods that are included in the human diet are those that are nicknamed "superfoods". These include such foods as pomegranate, blueberries, green tea, salmon, broccoli, garlic and gugi berries. Though the term "superfood" is considered to be more of a marketing term, professionals admit that these types of foods are nutraceutical-rich and have been shown to be healthy and disease preventing in animal trials [92,93] as well as some human clinical trials [94-96]. Many of the nutraceuticals contained in the superfoods are broken down in the human gut by the microbiota and this transformation often turns them into physiologically active materials. Let us discuss some of them.

The health benefits attributed to polyphenols (a large family of compounds) found abundantly in a wide variety of foods and beverages, such as fruits, herbs, cereals, coffee, tea, cocoa and wine [97], depends to a large degree upon gut microbiota [98]. Most polyphenols, for example EGCG (epigallocatechin 3-gallate) from green tea, pass through the small intestine where they are partially broken down but are not well absorbed. When they reach the colon, they are converted to different kinds of metabolites by bacteria that result in their increased bioavailability [99]. Polyphenols also act as prebiotics by stimulating beneficial bacteria. Thus, there is a two-way interaction between polyphenolic compounds and gut microbiota, which has beneficial impact on human health. Polyphenols and their metabolites have been shown in animals and in some cases also in humans to have multiple physiological effects such as lipid lowering effects, reduction of cognitive decline, obesity prevention, reduction of insulin resistance and prevention of coronary heart disease and certain cancers [97].

Another example is the conversion of ellagitannins, found in pomegranate, nuts and berries, into urolithins [100]. Urolithins have been shown to induce mitophagy (the selective degradation of defective mitochondria) in *Caenorhabditis elegans* and increase muscle function in rodents [101].

A number of human gut bacteria have the ability to degrade toxins associated with food, such as mycotoxins, commonly found on maize [102] and also oxalic acid, a normal human metabolite and a component of a wide range of foods and beverages, including coffee, chocolate, rhubarb, spinach, nuts and other fruits and vegetables [103]. The ingestion of gram quantities of oxalate can result in precipitation of calcium oxalate in the kidneys (kidney stone disease). The ability of the gut bacterium *Oxalobacter formigenes* to degrade dietary oxalates prompted its successful use in clinical trials as a therapeutic and

prophylactic option in calcium oxalate nephrolithiasis and associated renal failure [104].

There are also some underappreciated consequences of microbial metabolism, e.g., lowering the pH of the colon to 5.5-6.5 [105], which inhibits many bacterial pathogens, and production of heat. Approximately 70% of body heat at rest is produced by bacteria [106].

Conclusion

The diet-microbiome interaction is multi-faceted. Diet and host select for those microorganisms which can multiply rapidly on the food substrate in that diet and within the specific host, leading to a specific diet-host-dependent microbiome and hologenome. The microbiome transforms those components in the diet, such as fiber and nutraceuticals, which escape digestion or are degraded only partially in the upper digestive tract, into active or-non-active compounds part of which are absorbed in the colon. Also, uncooked food brings with it novel microbes that occasionally enter the microbiome. Diet-induced changes in the microbiota contribute to the physiology of human holobionts by providing nutrients, priming the immune system, regulating development and behavior, and contributing to energy homeostasis and obesity and also under certain conditions to diseases. As more is known about the specific microbes that are involved in different physiological functions in the human body, it should become possible to optimize the microbiome and holobiont physiology through probiotics and different foods of which, now we know, act all as prebiotics.

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