Microbes Drive Evolution of Animals and Plants: the Hologenome Concept

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ABSTRACT The hologenome concept of evolution postulates that the holobiont (host plus symbionts) with its hologenome (host genome plus microbiome) is a level of selection in evolution. Multicellular organisms can no longer be considered individuals by the classical definitions of the term. Every natural animal and plant is a holobiont consisting of the host and diverse symbiotic microbes and viruses. Microbial symbionts can be transmitted from parent to offspring by a variety of methods, including via cytoplasmic inheritance, coprophagy, direct contact during and after birth, and the environment. A large number of studies have demonstrated that these symbionts contribute to the anatomy, physiology, development, innate and adaptive immunity, and behavior and finally also to genetic variation and to the origin and evolution of species. Acquisition of microbes and microbial genes is a powerful mechanism for driving the evolution of complexity. Evolution proceeds both via cooperation and competition, working in parallel.

So, like it or not, microbiology is going to be in the center of evolutionary study in the future—and vice versa.
—Carl R. Woese

The hologenome concept of evolution was first published 8 years ago (1, 2). Since then, numerous experimental and theoretical articles have appeared, providing additional support for the concept. We review here these data and ideas and discuss how they were the inspiration behind the hologenome concept of evolution and how they continue to expand and develop it.

Since certain specialized terms are used throughout this article, we begin with defining these terms. The term holobiont was introduced in 1991 by Margulis (3) to describe a host and its endosymbiont. In 2002, Rohwer et al. (4) described the coral holobiont to also include *Bacteria*, *Archaea*, protists, and viruses. We subsequently further generalized with respect to the term "holobiont" to include all animals and plants and introduced the term "hologenome" to describe the sum of the genetic information of the host and its symbiotic microorganisms (2). After we published several papers on the hologenome concept, Richard Jefferson informed us that he had used the term hologenome in a seminar that he had given in 1994. The microbiota refers to all of the microbes associated with an animal or plant, while the microbiome is defined as the sum of the genetic information of the microbiota (5). The term host generally refers to the larger, eukaryotic, multicellular organism in or on which the symbionts reside.

THE HOLOGENOME CONCEPT

The hologenome concept of evolution asserts that the holobiont with its hologenome, acts as a unique biological entity and therefore also as a level of selection in evolution (1, 2, 6). During the last few years, numerous experiments have provided support for the hologenome concept. The major arguments for considering the holobiont as a level of selection are the following.

(i) All multicellular organisms contain abundant and diverse microbiota. Often, the number of microbial cells and the sum of their genetic information are above that of their host.

(ii) Not only the host genome but also the microbiome can be transmitted between generations with reasonable fidelity and thus maintains the unique properties of the holobiont.

(iii) Microbiotas and their hosts interact in a manner that affects the fitness of the holobiont in many ways, including its morphology, development, behavior, physiology, and resistance to disease. Taken together, these interactions characterize the holobiont as a single and unique biological entity (7).

One of the important outcomes of accepting the holobiont as an independent level of selection (6, 8) is that several previously underappreciated modes of genetic variation and evolution become apparent. Genetic variation in the hologenome can be brought about by changes in the host genome and also by changes in the microbiome. Since the microbiome can adjust more rapidly and by more processes than the host genome to environmental dynamics, it plays a fundamental role in the adaptation and evolution of the holobiont.

ABUNDANCE AND DIVERSITY OF MICROBES ASSOCIATED WITH ANIMALS AND PLANTS

Microbes are present in large numbers on the surfaces of multicellular organisms and in their fluids (exosymbionts), including the skin, the digestive tract, and the airways, and also inside some animals and plant cells (endosymbionts). Humans, for example, contain about 10^{14} microbes in the digestive tract. Although it has often been asserted that the number of cells in the human microbiota is 10 times higher than the number of cells in the human

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TABLE 1 Examples of estimated number of bacterial species associated with animals and plants

Host	Estimated no. of bacterial species	Reference(s)
Invertebrates		
Drosophilia melanogaster	209	Wong et al. 2012 (92)
Marine sponge	2,567	Schmitt et al. 2013 (93)
Hydra	350	Franzenburg et al. 2013 (94)
Coral	1,508	Ainsworth et al. 2015 (95)
Termite gut	800	He et al. 2013 (96)
Vertebrates		
Human gut	1,000–10,000	The Human Microbiome Project Consortium 2012 (97); Sankar et al. 2015 (98)
Human skin	4,742	Fierera et al. 2008 (99)
Bovine rumen	5,271	Jami and Mizrahi 2012 (100)
Great ape gut	8,914	Ochman et al. 2010 (26)
Land iguana	356–896	Hong et al. 2011 (101)
Plants		
Phylosphere	252	Bulgarelli et al. 2013 (102)
Endophytes	77	Whipps et al. 2008 (103)
Rhizosphere	30,000	Berendsen et al. 2012 (104)
Marine green alga, *Ulva australis*	1,061	Burke et al. 2011 (105)
Pitcher plant, *Sarracenia*	1,000	Koopman et al. 2010 (106)

body, the ratio is actually quite variable and closer to 1 (9). Regarding plants, up to 10^8 bacteria per g are found on leafs (10), and the rhizosphere of plants contains up to 10^9 bacteria and 10^6 fungi per gram soil, the highest concentration being attached to the root epidermis (11).

During the last decade, there have been numerous reports on the number of bacterial species associated with different hosts (Table 1). These values are minimum numbers because minor species (<0.1% of the total) would not be detected with current methods. Although these rare bacteria would have little effect on the holobiont at present, they could become more abundant when conditions change and thus contribute to the fitness of the holobiont and to its adaptation and evolution.

The growing databank on microbiota associated with specific animals and plants has led to certain generalizations. (i) In addition to *Bacteria*, the holobiont may also include *Archaea*, protists, and viruses. (ii) Microbes associated with hosts are different from the microbial community in the bordering environment. (iii) The microbiota is host species specific, even in different environments. (iv) The compositions of microbial symbionts differ from tissue to tissue in the same organism. We suggest that the diversity of microbial species in holobionts depends on the variety of niches in different tissues, the activity of the immune system, and the changing environmental conditions, especially diet. In addition, bacteriophages may contribute to diversity by preventing any specific bacterial strain from dominating according to the "kill the winner" hypothesis (12).

Analyses of the microbiota of humans indicate that there is a core microbiota, which includes bacterial species that are common to all individuals and are present most of the time in relatively large numbers (13). The noncore microbiota includes those species that are readily exchangeable and vary as a function of environmental conditions, such as diet and disease state. It is usually the noncore microorganisms that are changeable by external manipulation (e.g., probiotics). Sometimes they can become stable inhabitants of the holobiont and part of the core microbiota (14).

MICROBIOTAS ARE TRANSMITTED BETWEEN HOLOBIONT GENERATIONS

For microbiotas to play a role in the evolution of animals and plants, they must be transmitted between generations. Not only the host genome but also the symbiont genomes must be transmitted. It has been demonstrated in recent years that microbial symbionts can be transmitted from parent to offspring by a variety of methods, including via cytoplasmic inheritance (15), eggs (16), coprophagy (consumption of feces) (17), direct contact during (18) and after (19) birth, and insect vectors (20), and in various other ways via the environment (21). Vegetative (asexual) reproduction takes place in many animals and plants. During vegetative reproduction, the microbiota is automatically transferred to offspring.

Ley et al. (22, 23) have demonstrated that different mammals have specific and typical microbiota that have coevolved and codiverged with them. In ants (genus *Cephalotes*), for example, it has been suggested that many members of the microbiota have been present since the diversification of the host genus in the Eocene (24). Great apes have retained many of their microbiota by vertical transmission over evolutionary timescales (25, 26). The fact that some human symbionts are transmitted with fidelity has led to their application in the study of human migration. In particular, the bacterium *Helicobacter pylori* has been used as a conserved marker of ancestry and migration (27). In summary, regardless of the means, it is now evident that an important fraction of the microbiota is transferred from one generation to the next. However, it is also possible that the presence of some of the microbes within the microbiota is a result of recent acquisition from the environment, via diet, for instance (22, 23).

In humans, most of the colonization of the newborn gut occurs by inoculation with maternal vaginal and fecal microbes when the baby transits the birth canal. Interestingly, recent data suggest that intrauterine fetuses are not sterile and that a prenatal mother-to-child efflux of commensal bacteria may occur (28, 29). An infant's first postpartum bowel movement is referred to as the meconium.

TABLE 2 Examples of microbial participation in the fitness of holobionts

Contribution of microbiota	Example(s)
Respiration and ATP production	Mitochondria (bacteria) in all eukaryotes
Photosynthesis	Chloroplasts (cyanobacteria) in all plants
Protection against pathogens	General
Provision of essential nutrients to host	General
Fat storage and obesity	In mice, chickens, and humans
Development	Squid eye organ, legume nodule, immune system, angiogenesis, muscle thickness
Behavior	Brain, metabolites, hormones, stress, autism, sleep, mating selection, group living
Detoxification of toxic substances	Plant and fungal toxins in food, heavy metals
Temperature adaptation	In fish, desert plants, grass

Unlike later feces, the meconium is composed of materials ingested during the time the infant develops in the uterus. The meconium had been thought to be sterile, but recent studies have indicated that it contains a complex bacterial community dominated by lactobacilli and enteric bacteria, such as *Escherichia coli* (30, 31). Another source of microbiota for the infant is breast milk (32). The fact that babies acquire microbial diversity from their mother's milk represents another mechanism for the transmission of microbiota between generations.

MICROBIOTAS ARE PART OF HOLOBIONT FITNESS

Table 2 lists some of the important contributions of microbiotas to the fitness of holobionts. It should be noted that the fitness of holobionts involves beneficial interactions between the host and its symbionts, as well as between the symbionts themselves. Although the term "outsourcing" has been applied to describe functions that microbiotas contribute to their hosts, the term "insourcing" may be more appropriate since microbiotas are an integral part of holobionts.

Mitochondria and chloroplasts can be considered "extreme symbionts" because they were derived from alphaproteobacteria (33) and cyanobacteria (34), respectively. Mitochondria are the major sites of energy production in all eukaryotes, and chloroplasts are responsible for photosynthesis and a number of additional functions, including fatty acid synthesis, amino acid synthesis, and the immune response in plants. Resident microbes also protect animals and plants against pathogens. Evidence for this comes mainly from studies performed with germ-free animals, which are extremely sensitive to infection and mostly die following administration of a pathogen (35). In humans, the resident microbiota has been shown to help protect against infection by pathogens along the alimentary tract (from mouth to colon), on the skin, and in the urinary tract and vagina. It has also been shown in plants that symbiotic bacteria can protect the holobiont against phytopathogens by direct interaction with the pathogen and by elicitation of induced systemic resistance (36).

Another important general fitness contribution of microbiota to the holobiont is performance of metabolic processes that the animal or plant cannot carry out without the microbiota, mainly regarding nutrient provision. Examples include nitrogen fixation in legumes (37), cellulose degradation in ruminants, termites, and cockroaches (38, 39), photosynthesis by microalgae in corals, mollusks, and sponges (40), and oxidation of inorganic compounds in deep-sea invertebrates (41). In some obligatory biosynthetic processes, cointeractions between microbiotas and their host are required. For example, the mealybug *Planococcus* contains the bacterium *Tremblaya princeps*, which in turn contains the bacterium *Moranella endobia* (42). In this holobiont, the synthesis of phenylalanine requires enzymes that are encoded by *Moranella*, *Tremblaya*, and the genome of the host insect (43).

In humans, gut microbiota plays an all-important function in the production of vitamins and amino acids, breakdown of dietary fiber to short-chain fatty acids, and detoxification of harmful chemicals (44). Bacteria and fungi associated with plant roots contribute to nitrogen metabolism, mineralization of organic materials, and phosphate uptake and increase access to water (45). Rhizosphere microbiotas are a key component of plant fitness.

It has been shown in mice, chickens, and humans that obesity is correlated with certain microbiota. More significantly, the Gordon group (46) showed directly that both microbiota and diet influence obesity. When germ-free mice were inoculated with microbiotas from the feces of obese and lean human twins, the mice that received bacteria from the obese twin showed a significantly greater increase in weight than those that received bacteria from the lean twin. Moreover, it is well known that obesity is correlated with reduction of reproductive fitness in men and women (47, 48). However, research has also shown that the numbers of these "obese bacteria" increase during the third trimester of pregnancy (49). Such a microbiota would induce metabolic changes that promote energy storage in fat tissue that in turn encourages growth of the fetus.

Animal and plant development is predicated on intimate relations with microbes (50, 51). In many organisms, microbially produced chemical signals trigger the development of organs (52). For example, the endosymbiont *Wolbachia* produces signals that prevent the ovaries of its parasitoid wasp host from undergoing apoptosis (53). *Wolbachia* bacteria are also responsible for the correct anterior-posterior patterning in nematodes (54). *Vibrio fischeri* bacteria are required for the development of the light organ in squids (55).

In vertebrates, the development of the immune and digestive systems is triggered by and not completed without gut bacteria (56, 57). In germ-free mice, gut-associated lymphoid tissue is absent or poorly developed. Also, they have insufficient intestinal capillaries and a T-cell repertoire so diminished that they have a severe immunological disorder which makes them highly sensitive to infectious diseases (58, 59). Thus, to a large degree, humans and other mammals "co-develop" with their symbionts (60).

Mouse studies have shown that the gut microbiota has an impact on the development of the mammalian brain and subsequent adult behavior. For example, germ-free mice spend significantly more time in the light compartment of a box than control mice. Inoculating the gut microbiota from healthy mice into germ-free mouse pups caused them to behave in the "normal" cautious manner (61). The hypothesis that the microbiota affects the brain is supported by experiments showing a more than 2-fold difference between germ-free and conventional mice in levels of gene expression in more than 100 genes in the brain (62). There is also recent evidence that microbial products released into the blood-

streams of mammals cross the blood-brain barrier and affect sleep and autism (63). In *Drosophila melanogaster*, the commensal bacterium *Lactobacillus plantarum* alters the level of sex pheromones and thereby influences mating behavior (64).

In addition to metabolizing food that cannot be digested by animals alone, microbes also protect them against environmental toxic materials, such as heavy metals, hydrazine, fungal and plant toxins, and oxalic acid (65). Changes in temperature present a problem to plants and ectothermic animals regarding how to carry out cellular metabolism at both the high and low temperatures. Microbiotas can help solve this problem by providing enzymes optimized for the different temperatures (66). It has frequently been reported that the survival of corals is threatened by increased seawater temperature resulting from global warming. Recently it has been shown that acquisition of certain strains of symbiotic algae increases the temperature tolerance of the corals by 1 to 2°C (67).

GENETIC VARIATION OF HOLOBIONTS

One of the most significant aspects of the hologenome concept is the introduction of novel modes of genetic variation and evolution. Prior to the formulation of the hologenome concept, genetic variation in animal and plants was assumed to occur exclusively as a result of genetic changes during sexual reproduction, chromosome rearrangements, and epigenetic changes and ultimately by mutation in the host. However, in holobionts, three additional processes can occur: microbial amplification or contraction, acquisition of novel microbial strains from the environment, and horizontal gene transfer (HGT). These three processes can occur rapidly and, as we describe in the next section, are important processes in the evolution of animals and plants.

Microbial amplification or contraction involves changes in the relative abundances of the diverse microbial symbionts in holobionts. This type of genetic variation in the microbiota is similar to duplication of chromosomal genes. However, alterations in the abundance of symbionts are rapid and responsive to the environment, whereas changes in host genes are slow and random. Environmental factors that drive changes in the microbiota include diet, changing temperatures, and exposure to antibiotics. For example, De Filippo et al. (68) have shown that a high-fiber diet results in a high abundance of bacteria from the genera *Prevotella* and *Xylanibacter*, whereas a high-carbohydrate diet results in abundant *Shigella* and *Escherichia*. Similarly, changing the diet from milk to solid foods in infants causes an increase in the abundance of *Bacteroidetes* (69). In mice, a 1-day change in diet from high fiber to high fat brought about a rapid change in the gut microbiota (70); because the diverse microbial population of holobionts contains a large amount of genetic information, gain or loss of microbiota can be a powerful mechanism for adapting to changing conditions. In general, gene variations in the microbiome can be transferred to offspring. This is particularly relevant to changes in the microbiota that occur during pregnancy (71).

Acquisition of novel symbionts from the environment is another mechanism for introducing genetic variation into holobionts. During their lifetime, animals, including humans, encounter numerous microorganisms in the food that they eat, the water that they drink, and the air that they breathe and by contact with other organisms. Plants acquire microbes from the soil and atmosphere and also from insect vectors. If the acquired microbe can overcome the immune system and find a niche in the holobiont, it can become established in the host. Acquiring a new symbiont introduces novel genetic material into holobionts. Probiotics, in some cases, could be considered applied examples of this principle. During the 20th century, research on the acquisition of microbes focused primarily on pathogens. Many of the principles derived from studies of the transmission of pathogens should also apply to beneficial microorganisms. Acquisition of beneficial bacteria probably occurs frequently but generally goes unnoticed.

Horizontal gene transfer (HGT), also termed lateral gene transfer, refers to the transfer of genes between organisms in a manner other than the vertical transmission of genes from parent to offspring via sexual or asexual reproduction. HGT is generally associated with gene transfer between different bacteria but can also take place from microorganisms to animals and plants and the other way around. Examples include transfer of fungal genes to aphids (72), transfer of cellulase genes from bacteria to a nematode (73), and transfer of genes for the cytoskeletal protein tubulin from eukaryotes to the bacterium *Prosthecobacter* (74). Many *Wolbachia* genes have been horizontally transferred from these bacterial endosymbionts to the chromosomes of their insect hosts (75). In general, it is clear that introduction of genes by HGT into eukaryote genomes has been a major force propelling genetic variation and evolution, as discussed in the next section.

EVOLUTION OF HOLOBIONTS

How does microbe-driven variation lead to evolution of complexity? Microbes were the only forms of life on this planet for 2.1 billion years. During that time, they "invented" biochemistry, evolved enormous genetic diversity, and split into two domains, *Bacteria* and *Archaea*. The first eukaryote was probably formed by the uptake of bacteria to eventually form mitochondria (76) and chloroplasts (77) and possibly by the uptake of an archaeon by bacteria to form the nucleus (78), i.e., by variations of acquisitions of microbes. Subsequent evolution of multicellular organisms proceeded both by the uptake of whole microbes and by HGT of genes from microbes into the microbiome and into the host genome, in addition to mutations. All of the fitness traits of holobionts ascribed to microbes fit into this category.

An example of a major evolutionary event that was driven by the acquisition of bacteria is the ability of some animals to use cellulose and other complex polysaccharides as nutrients. It is likely that the evolution of termite and cockroach hindgut microbiotas occurred by the gradual process of internalizing from the environment microorganisms that digest plant litter. Instead of plant cellulose/hemicellulose being broken down in the soil prior to ingestion, it "rots" in the hindgut after consumption (79). Similar claims have been made for the origin of herbivorous dinosaurs and the first plant-eating mammals.

An example of probably recent evolution of humans by HGT between bacteria is the ability of Japanese to digest agar because they have a bacterium in their gut that contains a gene that codes for agarase. Westerners lack this bacterium and cannot digest agar. The gene coding for agarase was obtained by HGT to a resident gut bacterium from a marine bacterium that was present on raw seaweed that is part of the traditional Japanese diet (80). In general, HGT between bacteria is a frequent event in the human body (81).

A key event in the evolution of placental mammals, including humans, was the acquisition by HGT, from a retrovirus, of the gene coding for the protein syncytin (82). Initially, the function of syncytin was to allow retroviruses to fuse host cells so that viruses

could move from 1 cell to another. Now, synctin is necessary for the development of the placental syncytium, the essential part of the barrier that prevents maternal antigens and antibodies getting into the fetal bloodstream. Similarly, retrovirus-derived molecules appear to have played a crucial function in the generation of the progesterone-sensitive uterine decidual cell, allowing nutrient provision to the developing embryo (83). These data indicate that the integration of viral DNA into a host genome played a primary role in a major evolutionary leap by enabling growth and maturation of the fetus in placental mammals.

Recent analyses have shown that HGT in animals and plants typically results in tens or even hundreds of active foreign genes. In humans, 145 genes (not present in other primates) were attributed to HGT (84). These genes play a variety of roles and are involved in such processes as fatty acid degradation and antimicrobial or inflammatory responses. Most of the foreign genes identified in the study came from bacteria, but some originated from viruses and yeasts. A total of 128 genes found in land plants but absent from algae were identified as derived from prokaryotes, fungi, or viruses. Many of these genes are related to essential or plant-specific metabolic and developmental processes (85).

SPECIATION

Experiments on speciation in animals provide further support for the hologenome concept of evolution. In 1989, it was reported that splitting a homogenous population of fruit flies and propagating some on a molasses medium and the others on a starch medium resulted in mating preferences. The "molasses flies" preferred to mate with other molasses flies, and "starch flies" preferred to mate with other starch flies (86). The experiment was considered important because mating preference is an early event in the emergence of new species (87). However, the occurrence of mating preference was too rapid to be explained by neo-Darwinian evolutionary theory. Recently, we were able to demonstrate that treatment with the antibiotic tetracycline abolished the diet-induced mating preference, suggesting that the fly microbiota was responsible for the phenomenon (64, 88). This was confirmed when it was shown that infecting antibiotic-treated flies with pure cultures of *L. plantarum* isolated from starch flies reestablished mating preference. Analytical data suggest that *L. plantarum* changes the levels of cuticular hydrocarbon sex pheromones. The fact that bacteria contribute to the odor of animals makes it likely that they play a general role in mating preference.

The microbiota also plays a role in post-zygote-stage reproductive success. When recently diverged wasp species were crossbred, the hybrids died during the larval stage. Antibiotics rescued hybrid survival. The authors offered the following conclusion. "In this animal complex, the gut microbiome and host genome represent a co-adapted hologenome that breaks down during hybridization, promoting hybrid lethality and assisting speciation" (89).

The "hologenomic basis of speciation" was also shown in two subspecies of house mice (90). Hybrid mice displayed aberrant immune gene expression and increased intestinal pathology. The authors stated their conclusion as follows. "These results provide unique insight into the consequences of evolutionary divergence in a vertebrate hologenome, which may be an unrecognized contributing factor to reproductive isolation in this taxonomic group."

CONCLUDING REMARKS

Although the hologenome concept is now widely accepted, it was initially met with considerable criticism. The first criticisms came from some coral biologists who claimed that the concept was based on the incorrect assumption that bacteria protect corals against bleaching. However, the hologenome concept was never based solely on this assumption. Furthermore, it was subsequently clearly shown that bacteria do protect corals against bleaching (91). A more substantial criticism was that the microbiome was not conserved with sufficient fidelity to play a role in evolution. The data are now clear that at least part of the microbiota (the core) is highly conserved. It is, in fact, the balance between the conserved and dynamic microbiotas that aids holobionts in adapting and evolving while conserving essential genes. Another critical claim was that holobionts are nothing more than environmental systems, such as small ponds. However, the close interaction between the microbiota and its host, the fact that the microorganisms in the holobiont do not resemble those in the surrounding environment, and the reproduction of the holobionts all define the holobiont as a unique biological entity that represents a level of selection in biological evolution.

Biology is undergoing a paradigm change. Animals and plants can no longer be considered individuals. All are holobionts, consisting of a host and numerous symbiotic microbes. The hologenome concept is a fundamental framework for understanding the interaction between hosts and microbes in the health, disease, and evolution of holobionts.

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