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Evolving Ecosystems: Inheritance and Selection in the Light of the Microbiome

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The importance of microorganisms in human biology is undeniable. The amount of research that supports that microbes have a fundamental role in animal and plant physiology is substantial and increasing every year. Even though we are only beginning to comprehend the broadness and complexity of microbial communities, evolutionary theories need to be recast in the light of such discoveries to fully understand and incorporate the role of microbes in our evolution. Fundamental evolutionary concepts such as diversity, heredity, selection, speciation, etc., which constitute the modern synthesis, are now being challenged, or at least expanded, by the emerging notion of the *holobiont*, which defines the genetic and metabolic networks of the host and its microbes as a single evolutionary unit. Several concepts originally developed to study ecosystems, can be used to understand the physiology and evolution of such complex systems that constitute ''individuals.'' In this review, we discuss these ecological concepts and also provide examples that range from squids, insects and koalas to other mammals and humans, suggesting that microorganisms have a fundamental role not only in physiology but also in evolution. Current evolutionary theories need to take into account the dynamics and interconnectedness of the host-microbiome network, as animals and plants not only owe their symbiogenetic origin to microbes, but also share a long evolutionary history together.

Key Words: Microbiome, Holobiont evolution, Missing heritability, Adaptability, Allostasis.

Ecological Evolution

The Object of Selection

Natural selection has been a controversial subject since Darwinian times. With the discovery of genes and the formulation of the modern synthesis some scientists thought that selection should act upon genes, since they were the subject of mutation and thus were the raw material of evolution (1). However, evolutionary biologists such as Ernst Mayr and Sewall Wright argued that selective pressures do not only act on single genes. Based on the observation that many genes' functionalities depend on the presence of other genes, Mayr and Wright proposed that the whole genome of an organism was the target of selection (2,3). This idea prevails, along with Mayr's definition of species, and both are among the few lasting modifications to the basic Darwinian theory of evolution. Nevertheless, we now recognize a vast number of ways in which selection acts apart from genetics. For example, selection can act upon the morphology of an organism (which may not depend entirely on genetics), on its behavior, on its metabolic capabilities, and over all of these (and many more) factors at the same time (Multilevel Selection Theory). It seems now that the object of selection is the

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individual as a whole and therefore, in addition to its genetics, we must also take into account the organism's capacity to modify its environment to its advantage, its heritage, and ultimately the interactions with individuals of the same species or from other species that change its survival and reproduction capabilities. Hence, if we consider this wholeness for each organism, we will be delving into the complex subject of ecosystem evolution.

An ecosystem can be described as a set of communities of different species of organisms living in the same place, at the same time, with a constant interchange of matter and energy. This constant flux of matter and energy opens up the possibility to determine the boundaries of an ecosystem mathematically, as fluxes inside an ecosystem must be greater within the community than with external components. It is important to mention that this interchange of matter and energy occurs between the biotic and abiotic components altogether, and the mechanisms by which the interchange occurs can also modify the environment itself. A change in environment can consequently change the dynamics and composition of the living parts of an ecosystem, creating a feedback loop where change is the only constant. Always depending on the intensity, frequency and type of changes, also known as perturbations, ecosystems can often withstand them. Sometimes the biotic composition of the ecosystem will remain unchanged, but often it will be forced into other equilibrium states in which the abundances, interactions and chemical reactions of the organisms that compose it, need to adapt to the new imposed challenges (4).

There are many spatial scales in which ecosystems can be defined. It is still a matter of debate where to draw the line in size (and in that sense the comparative measurements of fluxes mentioned above could be helpful), but research groups have defined and studied ecosystems as small as a piece of cheese (5), or as vast as the Biosphere (6). Nevertheless, a new kind of ecosystem is at hand: The *holobiont*, which is defined by the genetic and metabolic networks of the host and its microbes as a single evolutionary unit. The main reason the holobiont defies the standard concept of an ecosystem is because the "environment" in which the species that comprise it thrive, is another living organism. This is not a trivial factor. The fluxes between biotic and abiotic components in traditional ecosystems depend almost entirely on the abilities of the biotic to extract, use or transform the abiotic. However, in holobionts this exchange is highly regulated by the host, for example through its immune system (7). In traditional ecosystems, perturbations often come either from a catastrophic natural event (disruptions such as earthquakes, fires, floods, etc.) and/or are caused by the biotic components themselves. In holobionts this may not always be the case, as the host can quickly introduce or remove carbon sources and other metabolites through a change in diet, or even increase or decrease the diversity of the ecosystem through ingestion of pro/anti biotics. The holobiont concept defines the object of evolution as the fusion of the nuclear genome of the host, its organelles, and its microbiome. As an evolutionary unit, selective pressures applied to the nuclear genome prevent deleterious mutations and promote favorable ones. Selection over the microbiome encourage the development of beneficial microbes (mainly in digestive, immune and sexual processes) (8), while simultaneously suppress pathogenic organisms. It is also important to understand that the role of specific microbes in host biology is context dependent. This means than even though a strain is considered neutral under normal circumstances, its role can change in a different condition. These organisms, known as *amphibionts* or *pathobionts*, are known to become pathogenic in response to inflammation, antibiotics, infections and other types of stressful conditions (9). It has been shown, for example, that the highly antibiotic resistant bacterium *Clostridium difficile* is a common dweller of adult intestines, but it is only under certain, still unclear, conditions that it becomes pathogenic (10). In summary, if selection applies at the level of the holobiont, then dysfunctionalities (host or microbiome related) will impact the survival and reproduction of the individual, undergoing natural selection and thus evolving as a unified entity.

On the Origins of Complexity

By reconciling Mendelian genetics and Darwinian Natural Selection, the modern synthesis theory of evolution explains: a) the diversity between individuals from a genetic point of view, b) how natural selection can filter such genetic variations, and c) how new species originate through gradual and cumulative genetic mutations and recombination. However, it does not explain how complex organisms arise. For example, the modern synthesis cannot explain how eukaryotic cells were formed by the successive merging of prokaryotic cells (11). These limitations in the Darwinian Theory of evolution are understandable, as at the time of its formulation microbes were prominently catalogued as agents of disease. Additionally, the technology available to look into the genetics of such microbes was far from being developed. However, the origin of the eukaryotic cell is now widely accepted as being the result of endosymbiosis, and now we have a less biased view of microbial communities as well as many tools to study them.

The term "holobiont" was first proposed by Lynn Margulis (12) and derives from the Greek word *holos*, meaning *whole*. This term was originally proposed to describe symbiotic associations between organisms throughout most of their lifetimes, and now it refers to the collection of microbes associated with a host plus the host itself. In 1967 Lynn Margulis also demonstrated the endosymbiotic emergence of eukaryotic cells, proposed