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REVIEW ARTICLE

Microbiome, holobiont and the net of life

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Abstract

Holistic emerging approaches allow us to understand that every organism is the result of integration mechanisms observed at every level of nature: integration of DNA from virus and bacteria in metazoans, endosymbiotic relationships and holobionts. Horizontal gene transfer events in Bacteria, Archaea and Eukaryotes have resulted in the chimeric nature of genomes. As a continuity of this genomic landscape, the human body contains more bacterial than human cells. Human microbiome has co-evolved with the human being as a unity called holobiont. The loss of part of our microbiome along evolution can explain the continuous increasing incidence of immune and inflammatory-related diseases. Life is a continuous process in which the organism experiences its environment and this interaction impacts in the epigenetic system and the genomic structure. The emerging perspectives restitute the great importance of Lamarck's theoretical contributions (the *milieu*) and Darwin's pangenesis theory.

Keywords

Biome depletion, epigenetics, holobiont, microbiome, net of life

History

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> Nothing in Evolution Makes Sense Except in the Light of Biology
>
> E. Cervantes

Introduction: The fundamental naturalist

Evolution refers to the natural origin and transformation of the living inhabitants of the Earth throughout its geological history (Ho, 1998). Evolution by natural processes was a fact studied by many naturalists in France around the eighteenth and nineteenth century. Among the prominent figures who wrote about evolution we can mention Linnaeus, who accepted a limited transformation of species, G.L. Buffon, Frédéric Gerard, Geoffroy Saint Hilaire, Karl Von Baer, Pierre Trémaux (punctuated equilibrium and allopatric speciation) among others (Salvucci, 2012).

Biology also owes much to a scientist who in 1809 published a complete theory of evolution, Jean Baptiste Pierre Antoine de Monet, Chevallier de Lamarck. Lamarck was one of the first naturalists who used the word Biology in the modern sense (Coleman, 1977; Stafleu, 1971). He could develop a methodology and a new practice because he had covered a multitude of scientific disciplines such as botany, paleontology and zoology (Olarieta Alberdi, 2011; Sandín, 2010; Stafleu, 1971).

Lamarck settled a materialistic notion of life. Living matter moved by itself without an outside intervention. Life has the ability to (re)create itself and transform itself and it exists as a continuous process, a ''verb'' (Margulis & Sagan, 1995). This creation, therefore, is an internal act which Varela & Maturana called later *autopoiesis*. It is an intrinsic property of life emerging from the material itself and it is not rooted in anything supernatural: ''Nature has the means and the power needed to produce for themselves what we admire in it'' (Lamarck, 1809; Varela et al., 1974).

The causes of unjustified and exaggerated criticism against Lamarck could be that the work of the French biologist has not been translated into several languages and therefore is less read. This situation leads to simply repeating the ''official history''. In addition, many times the Lamarck's legacy is misunderstood or minimized to ''inheritance of acquired characteristics'' and ''use and disuse of organs'' hypotheses. But many authors studied more deeply the work of Lamarck and consider it not to be totally wrong (Handel & Ramagopalan, 2010; Ho, 1998; Olarieta Alberdi, 2011; Sandín, 2010).

Lamarck (and Biology in his time) focuses his attention on the environment, thus the concept of environment (*milieu*) in Lamarck is extraordinarily complex. He could introduce in biology concepts used in physics expanding the capacity of understanding. He stated a theory of fluids and made a classification in liquids and elastic fluids. The last ones were sub-classified as those which can be packaged (gases) and those which cannot (electromagnetic force, heat, light and other energies). He initiated a unified study of physics and biology. From his point of view, life implies physical and organizational components. The *milieu* is not only external but internal, there is no separation between these two faces because fluids are penetrating and organisms are in permanent communication with the environment as a unity (Lamarck, 1816; Olarieta Alberdi, 2011; Stafleu, 1971). Lamarck's study constitutes an anticipation of further advances. But the

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original idea was lost and the concept was misrepresented and reduced along time and today it mostly means only the ''outside'' circumstances (Canguilhem & Savage, 2001; Olarieta Alberdi, 2011). But life of a living being is the result of two factors: the self and the environment. ''At every moment, the vital phenomenon does not reside in the living being nor in the environment, but rather on the current relations of living being and the environment'' (Le Dantec, 1911).

In a neo-Darwinian view, the organism does not live by itself. It is a means, a vehicle, used by the genes. In turn, the inheritance, which resides only in the genes, is an individual concept that is not related to the environment and which consists of a set of characters that are innate, not acquired (Olarieta Alberdi, 2011; Sandín, 1997). It was pointed out that this view, included in the Synthetic Theory, is a new version of the old idealist metaphysics considering as the ''core'' the genes, while the organism (in contact with the environment) is undervalued. The organism just houses the genes and its development is the unfolding of a ''genetic programme'' encoded in the genome (Lakhotia, 2008; Olarieta Alberdi, 2011). Random mutations produce new characters and natural selection working on them, plus time will make new structures and, finally, new species emerge. These ramblings carry implicit a metaphysical separation of body and soul and mysterious impulses (the selfishness of genes propelling evolution). Under this view, life is studied without living beings. This is because life is systematically denied when are the organisms that actually move, grow, adapt, change, transform and thus evolve as a continuity with the environment.

Darwin includes the inheritance of acquired characteristics in his book ''*On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life*'', but later Darwinism does not accept that acquired traits can be inherited. However, the current knowledge shows that genomes are mosaics of genes containing bacterial and viral genes that have been acquired along evolution. There is increasing knowledge about acquired genes and characters which are heritable (Georgiades & Raoult, 2012; Hecht et al., 2010; Raoult, 2010; Raoult & Koonin, 2012).

The scientific validity and the tautological character of natural selection can now be discussed and many authors have extensively worked on these topics (Abdalla, 2006; Cervantes, 2011; Himmelfarb, 1962; Peters, 1976; Salvucci, 2012; Sandín, 2010, 1997; Vallejo, 1992). The old fashioned view does not correspond with the current state of knowledge. Nowadays, it becomes increasingly difficult to define and delimit a gene (Buchanan et al., 2009; Lakhotia, 2008, 1997). For many years the attention was focused on DNA as the answer to heredity and evolution. But the development of metabolomics, proteomics, epigenetics or *evo-devo* was necessary to get a better understanding. Focusing only in DNA was a reductionist and then incomplete approach. Genes are the result (as a memory) of the existence of a living being in a specific environment. Since they are not ''entities'' in a coherent sense, attributing attitudes like selfishness is a result of a projection of human behavior to nature. It is clear that no gene ever functions in isolation. Furthermore, no organism exists and evolves alone but in a net of life. For instance, the study of microbiome gives more substance to holistic visions and focuses on the environment as an essential and decisive factor in evolution.

The emerging perspectives based on recent findings allow us to restitute the great importance of Lamarck's theoretical contributions that consider the environment as an active part of the evolving organism. The great importance of viral integration along evolution, horizontal gene transfer (HGT), epigenetic mechanisms, holobiont evolution and new holistic perspectives that consider the integration of organisms, allow biology to retake a road that it has left. Along the way, life is discovered as an intricate network that evolves as a whole.

The net of life

The high prevalence of HGT events in Bacteria, Archaea and Eukaryotes has resulted in the chimeric nature of genomes. Different parts of a genome can have different evolutionary histories and it is difficult to identify a single common ancestor for the gene repertoire of any organism. Whole genomic sequences from various metazoan phyla suggest a chimeric origin for its major groups due to the presence of HGT and hybridization (Syvanen & Ducore, 2010). Ramulu et al. (2012) have pointed out that many proposals have emerged replacing the tree-like pattern with more complex models such as the ''reticulate evolution'', ''synthesis of life'', ''web of life'', ''network of life'' among others. Moreover, the evolution of species including metazoa is described like a rhizome by some researchers reflecting various origins of genomic sequences in each species (Georgiades & Raoult, 2012).

New perspectives take into account that genetic mosaicism is a natural condition of the genomes. Vertically heritable HGT is wide distributed in nature and involves all the domains of life (Archaea, Bacteria and Eukarya) (Hecht et al., 2010; Hotopp, 2011). *Wolbachia* is an endosymbiotic bacterium. *Wolbachia* gene transferences into the genomes of diverse invertebrate taxa have been identified. An entire bacterial genome (~1.4 Mb) was transferred into *Drosophila ananassae* Hawaii 2 L chromosome (Hotopp et al., 2007). Also, this transference to a wider range of insects (Hemiptera, Diptera, Coleoptera and Hymenoptera) has been described (Fenn et al., 2006; Hotopp, 2011; Hotopp et al., 2007).

HGT events among eukaryotes have also been identified. In animals, cases of eukaryote-to-eukaryote HGT include the acquisition of P elements by *Drosophila melanogaster* from *Drosophila willistoni* (Daniels et al., 1990; Hotopp, 2011; Ramulu et al., 2012) and the transfer of entire genes of carotenoid biosynthetic pathway from fungi (Moran & Jarvik, 2010) and 12 genes from bacteria to *Acyrthosphion pisum* (Nikoh et al., 2010; The International Aphid Genomics Consortium, 2010). The genomes of nematodes present genes from Bacteria, Fungi and Animalia (Hotopp, 2011; Kikuchi et al., 2011; Ramulu et al., 2012). For instance, *Pristionchus pacificus* contains high number of genes found in insects (Rödelsperger & Sommer, 2011) and *Heterodera glycines* contains a biosynthetic pathway for vitamin B6 from bacterial origin (Craig et al., 2009).

HGT can occur in human germ cells. For instance, heritable HGT was described in humans from the mitochondria-derived mini-circles to the eukaryote *Trypanosoma cruzi* (Hecht et al., 2010; Hotopp, 2011). This fact supports that many microorganisms considered parasites have an evolutionary history connected to their host. Thus, the fact that some microorganisms can cause an illness in the host can be assumed as a normal situation in evolution. The authors remark that heterogeneous mini-circle sequences were distributed randomly among families, with diversity increasing due to subsequent rearrangement of inserted fragments. New genes and pseudogenes were identified confirming the contemporary transfer of eukaryotic DNA to the human genome and its subsequent inheritance by descendants (Hecht et al., 2010).

Human genome sequencing has demonstrated the high content of bacterial- and viral-related genes including many retrotransposons (Hotopp, 2011). Human endogenous retrovirus element HERV-L is related distantly by homology to foamy viruses (Gifford & Tristem, 2003). Recently reported cases show the presence of endogenous viral elements in animal genomes from different families (Bornaviridae, Filoviridae, Bunyaviridae, Flaviviridae, Parvoviridae, Hapadnaviridae) (Holmes, 2011; Katzourakis & Gifford, 2010), lentivirus in primates (Gifford et al., 2008; Gilbert et al., 2010) and integration of ancient bornavirus and ebolavirus/marburgvirus sequences in vertebrate genomes (Belyi et al., 2010). The endogenous retroviral populations (ERVs) of reptiles, birds and mammals show significant differences and this is related to specificity in functional sequences (Johnson & Coffin, 1999). We can assume that the incidence of HGT is higher than it was supposed and it has a central importance in evolution of microorganism and metazoan hosts.

The genomic structure is fluid and exists in a dynamic equilibrium between genic and cellular processes. The DNA conformation is the result of the continuous feedback between an organism and the rest of living beings and the environment in a net of mutual building. Heredity does not reside solely in the DNA of the genome; it resides also in an epigenetic cellular state.

Epigenetics

Every living organism exists because its structure and metabolism are adapted. There is a flexibility that allows them to adapt to environmental variability. Responses involved in this event are directed by the genome, but also epigenetic processes are involved in the regulation of the system. The idea of allelic variants (''Mendelian'' genes) being the only source of variability within a population is outdated knowing the complexity of the genome. Although almost all genes are transcribed, few of them are translated into proteins. Much of the differences between individuals do not respond to allelic differences of some genes but to changes in the organization of the genome: number of repeated sequences, inversions and deletions related to the response to the environment mediated by epigenetic mechanisms (Heredia Doval, 2010; Jablonka & Raz, 2009).

Conrad Hal Waddington (1905–1975), was the first to use the word ''epigenetic'' to define that gene interaction with the environment leads to the generation of a particular phenotype. Epigenetic changes are based on a wide variety of mechanisms that reduce, activate or inactivate genes and regulatory networks (Liu, 2007). All these effects are the result of methylation of cytosine residues in DNA, remodeling of chromatin structure and RNA-mediated regulation. The interaction of all these mechanisms results in a particular metabolic or phenotypic behavior in response to a given environmental change or stimuli. These events generate an induced phenotype or character that can be inherited to future generations (Bossdorf et al., 2008; Jablonka & Raz, 2009). Examples of epigenetic heritable mechanisms are observed along nature and they show that environmental factors may increase the genomic flexibility and it could be maintained through generations (Liu, 2007) (Table 1).

The final metabolic and genetic response varies from cell to cell and it depends on the environment. In mice, environmental toxins and dietary supplements induce changes in DNA that are inherited. Mice with the same genotype do not express the genes in the same way as shows the case of coat color. *Avy* variety is dominant, caused by an insertion of a retrotransposon in a specific region (no random mutation).

Table 1. Epigenetic effect in different organism that persist in subsequent untreated generation.

Organism	Effect	References
Arabidopsis thaliana	Short-wave radiation increases the somatic homologous recombination in a transgenic reporter gene.	(Molinier et al., 2006)
Yeast	Prion sup35 activates the expression of ''silent'' gene changing the fidelity in the translation process	(Chernoff, 2001; Shorter & Lindquist, 2006; True & Lindquist, 2000)
Prions	Store and transmit acquired information by β-sheet conformations of certain proteins	(Maury, 2006)
Drosophila melanogaster	Decrease in heat shock protein HSP90 levels (involved in chromatin regulation) in response to environmental changes causes stable heritable phenotypes up to 4 generations	(Ruden & Lu, 2008)
Rat	Exposure to glucocorticoids or a low-protein diet causes changes in the expression of liver enzymes, elevated blood pressure and endothelial dysfunction	(Langley-Evans, 2000; Jensen Pena et al., 2012)
Humans	DNA methylation, histone modification and changes in microRNA involved in relationship between grandparents' nutrition and diabetes risk in their grandchildren. Inheritable microbiome is related with epigenetic changes and inflammatory response.	(Kaati, 2002; Myles et al., 2013)

This results in the mice variety *yellow*. When this promoter is silenced, *agouti* variety occurs. Some mice are spotted, i.e. both color stains that result from epigenetic silencing. Dietary changes during pregnancy cause changes in the proportions of yellow mice. This inheritance is the result of an incomplete epigenetic pass to the germline (Morgan & Whitelaw, 2008).

Gluckman et al. (2008) reviewed how early life events may be involved in susceptibility to chronic diseases, and also emphasized the concept of environmental plasticity including some examples where the environmental influences have heritable effects. Moreover, epigenetic marks such as DNA methylation, histone modification and changes in populations of microRNA seem likely to be involved in relationship between grandparents' nutrition and diabetes risk in their grandchildren (Kaati et al., 2002; Myles et al., 2013).

Epigenetic mechanisms were studied some time ago by many naturalists. Plant breeders including Luther Burbank (1849–1926) and Ivan Michurin (1855–1935) created plants with heritable characteristics acquired from both parent plants tissues. In addition, there are about 500 publications of these types of hybridization experiments mainly published in Russia. When several ''Western'' scientists have repeated some experiments and arrived at the same results, it was confirmed that it is possible to create variants which acquire persistent characteristics across generations (Heredia Doval, 2010; Liu, 2007).

Darwin took the idea of inheritance of acquired characters from Lamarck and postulated the theory of pangenesis to explain it: when an environmental change occurs, ''gemmules'' that are expelled by cells circulate through the body carrying the information necessary for the response, including germ cells. Currently, as a continuation of those ideas, it is postulated that endogenous retroviral vectors would capture RNA of somatic cells transducing then to germ cells. There, the RNA would be transcribed to DNA (reverse transcription) and recombined into the genomic DNA (Steele et al., 1999).

According to Weissmanń barrier hypothesis, the germline and somatic cells are totally independent and the transmission of acquired characters to offspring is impossible. However in the 70 s, Steele found that some of the offspring of mice were born with immediate responsiveness to an antigen that had been previously inoculated to a parent. Steele suggested the transmission of information regarding specific variable regions of the antibodies of the immune system to offspring. These regions rapidly mutate in an infectious state producing a variety of closely related antibodies against the antigens of an infectious agent (Steele et al., 1999).

Steele proposed his theory called *Somato germline loop*. The activity of endogenous retroviral particles would be able to transform the RNA of antibody genes in B lymphocytes (somatic line) into DNA (by viral transcriptase reverse) and encapsulate this material in a protein coat that leave the cell and go to the gonads (germ line). Finally, the viral particles enter the germ cells and insert information conferring an antigen pre-response. This mechanism is supported by the high presence of endogenous retroviruses in the genomes (8% in our species), the possession of reverse transcriptase in viruses and eukaryotes (telomerase) and the similarity to the life cycles of ''free'' retroviruses (Heredia Doval, 2010; Liu, 2007; Steele et al., 1999, 1979). It was also demonstrated that some conditions or susceptibilities are inherited by the offspring from the mother by epigenetic mechanisms (Myles et al., 2013).

The long list of examples of epigenetic mechanisms validates this mechanism as the key of life and, therefore, the evolutionary process. Epigenetics and HGT participation in both mechanisms of viruses, retroviruses, and several mobile genetic elements show again the vitality of Lamarckian explanations in the evolutionary process.

Virus and bacteria: building the net

Many authors insist on an ''armed race'' between viruses, bacteria and metazoans (Dobata, 2012). This is an anthropocentric way of thinking. Even worse, it is a way of thinking within a particular political ideology. This metaphoric language assumes that nature follows the political doctrines of a particular group of people. This way of studying nature can be questionable or reprehensible.

More than a struggle, strategies, weapons, selfishness, cheating, etc., nature shows a pattern of continuous association and integration. The integration along the evolutionary history is proven in the genome and the fact that symbiogenesis is a fundamental mechanism of evolution. It has become clear in the past two decades that gene flow between distant lineages and the consequent genomic chimerism might have a notable role in the evolution of eukaryotes (Aravind et al., 2012; Feschotte & Gilbert, 2012; Gilbert et al., 2010). In this gene flow, Viruses participate as gene weavers or builders (Hamilton, 2006). Viruses have the ability to integrate to cell genomes and they play a fundamental role in life evolution. Furthermore, they constitute the foremost gene pool in the planet. The continuous sequencing of virus genes shows that they mostly have no similarity with other known sequences. This supports the fact that they are the pieces that were inserted in the genomes (Rosario et al., 2009).

Virus gene rearrangements participate and underlie the process of generation of new structures, metabolic ways and gene regulation that result in evolutionary changes (Casjens, 2003; Feschotte & Gilbert, 2012; Johnson, 2008; Johnson & Coffin, 1999; Tristem, 2000). For instance, the action and expression of a gene derived from an endogenous retrovirus participates in the formation of placenta in mammals (Mallet et al., 2004). Retrotransposons are involved in the regulation of genes related to the histocompatibility in humans, other mammals and invertebrates (Ding & Lipshitz, 1994; Kim et al., 1989; McDonald et al., 1997). Viral sequences in the genome of metazoan have content with ''biological sense'' carrying elements of complex genetic information (Forterre, 2010; Hamilton, 2006; Hunter, 2008; Mallet et al., 2004; Mattick & Gagen, 2001; Sandín, 1997; Vitali et al., 2003). The integration of a complex system within another, i.e. the integration of genetic sequences in different individuals, changes deeply the process and the identity of the character. These changes alter the *meaning* of the process. These sequences are involved in regulating gene expression or codifying very similar proteins in different animal groups (Jamain et al., 2001; Medstrand & Mager, 1998; Mi et al., 2000; Villarreal & DeFilippis, 2000). The presence of these viral-related genes in prokaryotes and eukaryotes highlights

the importance of viral integration as a key mechanism in evolution of multi-cellular organisms.

Viruses are related to regulatory and structural functions in Bacteria. For example, the emergence of microcompartiments (Yeates et al., 2007). Organelles as carboxysome consist of thousands of protein subunits assembled in a viral-like structure or scaffold (Kerfeld et al., 2005). The insertive nature of virus and their known ability to insert themselves into chromosomes (integrating complex systems) is what allowed the structural, morphological change and the emergence of carboxysome.

All these observations bear out that the representation of the evolutionary pathway as a tree with a single common ancestor is incorrect. Raoult recommends that the evolution of species must be understood like a rhizome (Raoult, 2010). The evolutionary history of different organism as a rhizome was reported (Georgiades & Raoult, 2012; Merhej & Raoult, 2012). Similarly, an organelle like mitochondria has numerous ancestors (Georgiades & Raoult, 2012).

Viral activity has great importance in the adaptation of the host beyond the genetic trace. The virome is the viral community associated with human hosts. A study that compared cystic fibrosis and non-cystic fibrosis individuals has revealed that the disease is defined by metabolism. The non-diseased airway virome contains a more diverse viral community and a set of shared core metabolic functions, which differ from that found in the virome from the diseased airway (Willner et al., 2009).

It becomes clear that a theory considering the integration of complex systems (developed by von Bertalanffy, 1950) is an alternative to build a strong theoretical framework more adjusted to facts and recent discoveries.

Next level of integration: microbiome and holobiont

As a continuity of the genomic landscape, the human body contains more bacterial cells than human cells. *Microbiome* is the collective indigenous microbes associated to a host (Arumugam et al., 2011; Dominguez-Bello & Blaser, 2008; Hooper et al., 2013; Lederberg & McCray, 2001). Human gut microbiome is taxonomically complex and this ecologically dynamic community participates in several processes and mechanisms. These include vitamin production, digestion and utilization of carbohydrates and lipids, energy homeostasis, tryptophan metabolism regulation, integrity of intestinal barrier and angiogenesis, promoting the correct development of the capillaries network (Dominguez-Bello & Blaser, 2008; El Kaoutari et al., 2013; Kau et al., 2011). The main members are bacteria from phyla *Bacteroidetes* and *Firmicutes* (Eckburg et al., 2005; Xu et al., 2007). The microbiome metabolism is essential for the development, maturation and regulation (stimulation and suppression) of the immune system. It participates from the first day of life in the development of Gut-associated Lymphoid Tissue (GALT) and, particularly, in the B immune system (Hattori & Taylor, 2009; Hooper et al., 2013; Kau et al., 2011; Mai & Draganov, 2009; Mazmanian et al., 2005). Also, the dietary intake shapes microbial community structure. Microbial signals in the form of microbe-associated molecular patterns (MAMPs) modify local mucosal immune responses through innate signalling pathways such as the inflammasome (a complex multi-protein receptor related to inflammatory or apoptosis processes depending on the stimuli) or Toll-like receptors (Kau et al., 2011). These interactions develop a tolerance or recognition between the two associated counterparts.

Immune system is the evolutionary interface that was built in a continuous feedback with the organisms and the environment. Germ-free mice (microbiome-free mice) have an underdeveloped immune system, lower metabolic rates and longer digestion times than those that have a normal microbiome. Many studies have confirmed that alterations of this microbiome affect human health and promote disease state or disbiosis (Evans et al., 2013; Ley et al., 2005; Rogler, 2010; Tlaskalová-Hogenová et al., 2004). Microbiome and human host have co-evolved. The hologenome theory considers an organism and all of its associated symbiotic microbes, including parasites, mutualists, synergists, and amensalists as a unity called holobiont (Rosenberg & Zilber-Rosenberg, 2011). The holobiont is a result of the co-habitation and symbiosis of different organisms. Among them, we can include the virome that is integral part of this ''superorganism''. In this sense, it can be considered a result of the process known as *symbiopoiesis* (Margulis & Fester, 1991; Rosenberg & Zilber-Rosenberg, 2011). The complex metazoans are a result of integration of systems and the close association between living beings which implies physiological and, ultimately, genetic integration (Gilbert et al., 2010; Margulis & Chapman, 1998; Margulis & Fester, 1991; Margulis & Sagan, 1995; Rohwer et al., 2009; Salvucci, 2012; Savinov, 2012). Savinov has developed the concepts of autocenosis and democenosis to explain these levels of integration (Savinov, 2012). Also, he has developed the principle of obligatoriness of symbiosis and symbiogenesis since the evolution of all multi-cellular and most unicellular organisms are always based on the integration with other organisms (Savinov, 2012). Windsor (1997) remarks that the host-symbionts unity is the real organism (which he calls ''biocartel'') and considers that single-entity free living species are abstractions. Baluska (2009) stated that repetitive cycles of duplication, aggregation/merging are driving the increase in biological complexity during metazoan evolution.

These evolutionary perspectives ponders that every organism is a result of integration and this ''superorganism'' adjusts and transforms itself according to environmental changes causing evolution of the entire unity.

Microbiome in health and disease

Microbiome evolves along the human life. This microbiome is continuously influenced by environment. Mode of delivery and feeding type (breast or formula) are factors that impact on the composition and diversity of microbiome and their evolution (Dominguez-Bello et al., 2010; Johnson & Versalovic, 2012). Microbiome of vaginally delivered newborns represents the maternal vaginal and intestinal microbiome (*Lactobacillus*, *Prevotella*, *Escherichia*, *Bacteroides*, *Bifidobacterium*), while cesarean delivered newborns exhibit a microbiome representative of the maternal skin (*Staphylococcus* spp, *Propionibacterium,* and *Corynebacterium* spp). Breastfed infants have higher numbers of *Bifidobacterium* and

Lactobacillus in their gut than formula-fed infants (Dominguez-Bello et al., 2010). Also, the latter have increased colonization by *Clostridium* spp. and in particular *C. difficile*. These factors are important in the risk of developing allergies and inflammatory-related diseases. Vaginal delivery and breast feeding are related to lower risk to develop allergies, diarrhea, necrotizing enterocolitis, asthma, type-2 diabetes and obesity (Johnson & Versalovic, 2012).

The metabolism of microbiome and the host are intertwined constituting an integrated organism (Savinov, 2012). In fact, any organism lives together with other organisms; in this sense, no organism is a free-living specie *sensu stricto* (Windsor, 1997). Many bacteria can largely persist inside eukaryotic cells and they have access to metabolic function of the host cells (Proal et al., 2009). Viruses can also do the same. For example, herpes virus 1 lives in nervous system cells of 95% of human world population. This suggests the active association between microorganisms and the metabolic functions of the whole holobiont. In humans, microbial influence is not limited to immune system. Many studies reveal the importance of microbiome on the called gut–brain axis. Altered microbiome influences on anxiety and depressive behavior. Microbiome participates decisively in metabolism of GABA and serotonin, both major neurotransmitters related with anxiety, depression, and mood. Also, anxiety disorders are related to inflammatory state (Foster & McVey Neufeld, 2013).

Life exists as a net of relationships and organisms considered normally ‘‘parasites’’ are also part of our microbiome. They constitute 80% of known species in the world (Vannier-Santos & Lenzi, 2011). The continuous separation from some parasites, which were part of our microbiome, provokes that part of the world population can be severely affected by an infection with them. However, in certain regions, people can co-habit with these ‘‘old friends’’ with no detrimental effect or even improving the nutritional or health status (Cremonini & Gasbarrini, 2003; Li et al., 2007; Marini et al., 2007). Correale & Farez have demonstrated that multiple sclerosis parasite-infected patients showed a significantly lower number of exacerbations and minimal variation in disability scores after 4.6-year follow-up period (Correale & Farez, 2007). Parasites are cohabitants and the integration with this counterpart also drives the evolution of host organisms (Vannier-Santos & Lenzi, 2011; Windsor, 1997).

In recent years, the human holobiont has suffered the increase of emerging diseases. Biome Depletion Theory takes into account the holobiont and it can explain the continuous increasing incidence of immune and inflammatory-related diseases caused by the westernized way of life and diets (Kinross et al., 2008; Rook, 2009). The theory postulates that the increasing medical care, the technology development and changes in food processing and diets cause a loss and separation of our associated microbiome. An epidemiological transition occurred. As a result, the allergic disorders, autoimmune and inflammatory diseases have increased because of an over-reactive immune system (Figure 1) (Bakhtiar et al., 2013; Garn & Renz, 2007; Kau et al., 2011; Salvucci, 2013).

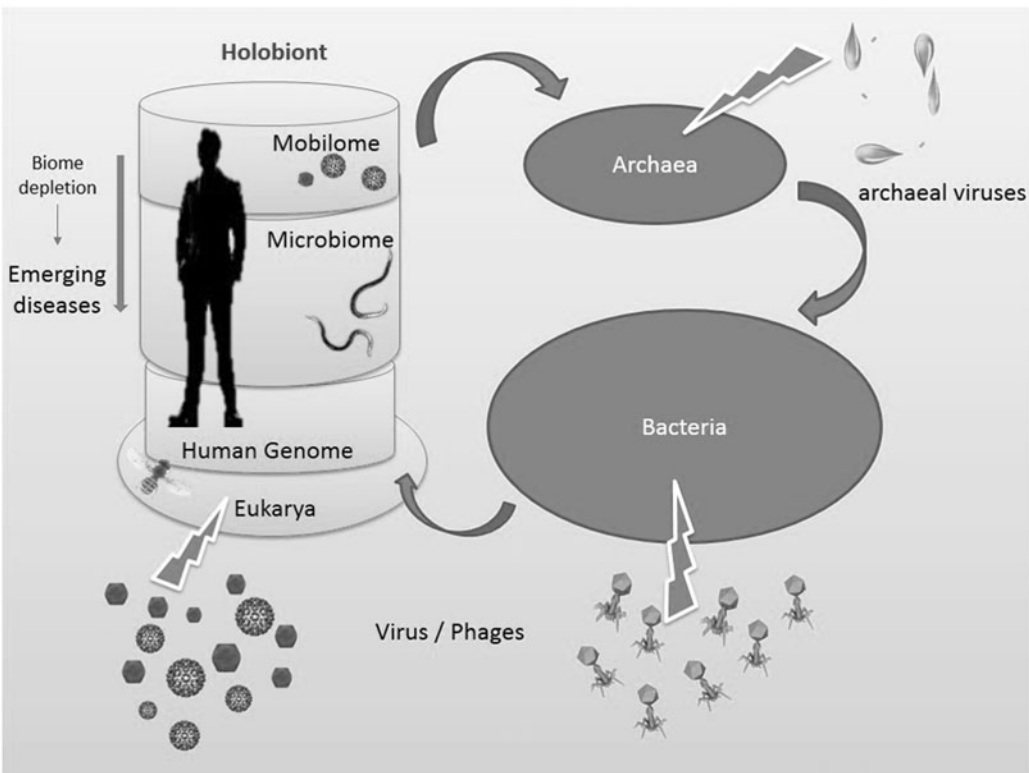

Figure 1. The human holobiont is the result of integration mechanisms along evolution. Integration of viruses allows the emergence of different cell types. Human genome contains genes from virus and bacteria. As a continuity of this landscape, human holobiont emerged by integration of different complex systems: host, microbiome and virome. The loss of part of this microbiome results in an increasing incidence of immune and inflammatory-related diseases.

The lost partners include not only the commensal bacteria but also metazoans ''parasites'' (or cohabitants) and the virome. The genetic mobile elements that include plasmids, transposons, integrons and bacteriophages also participate in the adaptation and evolution of a defined holobiont. All these elements constitute a genetic pool called *mobilome* (Jones, 2010; Siefert, 2009). Mobilome participates in the genetic flux within the microbiome, a key factor for adaptive response to the environment (Figure 1).

In a holobiont, both counterparts establish stable metabolic and gene interactions. When a vital part of this superorganism is lost an unbalance occurred and the depleted holobiont cannot auto-regulate its immune system. The development of these diseases is a result of the combination of the necessary genetic background and the influence of microbiome (extrinsic factors) (Hunter & McKay, 2004; Proal et al., 2009; Raison et al., 2010; Tilg & Kaser, 2011).

Crohn's disease (CD) is a condition in which the lining of the gastrointestinal tract becomes inflamed, causing severe diarrhea and abdominal pain (Reddy & Fried, 2009). It was demonstrated that elimination of the intestinal helminthes promotes CD. Furthermore, the incidence of CD remains low and it is rare in underdeveloped areas where intestinal parasites are highly prevalent (Colombel et al., 2007).

Nowadays, helminthic therapies are emerging as an interesting alternative to restore the immunologic balance (Salvucci, 2013). These therapies are based on the feedback regulation of two main immune responses Th1 and Th2. Some parasites stimulate antigenic homeostasis developing a suppression of the response to weak antigens and, on the other hand, they activate T reg cells and induce higher levels of anti-inflammatory cytokine interleukin 10 (IL-10) (Fallon & Mangan, 2007; Hunter & McKay, 2004; Reddy & Fried, 2009). Autoimmune diseases like type-1 diabetes, artritis, lupus and chronic inflammatory diseases like inflammatory bowel disease (IBD), ulcerative colitis, asthma, diabetes or autism could be treated with a biome restoring process that is nowadays done by probiotic administration or helminthic therapies.

Obesity and metabolic syndrome are also other western epidemics related to microbiome depletion. Patients with these conditions present an altered microbiome. Obese subjects have lower proportion of Bacteroidetes and more Firmicutes than lean and healthy people (Aggarwal, 2013). The obese microbiome has an increased capacity to harvest energy from the diet and produces significantly higher total body fat (Ley et al., 2005; Turnbaugh et al., 2006). In addition, obesity in mice and humans is associated with the infiltration of adipose tissue by macrophages, $CD8^+$ T cells and $CD4^+$ T cells, and with the expression of inflammatory cytokines such as IL-6, IL-17, TNF-α and interferon-γ (Kau et al., 2011). Obese patients present increased levels of lipopolysaccharides (LPS) in serum causing endotoxemia which in turn leads to an increase in the concentration of the proinflammatory cytokines in various tissues and enhancing the symptoms of fatty liver. Supplementation with oligofructose stimulates the bifidobacterial growth and it lowers the uptake of LPS from the gut lumen by reinforcement of tight junctions of epithelial cells. This effect is also correlated with an improved glucose tolerance and insulin sensitivity (Cani et al., 2007; Kau et al., 2011; Tilg & Kaser, 2011).

In those diseases, immune system is unbalanced as a whole and we cannot find a biologic therapy, i.e. a probiotic or prebiotic or prebiotic-probiotic (a synbiotic), that could restore the separation of our partners in all patients but it is essential to find the best therapy for each case. For this, it is necessary to evaluate the particular microbiome profile in a huge range of patients from different regions and different microbiome-related diseases.

Recently, Myles et al. (2013) have confirmed that microbiome is a heritable acquired character. Epigenetic modification and microbiome structure in parents are heritable by descendants. The risk of over reactive immunity (developing inflammatory and autoimmune-related diseases) also depends on the environmental factors (mainly diet) of the parental generation.

The new findings seem to bear out Lamarck's basic propositions. Epigenetic mechanisms mediating non-random, directed genetic changes constitute not exceptions but essential evolutionary mechanisms. They reveal the complexity and dynamism of life and organism evolution in which integration processes are critical. Those processes alter genomes within the lifetime of all organisms (Ho, 1998; Steele et al., 1979). The inheritance with modification, Lamarck's idea of transformation, is not a simple process that can be explained as a projection of the differences within populations. The process that occurs in a ''fluid genome'' is not entirely random, but is subject to physiological and cellular control and has a ''meaning'' (Ho, 1998; Sandín, 1997). Gene jumping, recombination, HGT and other alterations of the genome are frequent responses to stress that enable them to adapt or adjust to new situations. Every character is the result of individual development of a particular generic hereditary principle. Gen rearrangements and also changes in cytoplasmic organization could be stably inherited, the latter independently of nuclear or cytoplasmic DNA (Ho, 1998; Jablonka & Raz, 2009; Malacinski, 1990; Ruden & Lu, 2008).

The organism faces its environment in a continuous *process* (the *milieu* from Lamarck). As a result of fine-tuning and modifying, heritable characters mediated by epigenetic mechanisms are imprinted. Also genome rearrangement occurs including integration of DNA sequences. All of them are passed on to subsequent generations. The organism actively participates in shaping its own development as well as the evolution of its ecological community. Microbiome is inherited and defined by the milieu.

Conclusions

Life is a continuous process of integration. These levels include the genomic, the organismal and the ecological levels. The genomic structure of organism reveals the fundamental role of integration and gene shuffling along evolution. Virus has a major role in this mechanism. Symbiopoiesis, as continuance, can explain the emerging of novel cell type and structures. Finally, no organism can live and exist alone but in continuity with environment and other organism constituting a net of life.

Microbiome is an integral part of the human holobiont which is part of the Net of Life evolving as complex systems

into other systems (Rook, 2009; Salvucci, 2013). The integration between host and microbiome defines the correct development of the whole unity. This integration includes immunologic, nutritional, endocrine and neurologic aspects. The loss of part of our partners causes the emergence of western diseases. Microbiome is an acquired heritable character and restoring or modulating it (by diet, prebiotics and probiotics therapies) can neutralize the effects of that damage.

Novel emerging approaches can retake many fundamental ideas of the old naturalist and open new insights about life and evolution. Biology is now changing paradigms in the light of facts and recent discoveries. Evolution makes only sense in the light of nature and organisms. Evolution makes sense in the light of biology.

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Declaration of interest

The author reports no declaration of interest.

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